Guideline 12-15

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Approach to Fever Assessment in Ambulatory Cancer Patients Receiving Chemotherapy

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An assessment conducted in December 2023 deferred review of Guideline 12-15. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 12-15 is comprised of 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1376

Section 1: Guideline Recommendations
Section 2: Recommendations and Key Evidence
Section 3: Guideline Methods Overview
Section 4: Systematic Review
Section 5: Internal and External Review

For updated guidance on prevention and management of febrile neutropenia, please see GL-C50-27 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/38561

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Approach to Fever Assessment in Ambulatory Cancer Patients Receiving Chemotherapy

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2 .

GUIDELINE OBJECTIVES

- To provide advice regarding the assessment of fever in cancer patients in the community who are receiving chemotherapy, given the potential for serious complications that is associated with it.
    - To investigate whether there are predictors that are associated with a poor outcome; to determine where and how quickly the assessment should take place for these patients and who can/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.

NOTE: For updated recommendations on febrile neutropenia, follow the 2021 guidance in Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients: Clinical Practice Guideline.

TARGET POPULATION

The target population includes adult patients with cancer (i.e., solid tumours or lymphoma) receiving chemotherapy in an outpatient setting who have a fever at home. Emergency department, in-hospital, and outpatient management of febrile neutropenia or serious infection are beyond the scope of the guideline (Table 1-1). There is abundant advice on managing patients after the diagnosis of febrile neutropenia is made (1-5). Patients who have had 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.

Table 1-1: Summary of Target Population

Adult patients with cancer receiving chemotherapy experiencing a fever	
Including	Not including
• Solid tumour • Lymphoma/Myeloma/Chronic lymphocytic leukemia • Living at home • Unknown neutrophil count	• Hospital inpatients • Patients in the emergency department • Already diagnosed with febrile neutropenia • Hematopoietic stem cell transplantation, acute leukemia, myelodysplastic syndrome

INTENDED USERS

Family physicians, emergency physicians and nurses, medical oncologists, hematologists, pharmacists, chemotherapy and community nurses, and health system administrators.

RECOMMENDATIONS

1) Temperature: Cancer patients in the community receiving chemotherapy who experience a fever should be assessed. While fever is not a reliable predictor of unfavourable outcomes such as febrile neutropenia, infection, or death, it is a serious symptom.
   a) A fever is defined as an oral temperature of ≥38.3˚C or sustained temperature of 38.0˚C lasting more than one hour.
   b) Tympanic temperature measurement is a viable option and should be measured according to manufacturers' specifications.

2) Assessment: Patients with fever should seek urgent assessment. Insufficient evidence exists to make specific recommendations with respect to the timing, location, or personnel involved in the assessment of fever in the target population.
   a) 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.

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

Qualifying Statements

- *There is a lack of quality primary evidence to inform the definition of fever; thus, the consensus definition from existing guidelines on febrile neutropenia was recommended.*
- *There is wide variation in temperature readings across thermometer types.*
- *Administration of antipyretic medication may mask the presence of fever and should be avoided if possible.*
- *Some patients may be receiving growth factors to decrease the risk of febrile neutropenia. Their risk for poor outcome in the setting of fever may be lower, and fever may be a side effect of the growth factors themselves. The evaluation of fever in chemotherapy patients who also receive growth factors to prevent febrile neutropenia was outside the scope of this guideline, but no obvious citations that address this issue were identified during the literature review to inform management of this subgroup.*

Approach to Fever Assessment in Ambulatory Cancer Patients Receiving Chemotherapy

Section 2: Guideline – Recommendations and Key Evidence

PREAMBLE

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

Since chemotherapy is usually given in an outpatient setting, most fevers will occur in patients at home between clinic visits. Because fever may signal febrile neutropenia, patients experiencing a fever during chemotherapy need urgent assessment. Such episodes may occur during the night and on weekends; thus, patients' recourse has often been to present to the emergency department for assessment. Furthermore, there might be a need to attend the emergency department during business hours if clinics lack the resources to evaluate such patients. 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 following chemotherapy. Fever is one of the most common reasons, but only a subset of patients have febrile neutropenia or require admission for further management.

Despite the frequency of fever in patients on chemotherapy, evidence-based, consistent guidance regarding assessment (when, where, and by whom) is lacking.

The current approach to managing fever in these patients is not standardized; there is variability regarding definitions, information provided to patients and healthcare providers, and approaches to education.

GUIDELINE OBJECTIVES

- To provide advice regarding the assessment of fever in cancer patients in the community who are receiving chemotherapy, given the potential for serious complications that is associated with it.
    - To investigate whether there are predictors that are associated with a poor outcome; to determine where and how quickly the assessment should take place for these patients and who can/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.

NOTE: For updated recommendations on febrile neutropenia follow the 2021 guidance in Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients: Clinical Practice Guideline.

TARGET POPULATION

The target population includes adult patients with cancer (i.e., solid tumours or lymphoma) receiving chemotherapy in an outpatient setting who have a fever at home. Emergency department, in-hospital, and outpatient management of febrile neutropenia or serious infection are beyond the scope of this guideline (Table 2-1). There is abundant advice on managing patients after the diagnosis of febrile neutropenia is made (1-5). Patients who have had 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.

Table 2-1: Summary of Target Population

Adult patients with cancer receiving chemotherapy experiencing a fever	
Including	Not including
• Solid tumour • Lymphoma/Myeloma/Chronic lymphocytic leukemia • Living at home • Unknown neutrophil count	• Hospital inpatients • Patients in the emergency department • Already diagnosed with febrile neutropenia • Hematopoietic stem cell transplantation, acute leukemia, myelodysplastic syndrome

INTENDED USERS

Family physicians, emergency physicians and nurses, medical oncologists, hematologists, pharmacists, chemotherapy and community nurses, and health system administrators.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

RECOMMENDATIONS
1) Temperature: Cancer patients in the community receiving chemotherapy who experience a fever should be assessed. While fever is not a reliable predictor of unfavourable outcomes such as febrile neutropenia, infection, or death, it is a serious symptom. **a) A fever is defined as an oral temperature of ≥38.3˚C or sustained temperature of 38.0˚C lasting more than one hour.** **b) Tympanic temperature measurement is a viable option and should be measured according to manufacturers' specifications.** **2) Assessment: Patients with fever should seek urgent assessment. Insufficient evidence exists to make specific recommendations with respect to the timing, location, or personnel involved in the assessment of fever in the target population.** **a) 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.** **3) Education: Cancer patients receiving chemotherapy in the outpatient setting should be provided with standardized information about fever and fever-associated infection.** **a) Patients should be informed about how to measure their temperature and how to recognize when assessment by a healthcare provider is recommended.** **b) This information should be delivered at the time of chemotherapy initiation and may be provided in conjunction with other self-assessment education, and reinforced with take-home written material and communication with healthcare providers.**
Qualifying statements

- *There is a lack of quality primary evidence to inform the definition of fever; thus, the consensus definition from existing guidelines on febrile neutropenia was recommended.*
- *There is wide variation in temperature readings across thermometer types.*
- *Administration of antipyretic medication may mask the presence of fever and should be avoided if possible.*
- *Some patients may be receiving growth factors to decrease the risk of febrile neutropenia. Their risk for poor outcome in the setting of fever may be lower, and fever may be a side effect of the growth factors themselves. The evaluation of fever in chemotherapy patients who also receive growth factors to prevent febrile neutropenia was outside the scope of this guideline, but no obvious citations that address this issue were identified during the literature review to inform management of this subgroup.*

Key Evidence

Temperature

The basis for this recommendation is existing guidelines and consensus. Most existing related clinical practice guidelines focus on the management of febrile neutropenia and define fever as a one-time temperature measurement of 38.3°C or two readings of 38.0°C one hour apart (2,4-8). Slight variations in definition were noted in two guidelines (1,3). Evidence from a primary literature review found six studies addressing the predictive value of body temperature. These patients were already diagnosed with febrile neutropenia, and the cut-off used in five studies was 39°C (9-13). In these 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 in detecting fever (≥38°C) with tympanic membrane thermometry of 68%, 98%, 90%, and 92%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value for oral thermometry were 56%, 98%, 90%, and 89%, respectively (14).

Assessment

No evidence was found that directly pertained to the assessment of fever before a diagnosis of febrile neutropenia was made. Fever was included as one among several symptoms (e.g., fatigue, pain, nausea, and vomiting) in some studies of management of the adverse effects of chemotherapy. Approaches to symptom management in these studies included patient-initiated drop-in clinics (15,16), healthcare provider-initiated case management programs (17,18), and various remote monitoring strategies using cell phone applications, web-based and touch-tone phone interfaces, and automated programs (19-23). Evaluation of these 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 cancer patients. Improvement in symptoms was seen with interventions such as cognitive behavioural therapy provided by nurses (24); pre-chemotherapy education class supplemented with take-home reading materials and instructions on how and when to report symptoms (25); a symptom management toolkit describing self-assessment activities (19); and education, fever management algorithm, and thermometer (26).

INTERPRETATION OF EVIDENCE

Few primary studies were found that dealt with the target population of this guideline (i.e., pre-diagnosis of febrile neutropenia). 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.

There was no evidence to suggest that patients could delay getting medical attention, although the optimal assessment has been poorly defined. By default, many patients present to the emergency department for assessment. In this regard, the Working Group echoes the position of the National Institute for Health and Clinical Excellence guideline, which recommends urgent assessment of patients who develop a fever at home (1). Although this could cause unnecessary hospital visits (with potentially long wait-times and exposure to other sick patients), unnecessary use of antibiotics, and patient anxiety, the benefits conferred by urgent assessment currently outweigh the potential harms of febrile neutropenia complications and risk of death.

There was no evidence to suggest an ideal location for assessment of fever, but such studies would be welcome given the prevalence of this symptom and the number of related emergency department visits. The Working Group strongly endorses the need for formal studies that include a rigorous evaluation component to assess alternate models of care for this situation.

IMPLEMENTATION CONSIDERATIONS

There is concern in Ontario that there is over-use of emergency department services by cancer patients who develop fever while undergoing chemotherapy. One goal of this guideline was to determine whether alternate care paths could be supported by research evidence. At the present time, the conclusion reached here is that there is insufficient evidence to predict with certainty which patients who develop fever are at risk of poor outcome, and therefore all patients should be assessed, given the serious consequences of infection. In other words, there is no way to define what constitutes “over-use” of emergency department services; therefore, recommendations to reduce that use are not possible at present.

Despite 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, could be incorporated into assessment algorithms for chemotherapy patients with fever to identify low-risk patients that could be safely assessed outside the emergency department. This would require concomitant data collection to confirm the validity of this approach and provide much needed evidence to inform practice. There are also emerging data on the feasibility and efficacy of remote management of chemotherapy-related symptoms using technology and phone-based strategies. 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 there is a lack of standardization of the information provided to patients regarding what to do if they experience a fever. The Guideline Panel believed patients should be effectively educated to expect the potential adverse events during and following 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 should be considered to

support their care, such as having a dedicated on-call nurse through the systemic treatment clinic, or community services through pharmacies or laboratories. Technological advancements in obtaining a definitive neutrophil count at home or in the community may be possible in the near future.

It is essential that knowledge transfer regarding fever assessment involves all healthcare 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, for any strategies implemented, it should be recognized that evaluation of effect is essential. Because best practice is not currently defined, the future state 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 bad outcome in patients receiving chemotherapy and current guidelines show a lack of focus on fever. Studies are needed to examine the relationship between temperature and undesirable outcomes and how that relationship is modified by other factors such as patient characteristics, concurrent symptoms, or the risk of neutropenia associated with the treatment regimen.

Although some research is being conducted on the development and evaluation of remote symptom management and monitoring systems and patient self-assessment in chemotherapy patients, studies focusing specifically on new models of care for fever either alone or in the context of multisymptom management strategies are needed. Development and testing of modes of communication with patients through phone, mobile phone apps, and web-based interfaces are encouraged as part of these 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 such as alternative locations 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 needs to be defined. Management of fever in patients on emerging therapies such as immunotherapy also needs to be considered.

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Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4 .

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and any associated Programs is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

The current approach to managing fever in cancer patients during systemic therapy is not standardized; there is variability regarding definitions, information, and education. The current dearth of alternative approaches to fever assessment results in a high percentage of this patient population seeking care from the emergency department. Emergency departments may have long wait times for care, and some work suggests that the risk of obtaining an infection in this setting is increased.

GUIDELINE DEVELOPERS

This guideline was undertaken by the Fever Assessment GDG, a group organized by the PEBC at the request of the CCO Systemic Treatment Program. The group was comprised of two medical oncologists, one malignant hematologist, one emergency physician, one infectious diseases physician, one primary care physician, one nurse practitioner, and one PEBC methodologist plus an Expert Panel comprised of medical oncologists, pharmacists, advanced practice nurse, and patient advisor (see Appendix 1 for membership).

The project was led by a small subcommittee, referred to as the Working Group from this point forward, whose members were responsible for creating the evidence base, drafting the first version of the recommendations, and leading the response to the external review. All members of the GDG contributed to final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Competing interests in the areas of professional interests were declared by two members; Appendix 1 provides further detail. Individuals with competing interests were not allowed to participate as a member of the Working Group unless otherwise stated. Conflicts of interest were managed in accordance with the PEBC Conflict of Interest Policy *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (27,28). This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework (29) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions.

For this document, a search was conducted of the SAGE Directory of Cancer Guidelines (www.cancerview.ca) and the National Guidelines Clearinghouse. In addition, the websites of several known high-quality guideline developers, including the American Society of Clinical Oncology (ASCO), the National Institute for Health and Clinical Excellence (NICE), and the Infectious Diseases Society of America (IDSA) were searched. Citations to guidelines were also retrieved in the literature search of MEDLINE and EMBASE. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument (http://www.agreetrust.org/).

Guideline Search Results

Eight guidelines were identified: NICE, ASCO, European Society for Medical Oncology (ESMO), Australian Consensus Guidelines (Australia), IDSA, German Society of Hematology and Oncology (DGHO), National Comprehensive Cancer Network (NCCN), and Alberta Health Services (Alberta) (1-8). The primary focus of the guidelines was the management of febrile neutropenia, particularly the care of the patient after febrile neutropenia was diagnosed. These guidelines offer limited information on the evaluation and management of fever in this patient population prior to a definitive febrile neutropenia diagnosis. All of the guidelines referred to the Multinational Association for Supportive Care in Cancer (MASCC) risk index for stratifying patients with chemotherapy-induced febrile neutropenia into low and high risk of complications or death (11). Several guidelines described the process of assessing suspected febrile neutropenia in patients who have already presented to an emergency department, the requirements for early discharge, the criteria for home care after discharge, recommended medication regimens, and follow-up care.

Although none of the guidelines directly addressed our target population, they contained some relevant information. Data extracted from the existing guidelines as well as from

systematic reviews and studies identified through a search of the primary literature are presented in the evidence section (Section 4 of this document).

Because information in the existing guidelines could potentially inform our recommendations, the AGREE II instrument was applied to the eight guidelines. For five guidelines (3-6,8), the AGREE II scores were available from the SAGE directory; for three guidelines (1,2,7), the AGREE II instrument was applied by the health research methodologist for this guideline (CWD) and another PEBC health research methodologist. The AGREE II scores are shown in Appendix 2. The NICE guideline had high scores in all six AGREE domains (scope and purpose, stakeholder involvement, rigour, clarity of presentation applicability, and editorial independence); the ASCO guideline had high scores across the first four domains. The scores for the other guidelines were low to medium across all domains.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The Fever Management Expert Panel and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Nadia Coakley, Craig Earle, Jennifer Fergenbaum, Esther Green, Swati Kulkarni, Mihaela Mates, Sheila McNair, Hans Messersmith, Dawn Stacey, Shailendra Verma, Eric Winquist for providing feedback on draft versions.
- Erin Redwood, Program Manager, Systemic Treatment Program, Cancer Care Ontario for facilitating Working Group meetings.
- Karen Spithoff for applying the AGREE II instrument for guideline review.
- Elizabeth Chan for conducting a data audit.
- Sara Miller for copyediting.

A complete list of the members of the Working Group and Fever Assessment Expert Panel, with their affiliations and conflict of interest information, is provided in Appendix 1.

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Section 4: Systematic Review

INTRODUCTION

Population-level studies from Ontario have shown that almost 50% of colon and breast cancer patients receiving systemic therapy have at least one visit to the emergency department, or are admitted to hospital during chemotherapy, and a large proportion of those patients have more than one visit. While fever, neutropenia, and infection are among the primary reasons, not all patients attending the emergency department have febrile neutropenia and most visits do not result in admission (http://www.csqi.on.ca/by_patient_journey/treatment/unplanned_hospital_visits_after_adjuvant_chemotherapy/)

Currently, there are several guideline documents available on febrile neutropenia, and in particular its management after diagnosis in the emergency department. However, there is a lack of guidance on pre-emergency department care, particularly involving the assessment of cancer patients on chemotherapy who develop fever. Some of these patients may need hospital-based assessment. Evidence-based advice is needed to support the choice of level of care at this stage (e.g., emergency department, urgent care, phone call to the oncologist or oncology nurse, primary care visit, pharmacist) as well as who should do the assessing, where should the assessment be done, and what findings trigger urgent follow-up?

Many centres have their own local procedures for managing fever, such as general instructions to patients in cancer centre handbooks (e.g., Juravinski Cancer Centre and Grand River) or handbooks specific to the cancer department (e.g., Juravinski Cancer Centre Hematology). Some centres distribute fever alert cards (e.g., Grey Bruce Health Network and London Health Sciences Centre). However, the approach is not standardized across the province.

The goal of this evidence review is to examine the literature on the assessment of fever in cancer patients in the community who are receiving chemotherapy and the subsequent potential for severe illness associated with it.

The target patient population of this guideline is non-hospitalized adult patients with cancer (i.e., solid tumours, myeloma, or lymphoma) receiving chemotherapy who develop a fever. Patients considered high risk (i.e., hematopoietic stem cell transplantation, acute leukemia, and myelodysplastic syndrome) are excluded. Infants, children, and adolescents are also excluded. Primary or secondary prophylaxis of febrile neutropenia or its management after diagnosis is beyond the scope of this guideline.

The Working Group of the Fever Assessment Guideline Development Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

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

METHODS

Literature Search Strategy

A literature search of the MEDLINE and EMBASE databases was conducted and covered 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 search strategies are in Appendix 3. The Cochrane Library was also searched and references of relevant retrieved articles were scanned.

An updated search was run to retrieve any relevant articles between March 2014 and November 2015.

Study Selection Criteria and Process

Retrieval from the MEDLINE/EMBASE searches was exported to EndNote. The research methodologist (CWD) reviewed the titles and abstracts that resulted from the searches. For those items that warranted full-text review, the research methodologist reviewed each item independently and conferred with the Working Group members.

Articles (full-text reports or conference abstracts) were considered for inclusion according to their study design and relevance to the research questions. The research questions pertained to risk factors, prediction models, and relationships rather than 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 these criteria were also considered.

For each research question, studies also had to meet the following criteria:

1. How does temperature relate to risk for febrile neutropenia, serious infection, or death?
    - Studies that compared patients with different cut-offs of temperature and evaluated risk for unfavourable outcome (e.g., febrile neutropenia, serious infection, hospital admission, or death) or investigated the measurement of temperature were eligible.
2. What are the clinical predictors for the development of febrile neutropenia?
    - Studies of clinical prediction rules with the generation of the rule in one or more sets of patients (derivation set) and testing 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 these studies were based on the JAMA Users' guides to the medical literature article on clinical decision rules (30).
3. What is the relationship between the timing or location of fever assessment, or the personnel doing the fever assessment, and the outcome of a fever episode?
    - Prospective or retrospective studies of patient assessment focusing on location, timing, or personnel doing the assessment that evaluated the risk for unfavourable outcome.
4. Do the type, quantity, and content of information provided to patients affect their choice about when and where to seek care for fever?
    - Prospective or retrospective studies of education or information about managing fever provided to patients or care givers.

Studies that included patients considered to be high risk (i.e., hematopoietic stem cell transplantation, acute leukemia, and myelodysplastic syndrome) and studies of infants, children, or adolescents were excluded.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was performed by the research methodologist. Important quality features such as study design, study setting, patient numbers and characteristics, description of risk factors or interventions, and outcomes were extracted for each study. Since randomized, nonrandomized, diagnostic, and clinical prediction studies were included in this review, no specific quality assessment tool was used.

Synthesizing the Evidence

Because of the differences among study designs, outcomes assessed, and results reported, meta-analysis was not feasible.

RESULTS

Literature Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the literature retrieval process and results is in Appendix 4. Of the 119 articles that were assessed for eligibility, 45 were included. The majority of excluded articles were ineligible because they were non-systematic reviews, studies that did not address a study question, or studies that described clinical prediction rules but did not contain a validation set of patients. Of the 45 included articles, seven were guidelines or summaries of guidelines that have been described above.

Studies were categorized by the research question to which they pertained.

1. How does temperature relate to risk for febrile neutropenia, serious infection, or death?: seven studies (9-14,31).
2. What are the clinical predictors for the development of febrile neutropenia?: 15 studies (9,11,13,32-43).
3. What is the relationship between the timing or location of fever assessment, or the personnel doing the fever assessment, and the outcome of a fever episode?: 16 studies (15-23,26,44-49).
4. Do the type, quantity, and content of information provided to patients affect their choice about when and where to seek care for fever?: six studies (19,24-26,45,50).

Three studies addressed questions 1 and 2 (9,11,13); three studies addressed questions 3 and 4 (19,26,45).

Study Design and Quality

The nature of the research questions determined the types of study designs that were included. For the most part, answers to the study questions were not amenable to intervention studies (for ethical reasons); thus, a validated risk of bias tool was not used to perform quality assessment. The quality of the evidence was generally low. Many studies were not comparative, making an evaluation of benefits and harms difficult. Eleven studies were reported in conference abstracts. The topics of these studies were relevant to the research questions, but in most cases insufficient information was provided about design issues or study details to fully evaluate the study quality. Few studies directly addressed the topic of fever except as one among many symptoms or adverse effects associated with chemotherapy.

Studies pertaining to question 1 were mostly designed as diagnostic accuracy studies, but only one included blinded interpretation of clinical predictors. Studies pertaining to question 2 were clinical prediction rules. For most of these studies, the performance of the risk score was evaluated by conducting an accuracy study with calculation of sensitivity, specificity, and positive and negative predictive values. Blinded assessment of predictor variables or outcomes was not reported in any of the studies. Studies pertaining to questions 3 and 4 were

mainly case series or surveys with no comparison groups. Of the four randomized controlled trials (RCTs) identified, one described allocation concealment.

Outcomes

1. **How does temperature relate to risk for febrile neutropenia, or serious infection, or death?**

Evidence and Recommendations from Relevant Guidelines

The guidelines generally agreed on the definition of febrile neutropenia (Table 4-1). Six guidelines described the fever component as a temperature of ≥38.3˚C (2,4-8). The European Society for Medical Oncology (ESMO) guideline stated a slightly higher one-time temperature of >38.5˚C (3). The National Institute for Health and Clinical Excellence (NICE) guideline used a cut-off of >38.0˚C or signs or symptoms consistent with clinically significant sepsis (1). Six guidelines stated a sustained temperature of ≥38.0˚C lasting more than one hour also indicated febrile neutropenia (3-8). Seven guidelines defined neutropenia as an absolute neutrophil count (ANC) $\leq 0.5\times10^9$ cells/L or an expected decrease to 0.5×10^9 cells/L (1,3-8). Only the American Society of Clinical Oncology (ASCO) guideline used an ANC cut-off of $<1.0\times10^9$/L (2).

Table 4-1. Definitions of febrile neutropenia in guidelines

Guideline	Fever	Temperature measurement method	Neutropenia
National Institute for Health and Clinical Excellence (NICE) 2012 (1)	>38.0˚C or other signs or symptoms consistent with clinically significant sepsis	Not stated	ANC $\leq 0.5\times10^9$ cells/L
European Society of Medical Oncology (ESMO) 2010 (3)	>38.5˚C or 2 readings >38.0˚C lasting 2 hours	Oral	ANC $<0.5\times10^9$ cells/L or expected to decrease to $<0.5\times10^9$/L
Australian Consensus Guidelines 2011 (4)	≥38.3˚C or 2 readings ≥38.0˚C	Not stated	ANC $<0.5\times10^9$ cells/L or $<1.0\times10^9$/L with expected decrease to $<0.5\times10^9$/L
German Society of Hematology and Oncology (DGHO) 2003 (6)	≥38.3˚C or 2 readings ≥38.0˚C lasting ≥1 hour or measured twice within 12 hours	Oral	ANC <500 cells/µL or <1000/µL expected to decrease to 500/µL within the next 48 hours
Infectious Diseases Society of America (IDSA) 2010 (5)	≥38.3˚C or ≥38.0˚C sustained over 1 hour	Oral	ANC <500 cells/mm^3 or an ANC expected to decrease to <500 cells/mm^3 within the next 48 hours
American Society of Clinical Oncology (ASCO) 2012 (2)	≥38.3˚C	Oral or tympanic	ANC $<1.0\times10^9$/L
National Comprehensive Cancer Network (NCCN) 2013 (7)	≥38.3˚C or ≥38.0˚C sustained over 1 hour	Oral	ANC <500 cells/µL or <1000/µL expected to decrease to ≤500/µL within the next 48 hours
Alberta Health Services 2012 (8)	≥38.3˚C or >38.0˚C sustained over 1 hour	Oral	ANC $<0.5x10^9$ cells/L or $<1.0x10^9$/L with

			expected decrease to $<0.5x10^9$/L within the next 48 hours

ANC=absolute neutrophil count
500 cells/mm^3 = 500 cells/μL = 0.5×10^9/L
1000 cells/mm^3 = 1000 cells/μL = 1×10^9/L

NICE

The NICE guideline used the term "neutropenic sepsis" throughout the guideline rather than febrile neutropenia. The guideline did not identify any studies designed to test different definitions of neutropenia and fever in cancer patients with potential neutropenic sepsis. It included 11 studies with inclusion criteria of both neutropenia and fever (six in children and four in adults), which excluded patients at low risk for bacterial infection and therefore may have underestimated the value of neutropenia and temperature as predictive factors for neutropenic sepsis. The NICE Guideline Development Group highlighted that having a narrow definition of neutropenic sepsis could lead to some patients with sepsis being missed (false negatives) while a broad definition could result in over-treatment or unnecessary investigation of patients without infection (false positives).

NICE Recommendation: Diagnose patients receiving anticancer treatment with neutropenic sepsis if they have a neutrophil count $\leq0.5x10^9$/L and body temperature >38°C or other signs or symptoms consistent with clinically significant sepsis (1).

Primary Literature

Seven studies were relevant to this research question (9-14,31). The study characteristics and outcomes are shown in Table 4-2. Six studies included data on the predictive value of body temperature (9-13,31). One study compared the diagnostic accuracy of different thermometers in detecting rectal fever in patients with febrile neutropenia (14).

Five of the studies used a temperature of ≥39°C as the threshold for unfavourable outcome (9-13). This cut-off performed poorly as a predictive factor with sensitivity ranging from 39% to 64% and specificity ranging from 56% to 84%. In two studies, the temperature was measured with an oral thermometer (11,13); in three studies, the type of thermometer was not stated (9,10,12).

The study evaluating tympanic, axillary, and oral thermometry compared with rectal thermometry in neutropenic patients used a cut-off of ≥38°C (14). Tympanic thermometry had the best performance in detecting rectal fever, with sensitivities of 71.2% and 68.2% in the left and right tympanic membrane, respectively. However, examination of systematic reviews of thermometry beyond our target population showed wide variation in temperature readings across thermometer types (51-59) (Appendix 5).

Summary of Evidence for Question 1

- *The majority of studies that report the association of temperature with poor outcome are in patients already diagnosed with febrile neutropenia*
- *The available data show body temperature to be a poor predictor of unfavourable outcome; most studies used a cut-off of ≥39°C to indicate poor outcomes. The cut-off had a sensitivity ranging from 39% to 64% and specificity ranging from 56% to 84%.*
- *Most current guidelines recommend a temperature of 38.3°C as the threshold for febrile neutropenia but this is not supported by evidence*

Table 4-2. Temperature and risk for poor outcome.

Citation: Chayakulkeeree2003 (9)
Study design: Retrospective; development of prediction model and validation of MASCC score.
Setting: Hospital in Thailand.
Patients: 267 febrile neutropenia episodes in 220 patients.
Analysis: Univariate analysis of potential factors for predicting a favourable (fever resolution within 5 days without serious medical complications) or unfavourable (death, development of serious medical complications, modification of initial antibiotic treatment, relapse of fever, or fever not resolved after 5 days) outcome in febrile neutropenia patients.
Results: # patients ≥39°C with unfavourable outcome = 83/159
patients ≥39°C with favourable outcome = 48/108

	Unfav	Fav
≥39°	83	48
<39°	76	60

Sensitivity 52%
Specificity 56%

Citation: Dzarr2009 (14)
Study design: Prospective diagnostic accuracy study.
Setting: University hospital in Kubang Kerian, Malaysia.
Patients: 21 patients (age range 15 to 63 y) with a mix of hematological malignancies including lymphoma.
receiving chemotherapy and having neutropenia (neutrophil count <500 cells/mm^3).
Analysis: Infrared tympanic membrane (Braun Thermoscan), axillary & oral (non-self-adjusted mercury bulb thermometer) compared with rectal thermometry (non-self-adjusted mercury bulb rectal thermometer). Rectal thermometry used as the reference standard.
Oral, axilla, tympanic membrane, & rectal temperature measured 2×/day.
Tympanic thermometer placed until it beeped; mercury bulb thermometers in place for 4 minutes.
Temperature readings were blinded.
Results: 400 sets of temperature readings were measured. Rectal fever was defined as ≥38°C.
Right tympanic membrane showed highest agreement with rectal temperature.
Sensitivity, specificity, positive predictive value, negative predictive value:
Left tympanic membrane 71.2%, 95.7%, 82.5%, 92.2%
Right tympanic membrane 68.2%, 97.9%, 90%, 91.6%
Mean tympanic membrane 63.6%, 97.4%, 87.5%, 90.5%
Oral 56.1%, 98.3%, 90.2%, 88.8%
Axilla 34.8%, 99.6%, 95.8%, 84.4%
Adjusted oral (+0.3°C) 68.2%, 97.0%, 86.5%, 91.5%
Adjusted axilla (+0.5°C) 65.2%, 94.4%, 76.8%, 90.6%
Either left or right tympanic membrane thermometry acceptable.

Citation: Ha2011 (10)
Study design: Retrospective; development of a scoring system to predict bacteremia.
Setting: Emergency department in Korea.
Patients: 993 low risk febrile neutropenia episodes in 802 patients.
Analysis: Variables significantly associated with bacteremia in a univariate analysis were entered into a multivariate logistic regression analysis. An initial body temperature of ≥39°C was analyzed in a univariate analysis.
Results: Initial body temperature and risk for bacteremia

	Bac	No Bac
≥39°	65	352
<39°	37	534

Sensitivity 64%
Specificity 60%
Univariate OR 2.67 (CI 1.76 to 4.05)
Multivariate OR 1.86 (CI 1.12 to 3.11)

Citation: Klastersky2000 (11)
Study design: Prospective; development & validation of risk index (MASCC).
Setting: 20 institutions in 15 countries.
Patients: 1139 patients (in hospital and outpatients) with febrile neutropenia.
Analysis: Univariate analysis of patient characteristics in the derivation set associated with outcome (resolution of febrile neutropenia episode without occurrence of serious medical complications).
Number of patients with temperature ≥39°C and <39°C × the rate of resolution provides the false positive and true negative data.
Results: # patients ≥39° = 248; resolution rate = 79%
patients <39° = 508; resolution rate = 88%

	Unfav	Fav
≥39°	52	196
<39°	61	447

Sensitivity 46%
Specificity 70%

Citation: Lynn2013 (31)
Study design: Retrospective; case-control study.
Setting: Emergency department in Taoyuan, Taiwan.
Patients: Patients presenting to the emergency department with febrile neutropenia. 81 febrile neutropenia episodes in 78 patients.
Analysis: Patients were classified as having serious or no serious complications according to demographic and clinical attributes.
Results:
Serious complications: 25 patients; median temperature 38.3°C
No serious complications: 56 patients; median temperature 38.2°C
p=0.68
Odds ratio 0.86 (CI 0.48 to 1.53), p=0.60

Citation: Offidani2004 (12)
Study design: Retrospective; historical cohort study. Development of risk model.
Setting: University hospital in Italy.
Patients: 110 hematologic inpatients with fever and pulmonary infiltrates.
Analysis: Univariate analysis of patient characteristics associated with favourable or unfavourable (death) outcome.
Number of patients with temperature >39°C and ≤39°C × survival rate (favourable outcome) provides the false positive and true negative data.
Results: # patients >39°C = 47; survival rate = 76%
patients ≤39°C = 63; survival rate = 79%

	Unfav	Fav
>39°	11	36
≤39°	13	50

Sensitivity 46%
Specificity 58%
Odds ratio 1.08, p=0.75

Citation: Uys2004 (13)
Study design: Prospective; validation of MASCC score.
Setting: Hospital in Johannesburg.
Patients: 64 patients admitted to hospital on presenting with febrile neutropenia. 80 febrile neutropenia episodes.
Analysis: The MASCC score was used to classify patients as low risk (score ≥21) or high risk (score <21). Low risk indicated an uncomplicated recovery, and high risk predicted serious medical complications.
Results: Temperature at presentation:
episodes ≥39°C = 9 (low risk), 7 (high risk)
episodes <39°C = 49 (low risk), 15 (high risk)

	High	Low
≥39°	7	9

	<39°	15	49

Sensitivity 7/22=32%
Specificity 49/58=84%

MASCC=Multinational Association for Supportive Care in Cancer

2. What are the clinical predictors for the development of febrile neutropenia?

Evidence and Recommendations from Relevant Guidelines

No guidelines were identified that addressed patients receiving chemotherapy with a fever before a diagnosis of febrile neutropenia. The existing guidelines focused on identifying risk among patients already diagnosed with febrile neutropenia using a predictive model or decision tool (e.g., Multinational Association for Supportive Care in Cancer [MASCC]), to determine whether patients were low risk or high risk, and if they could be managed as outpatients. The maximum MASCC score is 26 and a score ≥21 indicates low risk (Table 4-3).

Table 4-3. Multinational Association for Supportive Care in Cancer Risk-Index Score (MASCC) (11)

Characteristic	Weight
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour or no previous fungal infection	4
No dehydration	3
Burden of illness: moderate symptoms	3
Outpatient status	3
Age <60 years	2

Points attributed to burden of illness are not cumulative. Maximum score = 26
Low risk is considered a score ≥21.

NICE

There was no direct evidence about which signs or symptoms experienced by patients in the community might predict neutropenic sepsis. The only data available were from studies of secondary care in which patients had already presented to hospital with treatment-induced neutropenia and fever. Of the eight included studies, six were in children, and the overall quality was considered very low. The data showed that symptoms such as confused mental state, chills, and feeling or looking unwell correlated with a poor outcome, although the absence of those symptoms did not predict a good outcome. Despite the lack of high-quality, relevant supporting evidence, the NICE Guideline Development Group indicated that patients who became unwell at home should be urgently assessed and that the harms of unnecessary hospital attendance, follow-up, and patient anxiety were outweighed by the benefits of not missing a diagnosis of neutropenic sepsis and possible associated mortality.

NICE Recommendation: Suspect neutropenic sepsis in patients having anticancer treatment who become unwell. Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care.

The guideline also recommended that a research study should be done to determine which signs and symptoms experienced by patients in the community predict neutropenic sepsis and ensuing outcomes (1).

ASCO

There was no evidence that addressed the risk for developing febrile neutropenia in outpatients. Studies of inpatients or mixed populations identified variables related to patients' health status, underlying cancer, and specific chemotherapy regimen.

ASCO Recommendation: Risk for febrile neutropenia should be systematically assessed (in consultation with an infectious disease specialist as needed) including patient-, cancer-, and treatment-related factors (2).

Primary Literature

In the primary literature, we sought clinical prediction rules that developed a prediction model in one group of patients and validated the model in a separate group of patients. This approach is proposed as the most rigorous study design for diagnosis and prognosis assessments in the JAMA Users' Guides to the Medical Literature (30). Two systematic reviews (41,43) and 13 studies (9,11,13,32-43) reported clinical prediction rules for predicting febrile neutropenia. The systematic reviews did not restrict their inclusion criteria to clinical prediction rules, but included studies that correlated neutropenia with risk factors or patient characteristics (43) or studies with univariate and/or multivariate analysis for febrile neutropenia risk factors (41).

Several studies dealt with patients after the diagnosis of febrile neutropenia and examined prognosis, complications, and classification of patients as low and high risk using the MASCC risk score (9,11,13,32-36,38,42). The post-diagnosis febrile neutropenia period is beyond the scope of this guideline; therefore, these studies are not discussed further (they are described in Appendix 6).

Two studies described the derivation and validation of a prediction model to identify patients at risk for febrile neutropenia (37,39); however, both assessed the baseline risk of febrile neutropenia in all patients receiving chemotherapy (i.e., **before** they developed a fever). Hosmer et al developed and tested a prediction model for the risk of febrile neutropenia during the first cycle of chemotherapy in older patients (≥65 years of age) with breast, lung, or colon cancer using the SEER-Medicare database (37). Lyman et al developed and tested a clinical risk model for the occurrence of febrile neutropenia in a prospective cohort of community oncology patients beginning a new chemotherapy regimen (39). The model from Lyman et al was also tested in a subgroup of patients receiving intermediate-risk chemotherapy regimens (40).

The studies are described in detail in Table 4-4. The model in Hosmer et al was moderately predictive in identifying patients at high risk for febrile neutropenia during the first cycle of chemotherapy. The patient characteristics associated with greater risk for febrile neutropenia were stage 2 or greater cancer, increasing number of comorbid conditions, and beginning chemotherapy less than one month from diagnosis (37). The model described by Lyman et al also showed increased risk for neutropenic complications early in the course of chemotherapy and was affected by cancer type and treatment regimen (39). The model had good performance in predicting neutropenic complications in the subgroup of patients receiving intermediate-risk chemotherapy (40).

Summary of Evidence for Question 2

- *Few studies examine the risk factors for developing febrile neutropenia among cancer patients receiving chemotherapy and no studies examine the risk in the subset of patients with fever; most studies examine risk of complications or poor outcome after febrile neutropenia is diagnosed.*

- *The two relevant studies examining predictors for the development of febrile neutropenia help identify high-risk patients and may be helpful in assessment algorithms, but lack sufficient predictive power to be used routinely without further development and evaluation.*

Table 4-4. Predictors for development of febrile neutropenia

Citation: Hosmer2011 (37) Study design: Retrospective; development & validation of prediction model. Setting: SEER Medicare database (6 metropolitan areas & 5 states in the US) 1 year before cancer diagnosis to 1 month after first chemo cycle. Patients: 86,693 patients with breast, lung, prostate, or colorectal cancer during the first chemo cycle. Description of risk assessment: Predictor variables were cancer stage, receipt of chemo, chemo agents, time between chemo treatments, comorbid conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, other cardiovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, liver disease, diabetes, paralysis, renal disease, & AIDS). Patient sample split into training set (2/3) and validation set (1/3). Predictive accuracy of the model tested to identify patients at high risk of developing febrile neutropenia estimated using the C statistic (range 0.5 [no better than chance alone] to 1.0 [perfect prediction]). A cut-off of 10 points on the febrile neutropenia risk score (maximum 19) was associated with a risk for febrile neutropenia of 10%. Results: Multivariate analysis showed independent predictors of febrile neutropenia were cancer type (lung or colon), cancer stage ≥2, increasing number of comorbid conditions, and <1 month from time of diagnosis to initiation of chemo. The C statistic for both development and validation sets was 0.75, providing moderate predictive power. Using the 10-point threshold, the sensitivity, specificity, positive predictive value, and negative predictive value of the model was 24%, 93%, 12%, and 97%, respectively.
Citations: Lyman2011 (39) Study design: Prospective; development & validation of risk model. Setting: Community oncology practices in the US. Patients: 3760 patients with colorectal, lung, ovarian, lymphoma, or breast cancer beginning chemo. Description of risk assessment: Data collected on demographics and clinical variables, planned relative dose intensity, and hematology and chemistry laboratory data. Outcome was febrile neutropenia in cycle 1 chemo. The patient sample was split 2:1 into the derivation model (n=2500) and validation model (n=1260). A risk score was calculated based on multivariate analysis of the derivation model; higher score was associated with greater risk of febrile neutropenia. The predicted risk was stratified as high risk (>10%) and low risk (<10%). Results: Multivariate analysis showed the important prognostic factors for febrile neutropenia were previous chemo; receiving other immunosuppressive therapy; elevated aspartate aminotransferase, alkaline phosphatase, or bilirubin; reduced white blood cell count or estimated glomerular filtration rate; planned relative dose intensity ≥85%; and several classes of chemo (anthracyclines, taxanes, cyclophosphamide or ifosphamide, type I and II topoisomerase inhibitors, platinums, gemcitabine, or vinorelbine). Reduced risk for febrile neutropenia was associated with primary prophylaxis with a myeloid growth factor. Performance of the model in predicting febrile neutropenia in the validation set of patients was similar to that of the derivation set. Validation: Sensitivity 85%, specificity 58.7%, positive predictive value 36.1%, negative predictive value 93.4%, positive likelihood ratio 2.06 , negative likelihood ratio 0.26, diagnostic odds ratio 8.03 Area under the receiver operating characteristic curve 0.81 (CI 0.77 to 0.84), p<0.0001
Citation: Lyman2011ab (40) Study design: Prospective; validation of previously developed risk score (Lyman2011). Setting: 115 US oncology practices. Patients: 2270 patients initiating new regimen of intermediate-risk chemo placing them at high risk for neutropenic complications.

Description of risk assessment: The risk for severe neutropenia or febrile neutropenia was estimated with logistic regression adjusting for key clinical factors. Results: Severe neutropenia or febrile neutropenia occurred in 21.4% during cycle 1; 11% over 4 cycles. The risk score had a C statistic of 0.82 (CI 0.80 to 0.84). Performance of model: Sensitivity 89%, specificity 61%.

3. What is the relationship between the timing or location of fever assessment, or the personnel doing the fever assessment, and the outcome of a fever episode?

Evidence and Recommendations from Relevant Guidelines

The procedure for patient investigation before emergency department or hospital presentation was not a focus of discussion in the existing guidelines.

NICE

The NICE Guideline Development Group noted that patients with suspected neutropenic sepsis may present to various healthcare settings, including primary care, emergency departments, and as hospital admissions. The healthcare professionals within these settings may have varying levels of expertise; some may be unfamiliar with the management of neutropenic sepsis. Only two studies were found, and these pertained to training or staff re-education and the effect on time from assessment to administration of antibiotics. In both studies, patients were in a hospital setting.

NICE Recommendation: Healthcare professionals and staff who come into contact with patients receiving anticancer treatment should be trained on the identification and management of neutropenic sepsis (1).

ASCO

The ASCO guideline found no evidence regarding patient assessment prior to the diagnosis of febrile neutropenia. The literature review found a number of studies that compared inpatient with outpatient management of low-risk patients with febrile neutropenia.

ASCO Recommendation: Patients identified as low risk (after presentation and triage in the clinic, emergency department, or hospital) and selected for outpatient management should be observed for at least four hours prior to discharge (2). (ASCO defines low risk as a score ≥21 on MASCC [11] or Talcott's group IV: outpatients at onset of a febrile neutropenia episode without either serious comorbidity or uncontrolled cancer [60].)

Alberta

One of the questions in this guideline asked what pre-treatment investigations should be conducted for adult outpatients suspected of having febrile neutropenia. The recommendation is not linked to supporting evidence. The recommendation implies the patient is presenting at a healthcare facility.

Alberta Recommendation: Conduct a careful history and detailed examination including assessments of mental status, hydration status, oral and pharyngeal mucosa, skin (including any indwelling intravenous sites), respiratory system, abdomen, cardiovascular system, and special considerations (meningitis, sinusitis, herpes simplex, herpes zoster, thrush) (8).

Primary Literature

One systematic review (21) and 15 studies (15-20,22,23,26,44-49) were retrieved that described or evaluated symptom management protocols in cancer patients receiving chemotherapy. The studies described protocols for assessing, triaging, or managing the side effects of chemotherapy. The study details are shown in Table 4-5. Seven of these studies were conference abstracts and, thus, provided few details about the protocol. Only one study was retrieved that directly addressed the assessment of fever (26). In most studies, fever or body temperature was merely one of several chemotherapy-associated symptoms or adverse effects. Three studies focused on protocols specifically for managing febrile neutropenia (26,45,47).

Five studies described symptom management protocols that involved patients presenting *in person* (15,16,44,47,48). In two studies, patients could drop in to the oncology clinic with no appointment and be seen by clinic staff (15) or a nurse practitioner (16). Cox et al reported fever to be among the most common reasons for attendance (16). Three studies involved assessment during regular scheduled appointments (44,47,48). Cirillo et al compared nurses, physicians, and patients on symptom and toxicity reporting and found stronger agreement between patients and nurses than between patients and physicians (44). Moore et al described a standardized checklist for febrile neutropenia assessment in an effort to help nurses to be proactive in reducing the risk associated with febrile neutropenia (47). Nakaguchi et al evaluated nurses' recognition of the supportive care needs and symptoms of chemotherapy patients (48).

Two studies also involved patient-initiated contact, but patients contacted the oncology unit *by phone* for symptom management advice (26,49). These protocols included off-hours access to oncology staff. One study showed a trend toward reduced hospital visits compared with patients with no consultation access (49).

In two studies, symptom management was performed through *outreach by nurses* (17,18). In these studies, patients were contacted on a regular basis by clinic nurses for at-home follow-up during and after chemotherapy. Patients also had off-hours phone access for symptom management advice.

Six studies focused on *remote* systems of symptom management (19-23,46). These systems utilized phone or web-based automated protocols that allowed patients to record symptoms whenever they wanted or in response to reminders. Some systems were linked to patient records. In all protocols, worsening symptoms triggered alerts to oncology staff.

Four of the studies described above evaluated automated symptom management tools specifically for cancer patients receiving chemotherapy (19-21,23). An Internet search identified several additional symptom management systems in development. A description of these systems is in Appendix 7. The symptom-reporting mechanisms included web-based interfaces, mobile phone apps, and purpose-built devices. Features included alerts sent to oncology teams, links to electronic medical records, and reminders sent to patients. A few systems are commercially available, while others are still being developed and tested. Preliminary results of those systems that have been evaluated indicated that symptom management systems were favourably received by patients who found them easy to use and allowed them to keep track of their symptoms and serve as a memory aid in their interactions with healthcare providers (61-73).

Most of the studies focused on feasibility and acceptability of the intervention to patients, the types of symptoms for which care was sought, and whether the personnel delivering the intervention (frequently a nurse) could manage the symptom independently. The few studies that reported on patient and health system outcomes suggested some improvements in symptom control and decreased healthcare utilization (21,46,49).

Summary of Evidence for Question 3

- *The overall quality of the evidence related to this question is poor. Few studies provide data on patient outcomes in relation to interventions/approaches tested and most are evaluations of single institution experience.*
- *No studies target fever or body temperature specifically: a few include it as one of several symptoms associated with the adverse effects of chemotherapy.*
- *Nurses have a major role in providing support and feedback to patients regarding chemotherapy adverse effects. Preliminary studies suggest that access to nurses for symptom management between clinic visits shows promising results.*
- *Patient communication through phone, mobile phone app, and web-based interfaces are among the pathways being explored for symptom assessment. Contact may be initiated by the patient (e.g., filling out a web-based symptom questionnaire) or by the cancer clinic (e.g., follow-up phone call by the nurse, email reminders)*
- *More research in the nascent area of symptom management systems is required, especially regarding their impact on management of fever and outcomes such as symptom control/resolution, serious morbidity and death, and healthcare utilization.*

Table 4-5. Assessment of fever or chemotherapy adverse effects.

Citation: Antonuzzo2013ab (15) Objective: To provide direct and early management of chemotherapy toxicities. Timing: In person during the day (no appointment needed); telephone consult available. Location: Oncology day hospital unit. Personnel: Supportive care team (physicians and nurses). Fever: Not mentioned. Important features: Patient access to supportive care in-person or by telephone without an appointment. Results: Over a period of 7 months, 761 unplanned visits (median 6/day, range 0 to 13) and 1138 phone calls (median 9/day, range 2 to 24) occurred.
Citation: Baker2008 (17) Objective: To optimize management of patient receiving intensive chemotherapy. Timing: Patient contacted by research nurse after discharge and weekly; 24 hour phone or pager coverage. Location: At home. Personnel: Contact by research nurse, availability of physician and research nurse by phone. Fever: Fever was among reasons prompting action. Important features: Patients recorded symptoms (including temperature) and adverse effects in a diary; nurse contacted patients weekly; patient access to nurse or physician by telephone 24 hours. Results: Fever was among the most common adverse effects experienced by patients. Patients were instructed to go to the emergency department.
Citation: Cirillo2009 (44) Objective: To compare agreement among patients, nurses, and physicians in chemotherapy toxicity reporting. Timing: Regularly planned visits. Location: Oncology clinic. Personnel: Nurses and physicians. Fever: Fever was among the list of side effects on the questionnaire. Important features: Patients self-reported symptoms on a questionnaire at home and nurses and physicians recorded toxicity during patients' medical visits. The patient questionnaire was the reference standard. Results: Agreement was stronger between patients and nurses than patients and physicians. In some cases, nurses recorded more toxic events than patients.
Citation: Compaci2011 (18)

Objective: To assess the feasibility of nurse-initiated telephone calls and follow-up of patients with diffuse large B cell lymphoma receiving chemotherapy. Timing: Patient contacted by nurse at set time twice a week; off-hours access. Location: At home. Personnel: Patient access to oncology unit hot line and oncologist and nurse email. Fever: Not mentioned. Important features: Nurse contacts patient regularly; patient access to clinical staff by telephone and email; follow-up interventions triggered by information collected on patient call form. Results: The patient-nurse interaction was graded according to the level of intervention required: 1) none, 2) intervention for expected nonlife threatening complications (e.g., noncomplicated febrile neutropenia managed by oral antibiotics at home), 3) direct intervention of the oncologist (e.g., severe sepsis). In 95% of cases, the nurse was able to perform follow-up with only minimal intervention of the oncologist.
Citation: Cox2012ab (16) Objective: To assess the role of a cancer nurse practitioner. Timing: In person to the chemotherapy unit without an appointment. Location: Chemotherapy unit. Personnel: Nurse practitioner ordered appropriate investigations and began treatment regimens in response to presenting problems. Fever: Fever was among reasons for presenting to the nurse practitioner. Important features: Patient access to a nurse practitioner without an appointment. Results: Over a 6-month period, 87 patients presented to the unit. Nurse practitioner was able to assess patients and initiate treatment. Medical advice was sought for 59% of the patients but medical review was not required for 52%.
Citation: Decker2009 (19) Objective: To develop and test an automated voice response system. Timing: Patients received automated telephone calls at prearranged day and time each week. Location: At home. Personnel: Nurses performed recruitment, intake and exit interviews; and made intervention calls triggered by patient responses on the automated system (nonadherence to medication or problems with symptom management). Fever: Fever was one of the symptoms included in the system. Important features: Regular contact with patient; standardized information retrieval; follow-up interventions activated by information collected. Results: Fatigue and pain were the most common symptoms requiring nurse intervention. Fever occurred in one patient and did not warrant a nurse intervention. Patients found the system easy to learn and use. Patients who received a nurse intervention all reported help with nonadherence and more than two-thirds reported help with symptoms. Of 30 patients in the study, 4 were admitted to the hospital, 1 presented to the emergency department for a problem unrelated to chemotherapy, 7 had primary care visits, and 1 received home healthcare services.
Citation: Judson2013 (20) Objective: To determine the feasibility of a web-based patient-reported outcome system. Timing: Any time; automated emails reminded patients to self-report. Location: At home; also available on tablet and kiosk computers in the oncology clinic. Personnel: Clinic staff received reports from the system before each clinic visit. Nurses received alert emails in the event of worsening symptoms. Fever: Not mentioned. Important features: 7 plain-language questions about symptomatic toxicities, health state, and performance status; report available to healthcare providers; alerts sent to nurses if symptoms worsened from previous login or grade 3 or 4 toxicities reported. Results: A median of 17 logins per patient occurred during the study (mean follow-up, 34 weeks), 71% from home and 29% from the clinic. Average monthly compliance was 83%, with the main reasons for missing a report being forgetfulness (42%) or too busy (21%). Reporting compliance was associated with older age and higher education level. Patients were more likely to be compliant during the first 12 weeks of the study.

Citation: Kitao2012ab (45)
Objective: To assess the feasibility of a self-assessment system for febrile neutropenia.
Timing: Any time.
Location: At home.
Personnel: Multidisciplinary team.
Fever: A febrile episode was defined as body temperature >38.0°C.
Important features: Patients receiving chemotherapy were managed by a self-assessment system that comprised antibiotic prescription, education by clinic team (doctors, pharmacists, and nurses) including written material, and evaluation at the hospital of a febrile episode.
Results: 476 patients were managed by the self-assessment system. A febrile episode occurred in 33% of patients; 9% were admitted to hospital. 30-day mortality rate was 0%.

Citation: Kofoed2012 (21)
Objective: To report studies of remote monitoring systems that quantified changes in patient outcomes, healthcare system utilization, or health system costs. 5 studies met criteria; 3 studies were of patients receiving chemotherapy. 2 systems used touchtone phones, 1 system used a mobile phone app.
Timing: Any time.
Location: At home.
Personnel: Data were transmitted to clinic staff daily in 2 studies and twice daily in 1 study. Alerts were triggered to healthcare coordinator or nurse when symptoms reached certain thresholds.
Fever: Not mentioned.
Important features: Automatic alerts are sent to clinic staff; patients received self-care feedback relevant to the symptoms reported.
Results: Evidence of improved health-related quality of life, fewer clinic visits, and decreases in some symptoms.

Mooney2012ab (46)
Objective: To report 2 randomized controlled trials testing an automated telephone-based monitoring system for patients receiving chemotherapy.
Timing: Patients were asked to call the automated system daily. Patients used the system during the second and third chemotherapy cycles.
Location: At home.
Personnel: 2 randomized controlled trials: Study 1 (n=250) compared telephone care with usual care; reported symptoms were emailed to oncologist and oncology nurse. Study 2 (n=335) compared telephone care with usual care but the symptoms were sent to a study nurse practitioner. Patients in the usual care group used the monitoring system as well but their data were not forwarded to healthcare providers.
Fever: Not mentioned.
Important features: Study 2: A dedicated study nurse practitioner who responded by telephone to patients by phone using evidence-based guidelines to address unrelieved symptoms.
Results: Study 2: The telephone group had lower symptom score ($p<0.001$), fewer severe symptom days (3.16 versus 10.24, $p<0.001$), fewer moderate symptom days (8.91 versus 19.06, $p<0.001$), and more no symptom days (66.06 versus 52.02, $p=0.01$).

Mooney2014 (22)
Objective: Full publication of study 1 from Mooney2012ab.
Timing: Patients were asked to call the automated monitoring system daily during chemotherapy cycles 2 and 3.
Location: At home.
Personnel: 11 provider teams of oncologists and nurses participated.
Fever: Fever was 1 of 10 symptoms patients were asked to report.
Important features: Patients used the touch tone keypad of the phone to make responses. For fever, the temperature was entered as a number. The system immediately faxed or emailed symptom alert reports to the patient's oncologist and oncology nurse. The report included severity and distress and answers to drill-down questions such as number of vomiting episodes, oral intake, and dizziness.
Results: The groups did not differ for symptom severity or distress scores ($p=0.58$); number of no, mild, moderate, or severe symptoms days ($p>0.05$); number of unscheduled contacts between patients and

providers (p=0.73); or discussion of symptoms during patient-initiated contacts (p=0.19). Oncology providers made few follow-up contacts. Patients reported high satisfaction with the system.

Citation: Moore2010 (47)
Objective: To evaluate the utility of a standardized febrile neutropenia risk assessment tool for nurses.
Timing: Beginning a new chemotherapy regimen; during regular clinic appointments.
Location: Oncology clinic.
Personnel: Oncology nurses performing new patient assessment and teaching. Nurses used a standardized checklist and recorded patient risk factors and initiated interventions in response to findings.
Fever: Not mentioned.
Important features: Use of the checklist prompted recording of risks for febrile neutropenia.
Results: In 94% of patients, nurses detected risk factors that prompted interventions to reduce duration of febrile neutropenia and its complications. The most frequent intervention was closer monitoring of the patient (64%). Other interventions were prescription of prophylactic granulocyte colony-stimulating factor (27%), a change in chemotherapy regimen (2%), and change in chemotherapy dose (0.7%). Most nurses found the tool helpful (67%) and easy to use (87%).

Citation: Nakaguchi2013 (48)
Objective: To evaluate the accuracy of nurses in recognizing patients' supportive care needs and symptoms.
Timing: During chemotherapy.
Location: Chemotherapy unit.
Personnel: Patients receiving chemotherapy completed a self-administered questionnaire at home after a regular clinic appointment and returned it the next day. The questionnaire assessed 5 domains of need: psychological, health system and information, physical and daily living, patient care and support, and sexuality. Nurses completed a similar questionnaire addressing patients' supportive care needs.
Fever: Not mentioned.
Important features: The questionnaires used validated survey tools. Nurses were blinded to patient questionnaire responses.
Results: Nurses were suboptimal in recognizing supportive care needs, particularly in the psychological domain, which patients ranked high in prevalence. The greatest supportive care needs ranked by patients were psychological (77%), health system and information (64%), and physical (60%), whereas nurses ranked health system and information as the highest need (74%). Nurses were accurate in recognizing physical symptoms associated with chemotherapy such as hair loss, fatigue, and appetite loss and performed less well in detecting nonspecific symptoms such as dyspnea, pain, and insomnia.

Citation: Noguchi2013ab (49)
Objective: To assess the effect of a telephone consultation service.
Timing: During chemotherapy cycle; unknown if access was restricted to certain times of day.
Location: At home.
Personnel: Clinic staff; unknown what particular personnel provided telephone consultation or whether it was accessible 24 hours per day.
Fever: Fever among frequently reported symptoms.
Results: Frequent patient problems were pain (14.4%), fever (11.5%), nausea and vomiting (5.8%), and confirmation of dosing instructions (6.5%). Three-quarters of calls were during the first 4 chemotherapy cycles. Compared with patients with no consultation access, patients with access had a borderline statistically significantly lower rate of unplanned hospital visits (7.2% versus 31.3%, p=0.06). Groups did not differ in rate of unplanned admissions (1.2% versus 7.2%, p=0.151).

Citation: Shah2009ab (26)
Objective: To assess the feasibility of patient-initiated management of febrile neutropenia.
Timing: Any time.
Location: At home.
Personnel: On-call oncologist could be contacted by telephone if patients developed a fever. Patients had been provided with education, an algorithm to follow (details not provided), thermometer, and oral antibiotics.
Fever: Patients initiated contact if febrile.

Important features: Protocol aimed at managing fever; featured a self-assessment aspect as patients had tools and information to help them manage their symptoms. Results: Of 53 patients, 9 patients (17%) experienced ≥1 febrile episode. Neutropenia was present in 13 of the episodes. 9 of 12 episodes were managed as outpatients. Patients had no difficulty adhering to the protocol.
Citation: Velikova2012ab (23) Objective: To report the development of a web-based patient-reported outcome system. Timing: Anytime. Location: At home; also available on computers at the hospital. Personnel: Oncology unit staff. Fever: Fever one of the symptoms on the web-based system. Important features: Patients enter adverse event data in response to a standardized questionnaire; the data are integrated into the electronic patient record; clinician alerts are generated; the system provides patient self-management advice. Results: During feasibility testing, the interface underwent 3 iterations of testing, oncology professionals helped map the chemotherapy management/admission pathway, and training requirements were identified. An audit of patient calls found 40% were 1 to 7 days post treatment; common symptoms were pain, nausea/vomiting, fever/infection, diarrhea, and breathlessness. 48% of patients had grade 1 adverse events, 14% grade 2, and 18% grade 3. 83% of patients with grade 3 adverse effects were admitted while 68% of patients with grade 1 events received advice.

4. Do the type, quantity, and content of information provided to patients affect their choice about when and where to seek care for fever?

Evidence and Recommendations from Relevant Guidelines

NICE

Insufficient evidence was found on information and support to offer patients to reduce the adverse effects of neutropenic sepsis; thus, the NICE Guideline Development Group determined it could not make specific recommendations.

NICE Recommendation: Provide patients and their care givers with written and oral information, both before starting and during treatment about neutropenic sepsis, how and when to contact 24-hour specialist oncology advice, and how and when to seek emergency care.

The guideline also encouraged that research studies should be undertaken to determine what types of support and information patients and care givers are given, which types they found helpful, and whether additional forms of information are needed (1).

ASCO

Separate literature searches were done to identify evidence as well as Guideline Development Group members' suggestions.

ASCO Recommendations: This section of the guideline did not contain recommendations, but the following statements were made:

- Evidence was not identified from the guideline search strategy; separate literature searches and Panel members' suggestions.
- Discussions alone do not provide patients with sufficient understanding or skills to deal with adverse events. Patients require tools and resources to understand adverse events and reduce the risks associated with adverse events.
- Patients require effective education about monitoring body temperature and other symptoms of infection.

- Many patients are reluctant to seek help outside of office hours; therefore, provision of clear written instructions on when and how to contact healthcare practitioners is essential.
- It is important to communicate febrile neutropenia management guidelines to all concerned, including patients, care givers, and primary and secondary care staff.
- Dissemination and implementation of clinical practice guidelines to nursing professionals will support patient education goals.
- Coordination of care among primary and specialist settings and emergency departments is essential to ensure rapid response when a febrile neutropenic episode is suspected. Patients should be encouraged and supported to advocate for their care in emergency situations so they are not put at greater risk.
- Patients should have access to written or electronic copies of their febrile neutropenia management plans so healthcare providers making treatment decisions are aware of patients' needs (2).

ESMO

Statements on patient education and local policies were not linked to evidence.

ESMO Recommendations: The guideline made the following statements:

- Successful management of febrile neutropenia requires educating outpatients to monitor their symptoms, including body temperature.
- Clear written instructions on when and how to contact the appropriate service in the event of concerns.
- Effective written local policies are essential to ensure a rapid response whenever febrile neutropenia is suspected (3).

Australia

Statements on patient education and local policies were not linked to evidence.

Australia Recommendation: Patients must receive instruction on self-monitoring and measuring their temperature (4).

Primary Literature

Six studies described interventions for providing information or education to patients receiving chemotherapy (19,24-26,45,50). Two studies addressed the provision of information to deal specifically with fever (26,45). Two studies were RCTs (24,50) and two studies surveyed patients after an educational intervention (19,25). The study details are shown in Table 4-6.

One RCT tested the effectiveness of a cognitive behavioural therapy intervention provided by nurses to help patients manage chemotherapy side effects. Control group patients received usual care without emphasis on self-management (24). Symptoms measured included fever. The cognitive behavioural therapy intervention reduced symptom limitations and was particularly beneficial to younger cancer patients who were unused to symptom limitations.

Another RCT assessed the effectiveness of adding two 20-minute audiotapes with nutritional information and exercise and relaxation techniques in managing chemotherapy side effects to usual education (50). Approximately one-third of the patients allocated to the tapes listened to them, but those that did rated them as very helpful. Patients in the audiotape group reported fewer side effects, more self-care behaviours, and less anxiety than the control group.

One study reported the post-intervention evaluation of an education class offered to patients and families prior to their first chemotherapy treatment (25). The one-hour class was

led by a nurse and explained the side effects of chemotherapy (including fever), provided nutritional information, and explained other sources of support available (pharmacist, support groups, and off-hours phone numbers). Patients also received take home reading materials. Evaluation consisted of a patient survey mailed to patients' homes. Approximately two-thirds of the patients responded, and 84% rated the class as good or excellent.

Decker et al performed a pilot study to evaluate an automated voice response system, in which an automated system would call the patient at a prearranged time each week to assess the severity of 15 symptoms and oral chemotherapy agent adherence (19). As well as the telephone system, a symptom management toolkit was provided that outlined interventions patients could perform themselves in response to each of 15 symptoms (including fever). The toolkit also recommended how and when each symptom should be reported to the clinic staff. More than three-quarters of patients used the toolkit and were able to refer to the appropriate sections for managing symptoms.

The study by Kitao et al included patient education by a team of doctors, pharmacists, and nurses, and provision of written material (45). Although few details of the intervention are available and there was no comparison group, there was a low rate of hospitalization for febrile episodes.

In the study by Shah et al, patients were provided with education, a fever management algorithm, a thermometer, and a starter kit of antibiotics and were instructed to call the on-call oncologist if febrile (26). Because this was an abstract, details of the education and algorithm are not provided, but three-quarters of febrile episodes were managed out of the hospital and most patients could adhere to the protocol.

No studies were found that described or evaluated fever cards. An informal environmental scan by our group identified various forms of fever cards distributed by hospitals and oncology clinics. The fever card is designed to fit in a patient's wallet and would be presented to emergency healthcare providers in order to initiate a standardized protocol for suspected febrile neutropenia. The card includes instructions to the patient about what to do in the event of a fever (e.g., call the oncology clinic, go to the emergency department) and instructions to the healthcare team (e.g., take vital signs, assess for febrile neutropenia, order appropriate laboratory tests). The card should include the name of the patient's oncologist and the chemotherapy regimen.

Summary of Evidence for Question 4

- *One study directly addressed the management of fever but few details are available because the study is reported only as a conference abstract.*
- *Some higher-quality evidence evaluated information provided to patients in managing adverse effects of chemotherapy. This evidence suggested that 1) most education is provided by nurses; 2) patients differ in preferences for the presentation of information about managing side effects and not all patients avail themselves of education and information; and 3) in-person education needs to be supplemented by written materials patients can refer to at home.*
- *In studies of programs that emphasize patient self-assessment strategies, such programs were well received by patients, and were associated with a decrease in the need for emergency department visits and hospitalization. However, sufficiently powered studies that assess the safety of these approaches are not currently available.*
- *Availability of healthcare personnel in-person and by phone to educate and reinforce information is helpful.*

Table 4-6. Information or education provided to patients.

Citation: Decker2009 (19)

Study design: Post-intervention patient evaluation.
Setting: Cancer clinic and patient's home.
Patients: 30 patients with solid tumour cancer receiving nonhormonal oral chemotherapy.
Fever: Fever was one of the symptoms included in the toolkit.
Intervention: As well as receiving calls from an automated voice response system requesting details about symptom severity and medication adherence (see research question 2 above), patients received a symptom management toolkit that offered evidence-based interventions for the management of 15 symptoms (including fever). The interventions described self-care activities, how to engage family members for help, and how and when to report symptoms to their oncologist.
Results: 54% of patients responded to a satisfaction questionnaire after the study. Of the respondents, 76% used the symptom management tool, with a high rate of referral to the appropriate section to manage a symptom.

Citation: Doorenbos2005 (24)
Study design: Randomized controlled trial.
Setting: 4 community and 2 comprehensive cancer centres.
Patients: 237 newly diagnosed cancer patients within the first 2 cycles of chemotherapy.
Fever: Fever was one of the symptoms measured.
Intervention: Cognitive behavioural therapy: Nurses provided evidence-based resources for problem-solving strategies including self-care management, providing information and decision-making skills, counselling and support, and communication with providers. 10 contacts (5 in person, 5 on phone) over 18 weeks. 15 symptoms were targeted, including pain, fatigue, and fever. The patient and nurse developed an individualized care plan when symptom severity reached 5 on scale of 0 to 10. Up to 4 symptoms were addressed at each visit. A computer-guided protocol matched symptoms with problem-solving strategies and nurses' adherence to the protocol was monitored.
The control group received conventional care focused on direct treatment of the cancer without emphasis on support for self-managed behavioural, cognitive, or emotional responses to symptoms.
Results: At baseline, younger patients reported more symptom limitations than older patients; the difference diminished over time and eventually reversed during the course of treatment. Both groups improved between baseline and later observations in terms of symptom limitations, but the intervention group improved more than the control group at each measurement point controlling for age. Fatigue and pain were the most common symptoms, but vomiting and nausea were the most limiting symptoms. Higher symptom severity did not correspond with higher symptom limitations.
Fever had a severity mean of 3.48 and limitation mean of 4.52; constipation had a severity mean of 5.68 and a limitation mean of 2.61.

Citation: Kitao2012ab (45)
Study design: Retrospective study.
Setting: Ambulatory chemotherapy clinic.
Patients: 476 patients receiving chemotherapy.
Fever: A febrile episode was defined as body temperature >38.0°C.
Intervention: Self-assessment system for febrile neutropenia that involved prescription of ciprofloxacin; education by a team of doctors, pharmacists, and nurses; written material; and evaluation at the hospital if a febrile episode lasted >48 hours.
Results: A febrile episode occurred in 33% of patients; 9% were admitted to hospital. 30-day mortality rate was 0%.

Citation: Malone2007 (25)
Study design: Post-intervention patient evaluation.
Setting: Pre-chemotherapy class in a cancer centre.
Patients: Patients about to receive their first chemotherapy treatment.
Fever: Fever mentioned in information addressing blood counts.
Intervention: A chemotherapy education class held within 1 week before the first treatment. 1-hour classes were held in quiet area of cancer centre and led by an oncology nurse for 1 hour. Patients were encouraged to bring family members to class. Slides explained common side effects of chemotherapy in plain language. Patients received a folder with reading materials to review at home.
Topics covered included altered blood counts, nausea & vomiting, fatigue, diarrhea, mucositis, alopecia, diet & nutrition, and support. Patients were instructed to call the cancer centre if their temperature

reached ≥100.5F (38.05°C). Patients had access to a pharmacist by phone at any time to discuss concerns regarding medications and received a fridge magnet with phone numbers for daytime office hours and night and weekend hours. Results: 60% of patients responded to a mailed survey. 84% rated the class excellent or good. Patients responding fair or poor wanted more detailed information about specific side effects.
Citation: Shah2009ab (26) Study design: Prospective feasibility study. Setting: Outpatient setting. Patients: 53 patients before chemotherapy commenced. Patients were identified as being low risk for complications if febrile neutropenia developed. Fever: Patients measured their temperature. Intervention: Patient-initiated protocol for management of low-risk febrile neutropenia. Patients received education, an algorithm for fever management, thermometer, and starter kit of antibiotics. They were instructed to call the on-call oncologist if febrile and go to the emergency department for symptoms of severe sepsis. Patients received blood tests and telephone follow-up. Results: 9 patients (17%) experienced ≥1 febrile episode. Neutropenia was present in 13 of the episodes. 9 of 12 episodes were managed as outpatients. For 87% of the episodes, patients had no difficulty adhering to the protocol.
Citation: Williams2004 (50) Study design: Randomized controlled trial. Setting: Cancer centre in a university medical centre and a satellite cancer treatment clinic in North Carolina. Patients: 70 female outpatients about to receive chemotherapy for breast cancer. Fever: Not mentioned. Intervention: Patients were randomized to receive two 20-minute audiotapes plus standard education (n=38) or standard education alone (n=33). The audiotapes were recorded at the 5th grade level by a professional female orator in a sound studio and used background music. The tapes covered nutritional management of side effects, exercise and relaxation techniques to manage fatigue, anxiety, and difficulty sleeping. Patients were instructed to listen to the tapes 12 to 24 hours before the start of a chemotherapy cycle and as often as desired during their treatment. Standard education was given verbally in the chemotherapy clinic at the time of the first treatment. Instructions included how to handle more frequent side effects such as nausea, hair loss, and mucositis. Coverage depended on the nurse's time and teaching ability and the receptivity of the patient. Some patients received information published by a national organization. There was no standardized plan about the information that should be provided. Additional side effects were discussed at later treatment visits as patients reported them. All patients were interviewed 3 times by telephone by a trained interviewer: before chemotherapy, 1 month after chemotherapy began, and 3 months after chemotherapy began. Outcome measures were State-Trait Anxiety Instrument, state anxiety subscales, and self-care diaries (SCDs). SCDs recorded occurrence and intensity of side effects and use and effectiveness of self-care behaviours. SCDs were administered at 1 month and 3 months after chemotherapy. Results: 38% listened to the tapes at least once, 31% listened 2 to 6 times, and 28% listened 1 to 3 times/week. Helpfulness was rated median of 8 out of 10. The most frequent side effects reported were fatigue, nausea/vomiting, and taste change. At the first SCD, the audiotape group reported more of these side effects than the nonaudiotape group but this the rate was reduced by one-half by the second SCD; the audiotape group also reported less insomnia at the second SCD. The groups did not differ in the in severity of side effects. At first SCD, the audiotape group used more self-care behaviours for sore mouth and anxiety; there was no difference between groups at the second SCD. Both groups used more self-care behaviours for nausea and vomiting than for other side effects, but both reported decreased effectiveness for behaviours by the second SCD.

Updated Literature Search

Because the initial search was conducted in March 2014, an updated search was run from March 2014 to November 2015 to identify recently published studies meeting the inclusion criteria. Three studies that were found that were relevant to risk assessment in febrile neutropenia (74-76). None of the studies affected the guideline recommendations.

Ongoing, Unpublished, or Incomplete Studies

Protocol ID	Title and details of trial	Status
01799421	Risk Assessment of Febrile Neutropenia and Grade 3-4 Neutropenia in Patients With Non-hematological Cancer Treated With Conventional Chemotherapy (NEURISK)	Ongoing

DISCUSSION

Fever is a common and important symptom in cancer patients receiving chemotherapy because it may signal the development of febrile neutropenia, a potentially serious complication of systemic treatment. Currently, the management of cancer patients who develop a fever while receiving chemotherapy is not standardized. Many patients who experience a fever present to a hospital emergency department because an absolute neutrophil count is required to confirm a diagnosis of febrile neutropenia and there is an absence of alternate assessment options. This systematic review sought to compile the evidence on the management of fever in cancer patients receiving chemotherapy before they present to the emergency department.

Overall, the evidence was of low quality and most was not directly related to the research questions. Existing guidelines focused on the management of febrile neutropenia after it was diagnosed, with limited information on the pre-diagnosis assessment. The primary literature provided limited evidence because most studies addressed the adverse effects of chemotherapy without a specific emphasis on fever. Few studies were comparative, and many were conference abstracts, providing insufficient detail on which to draw definitive conclusions.

One of the goals of the review was to define “fever,” and to provide guidance on temperature measurement. Existing guidelines included a temperature cut-off that indicates risk for febrile neutropenia, with most defining fever as ≥38.3°C. Supporting evidence for this number is lacking. Primary studies that investigated a temperature cut-off and the risk of a poor outcome used a threshold of 39°C; however, these patients were already diagnosed with febrile neutropenia. These studies were a mix of prospective and retrospective designs, including some clinical prediction rules. Blinded interpretation of temperature readings was conducted in only one study (14). Overall, the results showed temperature to be generally a poor prognostic indicator.

Most studies that examine clinical predictors for poor outcomes in the setting o fever have been performed on patients who already have a confirmed diagnosis of febrile neutropenia. Two relevant studies produced models that were moderately predictive in identifying patients at high risk for developing febrile neutropenia (37,39). They provided no evidence on how the risk for developing febrile neutropenia should be assessed in outpatients who develop a fever, and sparse evidence on risk in all outpatient cancer patients undergoing chemotherapy. Prospective validation of algorithms incorporating the identified risk factors would be required before widespread adoption could be considered.

Little evidence is available on the topic of fever assessment in guidelines or primary studies. Among the primary studies, fever was often examined as only one of many side effects associated with chemotherapy. Insufficient details are available for many protocols because the research has only been published in abstract form. However, the available research suggests that nurses play a prominent role in symptom assessment. Review of relevant studies shows

that symptom assessment is an area of active research with investigation of patient-initiated contact, healthcare provider-initiated contact, and multi-system approaches including mobile phone apps, web-based interfaces, and automated systems. It is anticipated that the results of ongoing studies may be able to inform future recommendations on optimizing symptom management during chemotherapy, but management of fever specifically will require additional dedicated studies.

With respect to provision of patient education, there was no evidence specific to patient response to fever. Existing guidelines made general consensus statements or recommendations that were not linked to evidence on dealing with adverse effects of chemotherapy and management of febrile neutropenia. Several guidelines mentioned the importance of educating patients regarding monitoring body temperature.

Among the primary studies, interventions that combined in-person instruction and education with take-home materials showed promise. There is some evidence that strategies with patient self-assessment components may help control symptoms; however, these were not directly applicable to the symptom of fever. It appears that patient education is an ongoing process that may require an individualized approach involving in-person instruction, take-home written or video materials, and telephone and/or web-based interaction with healthcare providers. Although some centres distribute fever cards to cancer patients receiving chemotherapy, no evidence was found to support their use.

Given the quality of the evidence, further research is needed. Specifically, studies are needed that characterize the relationship between temperature and undesirable outcomes such as serious infection or death. Furthermore, studies that focus on identification and validation of other factors in addition to fever that predict outcome of a fever would be helpful to risk stratification. How to manage patients receiving growth factors during chemotherapy who experience fever is also important because the risk of febrile neutropenia is lower in this patient group and their assessment algorithm may need to be different (77,78). Because of the unique risks associated with fever in the setting of chemotherapy, prospective studies of new models of care specifically for fever management are essential. Promising models include urgent care clinics, patient self-management, and remote monitoring protocols. Finally, development and evaluation of effective patient education and self-management tools will be crucial to ensure best quality care.

CONCLUSIONS

Fever in cancer patients receiving systemic therapy is a common and potentially serious symptom that requires prompt assessment, but the quality of the evidence to inform best practices is poor. High-quality studies evaluating different models of care are needed. Until such evidence is available, emergency department assessment of fever in the cancer patient will remain a key option. In the meantime, standardization of definitions, management algorithms, and patient education materials are first steps to ensuring best quality care.

Approach to Fever Assessment in Ambulatory Cancer Patients Receiving Chemotherapy

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Guideline Development Group (GDG) Expert Panel and the Program in Evidence-Based Care (PEBC) Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 10 members of the Fever Assessment Expert Panel, nine members cast votes and one member withdrew, for a total of 90% response. Of those that cast votes, all members approved the document (100%). The main comments from the Expert Panel and the Working Group's modifications/actions/responses taken in response are summarized in Table 5-1.

Table 5-1. Modifications/actions/responses regarding main comments from the Expert Panel.

Main comments	Modifications, actions, or responses
1. The guideline does not address the issue of reducing the number of unnecessary visits to the emergency department, mainly due to adjuvant taxanes, in this population.	Unfortunately, the identified evidence did not allow for recommendations that would result in a reduction in visits to the emergency department, but it is unclear what constitutes an "unnecessary" visit. No changes were made.
2. Given the lack of data to support the recommendations, the guideline will not be useful unless accompanied by evidence collection, patient self-management tools, and nursing support to help patients with symptom management.	These concerns were highlighted in the Implementation Considerations.
3. The future research should mention how to address fever in patients on primary G-CSF prophylaxis. This is a group of patients for whom no evidence exists to guide recommendations and clinicians struggle with this population. In the absence of good supporting data, it would be helpful to highlight it as an area that requires further investigation.	A qualifying statement was added to address the use of G-CSF prophylaxis.
4. The recommendations were appropriately conservative and aligned with the available level of evidence. The evidence summaries were informative. The guideline should allow Ontario to focus on improvement strategies in the management of fever as a complication of treatment using some of the tools and strategies identified, recognizing that measurement of effect will be critical when best practice is not yet defined.	Add detail to the Implementation Considerations.
5. In light of the recommendation for defining a fever as **38.3°C**, the patient information generated by CCO should be altered to	This change will occur as part of the implementation process.

reflect this temperature as currently it is stated as 38°C.	

RAP Review and Approval

Three RAP members reviewed this document in March/April 2015. The RAP conditionally approved the document on April 12, 2015. The summary of main comments from the RAP and the Working Group's modifications/actions/responses taken in response are showed in Table 5-2.

Table 5-2. Modifications/actions/responses regarding main comments from RAP.

Main comments	Modifications, actions, or responses
1. The guideline title is misleading. "Management" includes treatment, but the guideline does not address this. It focuses on how febrile neutropenia is defined, that it should be assessed, and that patients should know of its importance.	The title of the guideline was changed to more precisely reflect the objectives and content.
2. The exclusion of certain patient populations (e.g., myelodysplastic syndrome) seems unreasonable given the already narrow topic. What would be done differently with those patients? Why do the recommendations not apply to all ambulatory outpatients receiving chemotherapy?	The exclusion of high-risk groups from the target population was explained. A table illustrating the included and excluded groups was added.
3. The methods for formulating the recommendations are inadequately described. How did the panel consider and integrate the data on prediction rules and studies of different models of care?	The decision-making processes of the Working Group were detailed in the Interpretation of Evidence section.
4. A serious condition warrants specific recommendations. In the absence of good-quality supporting data, a default approach that optimizes patient safety should be recommended.	Lacking evidence to suggest otherwise, the current practice of referring patients to the emergency department who experience a fever outside of clinic hours remains the safest and most reasonable option. This has been included in the recommendations.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Seven targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Five agreed to be the reviewers (Appendix 1). Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (n=5)

Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				3	2
2. Rate the guideline presentation.		1	1	1	2
3. Rate the guideline recommendations.		1		3	1
4. Rate the completeness of reporting.			1	3	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?		1	1	2	1
6. Rate the overall quality of the guideline report.			1	3	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			3	1	1
8. I would recommend this guideline for use in practice.		1		3	1
9. What are the barriers or enablers to the implementation of this guideline report?	The guideline lacks recommendations on management. The recommendations are unclear. The guideline does not apply to all categories of patients (e.g., G-CFS, acute leukemia, myelodysplastic syndrome).				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. The guideline recommendations were difficult to find.	We have replaced the bulleted list of recommendations with a numbered list and reorganized the presentation to be less confusing.
2. The guideline does not address the management of febrile neutropenia.	The management of febrile neutropenia is beyond the scope of the guideline. We have added references to guidelines and advice documents on the management of febrile neutropenia in the target population paragraph.
3. The recommendations need to be more specific.	We have reworded the recommendations to be more actionable.
4. Given the lack of good-quality evidence, there is a need for practical, expert advice to guide practice: For example, a statement that encourages the routine use of the MASCC score in the systematic evaluation of patients.	We added a statement about the MASCC score to the Implementation Considerations.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. The PEBC database was searched for clinicians with the following specialties: medical oncologist, family practitioner, nurse practitioner, nurse, hematologist, emergency physician, or infectious disease physician. Members of relevant professional organizations affiliated with CCO were contacted (Systemic Treatment Program committee, Toxicity Advisory Committee, Ontario Cancer Symptom Management Collaborative) and the Canadian Association of Provincial Cancer Agencies was

asked to inform its members of the survey. A link to the guideline was disseminated to 311 Ontario health professionals, who were invited to complete and return the survey. Forty-five (14.5%) responses were received. The results of the feedback survey from 45 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Reviewer ratings (n=45)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	2	2	10	21	10
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	3	7	14	15	6
3. I would recommend this guideline for use in practice.	2	5	10	17	11
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Lack of useful or practice-changing data. • Communication across all areas that care for patients receiving chemo, particularly primary care providers. • Definition/indication of fever (use of a 2-part definition, i.e., 38.3°C or sustained temperature of 38.0°C over 1 hour harder to remember than a single cut-off; data possibly not convincing enough to change peoples' practice; no evidence for most accepted values; other criteria than just temperature should be included to patients such as rigors, shortness of breath, and dizziness to identify the urgency of dealing with a fever). • Low-quality evidence. • Emergency department (no guidance regarding the urgency of assessment when patients present to the emergency room; it is troubling that there is no other recourse than the emergency room for the target patients during the night or on weekends). Enablers: • Identifies the gaps in current knowledge. • Identifies areas for future research. • Reminder of the uncertainty of the area and the current consensus on vigilance.				

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	**Responses**

1. Some reviewers noted the challenge of communicating standard approaches of fever assessment across different fields of healthcare.	The Working Group added a statement to the Implementation Considerations about knowledge transfer.
2. Some reviewers believed the fever definition was unnecessarily complicated and urged the use of one cut-off.	The Working Group believed it was more important to be precise as possible about temperature measurement, and retained the definition of 38.3°C and sustained temperature of >38.0°C for 1 hour. With respect to other symptoms experienced by patients such as rigors, the Working Group emphasized that symptoms other than a temperature are too nebulous to be of any use to the clinician performing the assessment.
3. Communication across all healthcare areas.	The Working Group added more discussion to the implementation considerations and future research sections.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1. Members of the Fever Assessment Guideline Development Group, PEBC Report Approval Panel, Targeted Reviewers and their COI declarations (see the PEBC COI Policy).

Working Group Members

Name	Affiliation	Declarations of interest
Monika Krzyzanowska Working Group Chair Medical Oncologist	Clinical Lead, Quality Care and Access, Systemic Treatment Program, CCO Princess Margaret Hospital Toronto, Ontario	Principal investigator for a CCO-funded clinical trial focusing on toxicity management during chemotherapy. This potential conflict of professional interest was waived by the PEBC Director.
Clare Atzema Emergency Physician	Scientist, Institute for Clinical Evaluative Sciences, Associate Professor, University of Toronto, Scientist, Sunnybrook Research Institute Toronto, ON	None declared
Andrew Morris Infectious Diseases Physician	Director, Antimicrobial Stewardship Program Mount Sinai Hospital University Health Network Associate Professor, Division of Infectious Diseases Department of Medicine, University of Toronto Mount Sinai Hospital Toronto, Ontario	None declared
Rasna Gupta Medical Oncologist	Windsor Regional Cancer Program Windsor, Ontario	None declared
Rachael Halligan Primary Care Physician	Regional Primary Care Cancer Lead Waterloo Wellington Regional Cancer Program Waterloo, Ontario	None declared
Tom Kouroukis Malignant Hematologist	Juravinski Cancer Centre Hamilton, Ontario	None declared
Kit McCann Nurse Practitioner	Windsor Regional Cancer Program Windsor, Ontario	None declared
Cindy Walker-Dilks Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared

Expert Panel Members

Name	Affiliation	Declarations of interest
Leonard Kaizer Medical Oncologist	Provincial Head, Systemic Treatment, CCO	None declared
Kathy Vu Pharmacist	Clinical Lead, Safety Initiatives, CCO	None declared
Andrea Crespo Pharmacist	University Health Network	None declared
Maureen Trudeau Medical Oncologist	CCO Systemic Treatment Program Committee, Head, Toronto Central North	Grant or research support from a relevant business entity; managerial responsibility for an organization that has received more than $5000.00 in a single year from a relevant business entity
Katherine Enright Medical Oncologist	CCO Systemic Treatment Program Committee, Regional Quality Lead, Central West	None declared
Silvana Spadafora Medical Oncologist	CCO Systemic Treatment Program Committee, Regional Quality Lead, North East	None declared
Ted Vandenberg Medical Oncologist	CCO Systemic Treatment Program Committee, Regional Quality Lead, South West	None declared
Lynne Jolicoeur Advanced Practice Nurse	The Ottawa Hospital	None declared
David Warr Medical Oncologist	University Health Network	None declared

Members of the PEBC Report Approval Panel

Name	Affiliation	Declarations of interest
Melissa Brouwers Director, Program in Evidence-Based Care	McMaster University Hamilton, Ontario	None declared
Craig Earle Medical Oncologist	Sunnybrook Health Sciences Centre Toronto, Ontario	None declared
Eric Winquist Medical Oncologist	London Health Sciences Centre London, Ontario	None declared

Targeted Peer Reviewers

Name	Affiliation	Declarations of interest

Mihaela Mates	Cancer Centre of Southeastern Ontario Kingston, Ontario	None declared
Esther Green	Patient Centered Care, Canadian Partnership Against Cancer Toronto, Ontario	None declared
Dawn Stacey	School of Nursing, University of Ottawa Ottawa, Ontario	None declared
Shalendra Verma	Ottawa Hospital Cancer Centre Ottawa, Ontario	None declared
Swati Kulkarni	Windsor Regional Hospital Cancer Program Windsor, Ontario	None declared

Appendix 2. AGREE II scores for relevant guidelines.

AGREE II scores from the SAGE database for DGHO, Australia, Alberta, ESMO, and IDSA
http://www.cancerview.ca/cv/portal/Home/TreatmentAndSupport/TSProfessionals/ClinicalGuidelines/GRCMain/GRCSAGE/GRCSAGESearch?_afrLoop=2930858832543000&lang=en&_afrWindowMode=0&_adf.ctrl-state=sapr4enzi_171

AGREE II scores for NICE, ASCO, and NCCN compiled by 2 PEBC health research methodologists.

Link DGHO 2003 (6)
Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
44.4%	13.9%	15.6%	61.1%	14.6%	0.0%

Lingaratnam Australia 2011 (4)
Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
55.6%	44.4%	35.4%	69.4%	50.0%	70.8%

Alberta 2012 (8)
Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
83.3%	33.3%	53.1%	80.6%	18.8%	33.3%

deNarois ESMO 2010 (3)
Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
30.6%	16.7%	18.8%	58.3%	10.4%	29.2%

Freifeld IDSA 2011 (5)
Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
61.1%	41.7%	61.5%	91.7%	64.6%	58.3%

NICE 2012 (1)

Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
91.7%	94.4%	93.8%	88.9%	81.3%	83.3%

ASCO 2012 (2)
Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
91.7%	77.8%	82.3%	94.4%	52.1%	54.2%

NCCN 2013 (7)
Number of reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
30.6%	41.7%	19.8%	75.0%	25.0%	70.8%

Alberta=Alberta Health Services; ASCO=American Society of Clinical Oncology; Australia=Australian Consensus Guidelines; DGHO=German Society of Hematology and Oncology; ESMO= European Society for Medical Oncology; IDSA=Infectious Disease Society of America; NCCN= National Comprehensive Cancer Network; NICE=National Institute for Health and Clinical Excellence

Appendix 3. Literature search strategies

12-15 Literature search
Fever & cancer & chemotherapy & (outpatient or emergency or information provided to patients & care givers)

4 March 2014

Database: Embase <1980 to 2014 Week 06>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp fever/ use prmz (33796)	
2 exp fever/ use emez (136113)	
3 exp body temperature/ use prmz (73044)	
4 exp body temperature disorder/ use emez (231550)	
5 exp febrile neutropenia/ use prmz (24)	
6 antineoplastic combined chemotherapy protocols/ae use prmz (23542)	
7 (fever: or febrile: or temperature: or pyrexia:).mp. (1591752)	
8 exp neoplasms/ use prmz (2502189)	
9 exp neoplasm/ use emez (3330015)	
10 (cancer: or tumor: or tumour: or carcinoma: or malignan:).mp. (5839007)	
11 or/1-7 (1661739)	Fever terms
12 or/8-10 (7131147)	Cancer terms
13 11 and 12 (196294)	Fever & cancer
14 exp ambulatory care facilities/ use prmz (42989)	
15 exp ambulatory care/ use prmz (44674)	
16 exp ambulatory care/ use emez (39096)	
17 exp outpatients/ use prmz (8571)	
18 exp outpatient/ use emez (54793)	
19 (outpatient: or ambulatory or communit: or home:).mp. (2050580)	
20 office visits/ use prmz (5320)	
21 exp telemedicine/ use prmz (15100)	
22 exp telehealth/ use emez (20063)	
23 teleconsultation/ use emez (6121)	
24 (office: and visit:).tw. (16381)	
25 (telehealth or tele-health or telemedicine or tele-medicine or telecare or tele-care).tw. (16603)	
26 (teleconsult: or tele-consult: or telehome: or tele-home:).tw. (1980)	
27 exp self care/ use prmz (38794)	

28 exp self care/ use emez (49506)	
29 exp community health services/ use prmz (482251)	
30 or/14-29 (2481507)	Outpatient terms
31 exp emergency service, hospital/ use prmz (48044)	
32 exp emergency treatment/ use prmz (92025)	
33 emergency ward/ use emez (57657)	
34 exp emergency treatment/ use emez (164459)	
35 (emergen: or urgent: or trauma:).mp. (1335111)	
36 or/31-35 (1505175)	Emergency terms
37 13 and 30 (7433)	Fever & cancer & outpatient
38 13 and 36 (6442)	Fever & cancer & emergency
39 exp teaching materials/ use prmz (93735)	
40 exp teaching/ use emez (65074)	
41 pamphlets/ use prmz (3092)	
42 (pamphlet: or leaflet: or algorithm:).tw. (321155)	
43 ((alert: or report:) adj2 card:).tw. (10286)	
44 ((electronic or email) adj report:).tw. (478)	
45 exp audiovisual aids/ use prmz (84283)	
46 exp audiovisual equipment/ use emez (77707)	
47 (video: or dvd:).tw. (169869)	
48 exp internet/ use prmz (47968)	
49 internet/ use emez (75272)	
50 exp social support/ use prmz (49755)	
51 social support/ use emez (57841)	
52 self help groups/ use prmz (7652)	
53 exp patient education/mt use prmz (12805)	
54 patient education/ use emez (88159)	
55 exp telephone/ use prmz (13460)	
56 telephone/ use emez (25108)	
57 exp hotlines/ use prmz (2186)	
58 ((hot: or help: or tele: or phone) adj line:).tw. (2188)	
59 ((patient: or consumer:) adj2 (decision: or choice: or preference: or support: or education:)).tw. (112287)	
60 (information adj2 (aid: or support: or need: or provision)).tw. (39171)	
61 (telephone: adj triag:).tw. (700)	

62 (triag: adj (tool: or pathway:)).tw. (743)	
63 or/39-62 (1167929)	Information provided to patients & care givers
64 13 and 63 (3485)	Fever & cancer & information
65 37 or 38 or 64 (16261)	Fever & cancer & (outpatient or emergency or information)
66 exp cancer chemotherapy/ use emez (239540)	
67 exp antineoplastic agents/ use prmz (811411)	
68 chemother:.mp. (841484)	
69 (systemic adj therap:).tw. (20126)	
70 (systemic adj treatment:).tw. (14740)	
71 or/66-70 (1541902)	Chemotherapy terms
72 65 and 71 (5542)	Fever & cancer & chemotherapy & (outpatient or emergency or information)
73 limit 72 to english language (5035)	

12-15 Literature search
Fever & cancer & risk assessment

4 March 2014

Database: Embase <1980 to 2014 Week 09>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp fever/ use prmz (33796)	
2 exp fever/ use emez (136113)	
3 exp body temperature/ use prmz (73044)	
4 exp body temperature disorder/ use emez (231550)	
5 exp febrile neutropenia/ use prmz (24)	
6 antineoplastic combined chemotherapy protocols/ae use prmz (23542)	
7 (fever: or febrile: or temperature: or pyrexia:).mp. (1591660)	
8 or/1-7 (1661647)	Fever/febrile neutropenia terms
9 risk assessment/ use emez (338085)	
10 (clinical: or risk).tw. (7736778)	
11 ((clinical: or risk) adj (assess: or predict: or decision)).tw. (170502)	
12 ((clinical: or risk) adj (assess: or predict: or decision) adj (rule: or guide: or tool: or model:)).tw. (10838)	
13 9 or 12 (345764)	Risk assessment/prediction tool terms
14 8 and 13 (9103)	Fever & risk assessment
15 exp neoplasms/ use prmz (2502189)	
16 exp neoplasm/ use emez (3330015)	
17 (cancer: or tumor: or tumour: or carcinoma: or malignan:).mp. (5838578)	
18 or/15-17 (7130718)	Cancer terms
19 14 and 18 (2352)	Fever & risk assessment & cancer
20 limit 19 to english language (2248)	

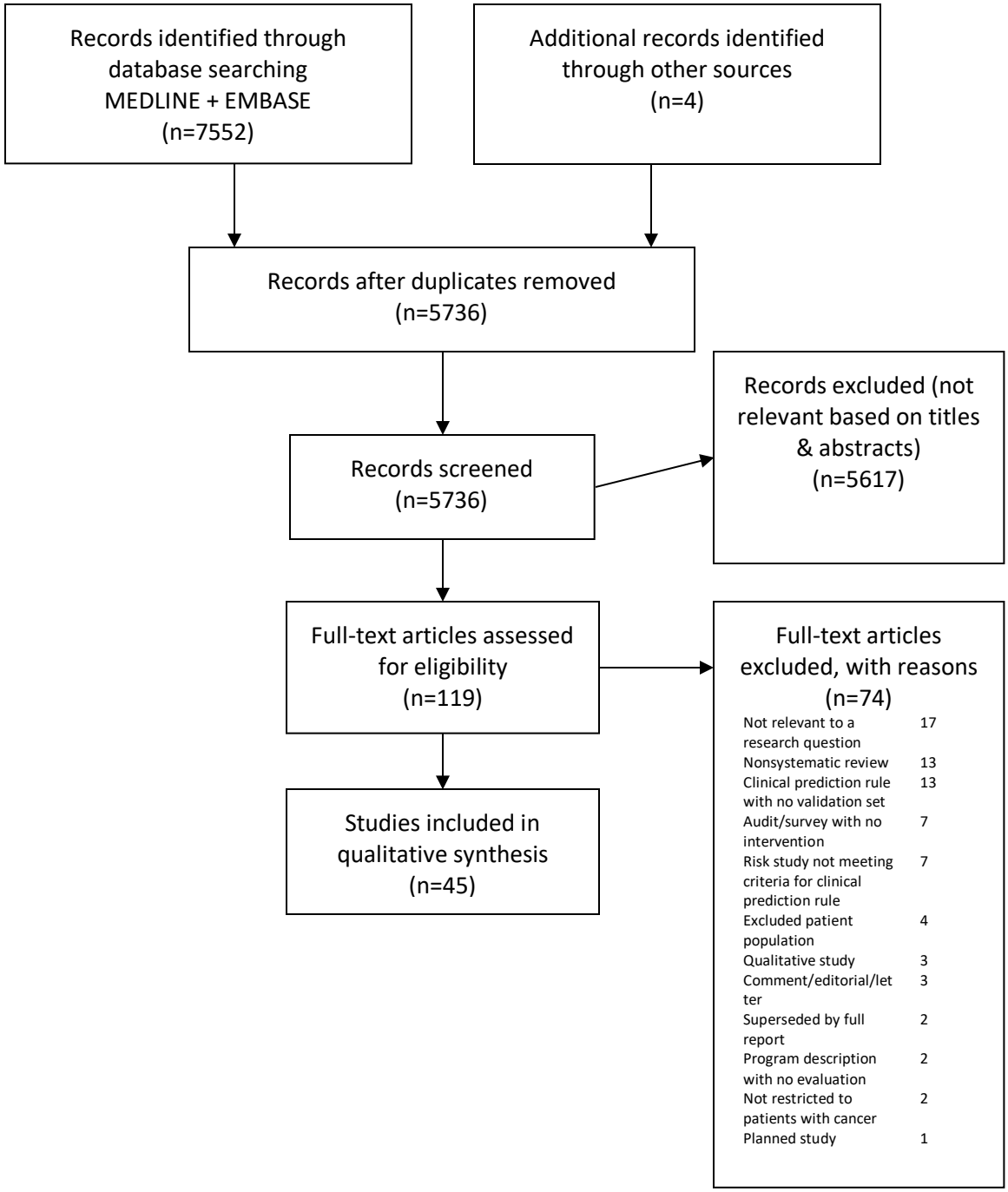
12-15
Search for studies on thermometers and measurement of fever/febrile neutropenia

14 April 2014

Database: Embase <1980 to 2014 Week 15>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

1	exp fever/ use prmz (34067)
2	exp fever/ use emez (135914)
3	exp body temperature/ use prmz (73483)
4	exp body temperature disorder/ use emez (230487)
5	exp febrile neutropenia/ use prmz (35)
6	antineoplastic combined chemotherapy protocols/ae use prmz (23861)
7	(fever: or febrile: or temperature: or pyrexia:).mp. (1572881)
8	exp neoplasms/ use prmz (2529004)
9	exp neoplasm/ use emez (3190176)
10	exp neutropenia/ use prmz (15139)
11	exp neutropenia/ use emez (75529)
12	or/1-7 (1642890)
13	or/8-11 (5749819)
14	12 and 13 (157477)
15	exp "sensitivity and specificity"/ (606076)
16	(predictive adj value:).mp. (297011)
17	15 or 16 (722410)
18	14 and 17 (2185)
19	thermomet:.mp. (13786)
20	fever/di (4922)
21	(febrile and neutropeni: and diagnos:).tw. (2254)
22	(neutropeni: and sepsis and diagnos:).tw. (1048)
23	or/19-22 (21223)
24	18 and 23 (261)
25	thermometer.mp. (7142)
26	exp neutropenia/ (90668)
27	25 and 26 (9)
28	24 or 27 (269)

Appendix 4. PRISMA Flow Dia



Appendix 5. Thermometry systematic reviews

Citation: Mazerolle2011 (51) Objective: To compare oral measurements taken at various body temperatures with a reference measurement (rectal, esophageal, pulmonary, or gastrointestinal site). Search time period: Up to July 2010. Study selection: Research articles in which authors directly compared body sites for the measures of body temperature in humans. Number of studies: 16. Results: Oral temperature assessment consistently provided inaccurate prediction of core body temperature during rest and exercise. Oral temperature underestimated the criterion standard temperature measurement by 0.60°C ± 0.51°C, regardless of condition (nonsteady state versus rest).
Citation: Hooper2006 (52) Objective: To compare oral, tympanic, and temporal artery noninvasive temperature readings and invasive core temperature readings in hospitalized adult patients. Search time period: 1982 to March 2005. Study selection: Hospital-based studies comparing tympanic, temporal artery, or oral temperature measurement with pulmonary artery and/or esophageal as invasive core measurement. Number of studies: 23. Results: Oral temperature measurements taken at the left or right posterior sublingual pocket provided an accurate reflection of invasive core temperature measurement. 10 of the 20 articles evaluating tympanic thermometry supported the technology as providing an accurate core temperature measurement; 6 were of poor quality; 4 were of acceptable quality. 1 study evaluating temporal artery measurement showed poor performance.
Citation: Sund-Levander2002 (53) Objective: To investigate the range of normal oral, rectal, tympanic, and axillary body temperature related to gender in healthy adult men and women. Search time period: Up to 1998. Study selection: Reports of studies focusing either on normal body temperature or the comparison of different methods of temperature measurement in healthy or nonfebrile adults. Number of studies: 27. Results: 20 of the 27 studies were considered strong evidence. The range among the strong or fairly strong studies for oral temperature was 33.2°C to 38.2°C, for rectal 34.4°C to 37.8°C, for tympanic 35.4°C to 37.8°C, and axillary 35.5°C to 37.0°C.
Citation: Jefferies2011 (54) Objective: To determine the accuracy of peripheral thermometers in detecting febrile core temperatures in critically ill patients. Search time period: Up to December 2010. Study selection: Clinical trials that investigated the accuracy of peripheral methods of temperature measurement compared with pulmonary artery catheter or bladder thermometry in adult patients with core temperatures >37.5°C. Number of studies: 3. Results: Heterogeneity of studies prevented a meta-analysis. Tympanic and oral thermometry showed accurate estimations of core temperatures within the febrile range while rectal thermometry did not.
Citation: Huggins2012 (55) Objective: To perform a meta-analysis to compare oral with rectal core temperature measurement in hyperthermic persons during exercise. Search time period: Up to 2009. Study selection: Studies had to include hyperthermia ≥38°C (100.46F) during exercise, and simultaneous rectal and oral mean and standard deviation measurements. Number of studies: 9. Results: Rectal core temperature was higher than oral core temperature before, during, and after exercise.
Citation: Bahr2010 (56)

Objective: To determine the accuracy of temporal artery thermometers in measuring temperature in acutely ill hospitalized adults. Search time period: 2003 to 2008. Study selection: Studies had to compare temporal artery thermometers with at least 1 other temperature measurement device in hospitalized adult patients. Number of studies: 6. Results: The evidence was limited by a small number of studies, inconsistent findings, and potential bias of studies conducted in collaboration with the developers of temporal artery thermometers. Temporal artery thermometer readings varied widely compared with other temperature measurements. Compared with pulmonary artery temperatures, considered the criterion standard, temporal artery thermometers were inaccurate.
Citation: Zhen2014 (57) Objective: To perform a meta-analysis to determine whether infrared ear thermometry is accurate and whether it can replace rectal thermometry in the clinical practice of children. Search time period: 1988 to 2013. Study selection: Included studies compared tympanic and rectal temperature and provided the mean difference and standard deviation. Number of studies: 28. Results: The overall pooled (random effects) mean difference between tympanic and rectal temperature was 0.22°C (95% CI −0.44 to 1.30). In a separate grouping of only febrile children, the difference was 0.15°C (95% CI −0.32 to 1.10). The accuracy of infrared ear thermometry in children was poor.
Citation: Craig2002 (58) Objective: To evaluate agreement between temperature measured at the rectum and ear in children. Search time period: Up to 2000. Study selection: Studies were included if temperature was measured at the ear (test site) and compared with temperature measured at the rectum (reference site) in the same child; electronic, mercury, or indwelling thermocouple devices were used at the rectum, and infrared devices at the ear; and participants were aged between 0 and 18 years. Number of studies: 44. Results: The pooled mean temperature difference (rectal minus ear) was 0.29ºC (95% CI –0.74 to 1.32). The study showed small mean differences, but wide limits of agreement between the two temperature sites. In children, the agreement of infrared ear thermometry with rectal temperature measurements is low, and differences were in either direction.
Citation: Dodd2006 (59) Objective: To investigate sensitivity and specificity of infrared ear thermometry compared with rectal thermometry to detect fever in children. Search time period: See Craig2002. Study selection: From a previous review of 44 studies (58) that compared temperatures taken at the ear (using infrared devices) and rectum (using either an electronic, mercury, or indwelling thermocouple device) in children aged between 0 and 18; those studies that presented sensitivity and specificity were included. Number of studies: 23. Results: Sensitivities ranged from 0% to 100% and specificities from 58% to 100%. Pooled estimates of sensitivity and specificity from random effects models were 63.7% (95% CI 55.6 to 71.8) and 95.2% (95% CI 93.5 to 96.9). Infrared ear thermometry would fail to diagnose fever in 3 or 4 of every 10 febrile children (with fever defined by a rectal temperature of ≥38°C).

Appendix 6. Clinical prediction rules after diagnosis of febrile neutropenia.

Citation: Azkona2012ab (32) Study design: Retrospective; validation of MASCC score. Patients: 101 patients with solid tumours presenting with 117 episodes of febrile neutropenia in 2010. Description of risk assessment: MASCC score was calculated for each patient within 48 hours of hospital admission. Patients were grouped as complicated febrile neutropenia or noncomplicated febrile neutropenia. Results: MASCC score indicated 27.8% were high risk. 23.8% were deemed complicated febrile neutropenia. Performance of MASCC score: Sensitivity 50%, specificity 87%, positive predictive value 54%, negative predictive value 84%.
Citation: Bajpai2010ab (33) Study design: Retrospective; validation of MASCC score. Patients: 178 febrile neutropenia episodes. Description of risk assessment: As well as MASCC, other clinical and laboratory parameters were explored for risk stratification during febrile neutropenia episodes. Results: The association between MASCC score and risk stratification could not be established. MASCC score could not be validated while other clinical and laboratory parameters had strong association in risk stratification.
Citation: Carmona-Bayonas2011 (34) Study design: Retrospective case-control study; application of MASCC to cases and controls. Setting: Hospital in Spain. Patients: 861 cancer patients with febrile neutropenia; 692 classified as apparently stable patients (ASPs) evaluated as outpatients; 169 clearly unstable patients transferred to ward. Of the ASP group, cases had unexpected serious complication after admission (n=51); controls were randomly selected without complication (n=124). Description of risk assessment: Risk factors were selected from the literature and emergency department setting. Variables tested were classified as baseline characteristics and medical history, laboratory results, and characteristics of the febrile neutropenia episode. Results: Significant factors from univariate analysis were included in multivariate analysis that produced 6 independent risk factors: ECOG ≥2, chronic obstructive pulmonary disease, chronic heart failure, stomatitis grade ≥2, monocytopenia, and stress hyperglycemia. The distribution of MASCC scores in the cases and controls was analyzed. MASCC ability to predict complications: Sensitivity 36%, specificity 94%, positive predictive value 32%, negative predictive value 94.9%. The sample was mostly low risk, providing few discriminatory factors to differentiate patients.
Citation: Chayakulkeeree2003 (9) Study design: Retrospective; development of prediction model and validation of MASCC score. Setting: Hospital in Thailand. Patients: 267 febrile neutropenia episodes in 220 patients. Description of risk assessment: Data were extracted from patient records and patients were classified as having a favourable outcome (fever resolved ≤5 days of starting treatment without serious medical complications) or unfavourable outcome (death or development of serious medical complications, modification of antibiotic treatment, relapse of fever or unresolved fever). A multiple logistic regression model was developed and a prediction score was calculated for each patient. The MASCC score was applied to the data set, and sensitivity, specificity, positive predictive value and negative predictive value of both sets were compared. Results: Favourable outcome=108; unfavourable=159. Multivariate analysis showed 4 independent factors associated with poor outcome: burden of illness, control of cancer, duration of neutropenia, and dehydration. At threshold of 21, MASCC had sensitivity 88.8%, specificity 45.5%, positive predictive value 52.8%, negative predictive value 85.5%.

The locally developed scoring system at a cut-off of 16 identified patients with a favourable outcome with sensitivity 76.6%, specificity 90.2%, positive predictive value 85.4%, negative predictive value 83.8%. The area under the receiver operating characteristic curve for the locally developed score was 0.908 (CI 0.87 to 0.945); for MASCC, it was 0.803 (CI 0.748 to 0.858).
Citation: deSouza Viana2008 (35) Study design: Prospective; validation of MASCC & comparison with new model. Setting: Hospital in Brazil. Patients: 53 cancer patients with 60 episodes of neutropenia and fever. Description of risk assessment: Applied MASCC score and identified low risk patients (score ≥21). The presence or absence of complex infection was assessed according to predefined criteria (major organ infection, sepsis, soft tissue wound infection, or oral mucositis grade >2). The proposed adjustment by complex infection (PACI) model was compared with the MASCC risk index scores. Results: The ability of the MASCC and PACI model to predict the presence and absence of a serious medical complication: MASCC: Sensitivity 87.9%, specificity 85%, positive predictive value 90.6%, negative predictive value 80.9%, accuracy 86.8% PACI: Sensitivity 100%, specificity 75%, positive predictive value 86.8%, negative predictive value 100%, accuracy 90.6%.
Citation: Eiras Martins2011ab (36) Study design: Retrospective; validation of MASCC score. Patients: 201 patients with 213 episodes of febrile neutropenia admitted for intravenous antibiotics. Description of risk assessment: Patient information and MASCC score were correlated to serious clinical complications. Receiver operating characteristic analysis defined optimal cut-off for differentiation of patient's categories. Results: 139 patients presented with ≥1 serious complication. MASCC: Score of 18 selected as cut-off (sensitivity 56%, specificity 62%, positive predictive value 76.3%, negative predictive value 48.4%, area under the receiver operating characteristic curve 0.69). 90/118 patients (76%) with MASCC score <18 developed complications; 49/95 patients (52%) with MASCC score ≥18 developed complications.
Citation: Hui2011 (38) Study design: Prospective; validation of MASCC in Chinese cancer patients Development & validation of artificial neural network (ANN) model Comparison of MASCC, Talcott, & ANN Setting: Hospital in Hong Kong. Patients: 227 cancer patients presenting with febrile neutropenia. Description of risk assessment: Talcott group I to IV and MASCC score applied to patients with sensitivity, specificity, positive predictive value, & negative predictive value calculated for outcome of febrile neutropenia episode (good or poor). True positives were low risk with uncomplicated recoveries. ANN development set was first 114 consecutive patients; validation set was subsequent 113 patients. Output score was 1 (low risk) or 0 (high risk). 14 parameters were included in the ANN model. Results: Ability of models to predict low risk: Talcott: Sensitivity 50%, specificity 72%, positive predictive value 84%, negative predictive value 33%, misclassification 44% MASCC: Sensitivity 81%, specificity 60%, positive predictive value 86%, negative predictive value 52%, misclassification 24% ANN validation set: Sensitivity 84%, specificity 60%, positive predictive value 85%, negative predictive value 58%, misclassification 22% Area under receiver operating characteristic curve (range 0.5 [no discriminative ability] to 1.0 [perfect discrimination]): Talcott 0.573, MASCC 0.808, ANN 0.737.
Citation: Klastersky2000 (11) Study design: Prospective; development & validation of risk index (MASCC). Comparison with Talcott. Setting: 20 institutions in 15 countries.

Patients: 1139 patients (in hospital and outpatients) with febrile neutropenia.
Description of risk assessment: Development set (n=756, 66.4%), validation set (n=383, 33.6%).
Risk factors identified at fever presentation were combined in in univariate and multivariate analysis and a score for prediction was calculated for each patient. Higher score was associated with lower risk. Prediction rules were derived with the aim of selecting patients at low risk using different thresholds of the score.
Characteristics in the final model were: Burden of illness with no or mild symptoms, burden of illness with moderate symptoms, no hypotension, no chronic obstructive pulmonary disease, solid tumour or no previous fungal infection, no dehydration, outpatient status, and age <60 years. Points were assigned to each; the maximum score was 26.
Results: The threshold of ≥21 corresponded to a relatively low misclassification rate (21%) and a large proportion of patients were identified as low risk (73%).
Performance of 21:
Derivation: Sensitivity 80%, specificity 71%, positive predictive value 94%, negative predictive value 39%
Validation: Sensitivity 71%, specificity 68%, positive predictive value 91%, negative predictive value 36%, misclassification 30%. 63% were identified as low risk.
Talcott applied to derivation: 29% with predicted low risk, sensitivity 32%, specificity 92%, positive predictive value 96%, negative predictive value 19%, misclassification 59%
Talcott applied to validation: 26% with predicted low risk, sensitivity 30%, specificity 90%, positive predictive value 93%, negative predictive value 23%, misclassification 59%

Citation: Lyman2014 (41)
Study design: Systematic review.
Description of risk assessment: Included: studies with univariate and/or multivariate analysis for febrile neutropenia risk factors in patients receiving systemic cancer chemotherapy.
Results: 8 studies reported univariate results, 4 reported multivariate results, 16 reported both, and 3 reported genetic markers associated with febrile neutropenia risk.
Patient-related risk factors: older age, poor performance status, female sex, comorbidities, laboratory abnormalities, body mass index, chemotherapy regimen, neutropenia prophylaxis.
Disease-related risk factors: tumour type and advanced disease.
Genetic risk factors: GSTP 1, UGT1A1, MDM2SNP309, TP53R72P genotypes.

Citation: Paesman2011 (42)
Study design: Retrospective; development & validation of MASCC score with integration of bacteremic status.
Patients: 2142 patients from 2 observational studies; the first to develop the MASCC score (n=1139) and the second to examine variables affecting neutropenia duration (n=1003).
Description of risk assessment: first study used for the development set; the second study used for the validation set.
A logistic regression model was constructed to predict the presence or absence of bacteremia. Bacteremia was subdivided as single Gram positive, single Gram negative, and polymicrobial.
Results: Ability of the scores to predict a successful outcome (no serious complications) in validation set
Area under the receiver operating characteristic curve:
MASCC score 0.756
MASCC score in combination with bacteremia 0.773
MASCC score in combination with Gram-negative bacteremia 0.755.

Citation: Uys2004 (13)
Study design: Prospective; validation of MASCC score.
Setting: Hospital in Johannesburg, South Africa.
Patients: 64 patients admitted to hospital on presenting with febrile neutropenia. 80 febrile neutropenia episodes.
Description of risk assessment: The MASCC score was applied to each patient and classified them as low or high risk.
Results: Among the 58 patients classified as low risk:

- Response to antibiotics: Success 81%; failure 19%.

• Resolution without complication 98.4% • Resolution with complication 1.6% • Death before resolution 0 Among the 22 high-risk patients: • Response to antibiotics: Success 9.09%; failure 91.9% • Resolution without complication 14.6% • Resolution with complication 50% • Death before resolution 36.4% 98.3% of low-risk and 86.4% of high-risk patients were correctly predicted; 1.7% and 13.6%, respectively, were incorrectly predicted. Incorrectly predicted patients had MASCC scores between 19 and 21.
Citation: Wilson-Royalty2001 (43) Study design: Systematic review. Description of risk assessment: Included: studies that correlated neutropenia with risk factors or patient characteristics. Results: 26 studies were included. Patient-related risk factors: advanced age, poor performance status Treatment-related risk factors: ANC nadir, early low blood count, precipitous early drop in blood count; certain chemotherapy regimens such as CHOP, MVPP, AC-T, sequential A-CMF; number of previous chemotherapy cycles; high-dose chemotherapy Disease-related risk factors: bone marrow involvement.

A-CMF=doxorubicin, cyclophosphamide, methotrexate, fluorouracil; AC-T=doxorubicin, cyclophosphamide, docetaxel; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; ECOG=Eastern Cooperative Oncology Group; MASCC=Multinational Association for Supportive Care in Cancer; MVPP=mustine, vincristine, procarbazine, prednisolone.

Appendix 7. Automated symptom management systems

System: Advanced Symptom Management System (ASyMS) Developer: Developed and tested in various UK academic centres. Chief investigator, Nora Kearney. Program details: Patients use mobile phones to report side effects during chemotherapy, including temperature. The responses generate alerts that are sent to the healthcare professional. The patient is contacted if necessary or sent self-care information. The risk model used to alert health professionals at the clinical site is based on a review of the relevant literature of the selected symptoms. Published evaluation studies: Randomized controlled trial (RCT) comparing patients using ASyMS through 4 cycles of chemotherapy with patients receiving standard care (61). Of 6 symptoms measured, patients using the ASyMS symptoms had a lower incidence of fatigue and a higher incidence of hand-foot syndrome. Included in systematic review (21); narrative review (62). Ongoing/unpublished evaluation studies: Cancer Research UK: ASyMS III study is in progress with expected completion in July 2014 (http://www.cancerresearchuk.org/cancer-help/trials/a-study-looking-using-mobile-phones-report-side-effects-chemotherapy-asyms-iii-study). European Commission: eSMART project is an RCT using ASyMS; 1108 patients in 17 European sites. Expected completion in 2019. (http://ec.europa.eu/research/health/medical-research/cancer/fp7-projects/esmart_en.html). Implementation: The system has been in development over the past 5 to 7 years and is still being tested. The system is not commercially available.
System: Symptom Tracking and Reporting for Patients (STAR) Developer: Memorial Sloan-Kettering Cancer Center Chief investigator, Ethan Basch Program details: A web-based system that allows patients to enter and track their own symptoms and generates longitudinal reports that can be available to staff. The essential features of STAR are a homepage at which users log in, online question items, a secure database, and an interface for generating longitudinal reports of previously entered data. Published evaluation studies: Feasibility study in 80 women with gynecological cancer (63). Feasibility study in 180 patients (64). Feasibility study in 286 outpatients receiving chemotherapy (20). Patient compliance with using the system was higher on a monthly basis than a weekly basis. Greater compliance was seen with older age and higher education. Included in narrative review (62). Ongoing/unpublished evaluation studies: Clinical Trials.gov: Pilot Study of STAR, an Internet-based System for Cancer Patients to Self-report Toxicity Symptoms, Performance Status, and Quality of Life. RCT comparing access to the STAR website versus periodic brief paper questionnaire. 1007 patients at the Memorial Sloan-Kettering Cancer Center. Expected completion in December 2014. (http://clinicaltrials.gov/ct2/show/NCT00578006?term=cancer+patients+self-report+toxicity&rank=1) Implementation: The system is still being tested and is not commercially available.
System: Pan-Canadian Oncology Symptom Triage and Remote Support (COSTaRS) Project Developer: Canadian Association of Nurses in Oncology Project chair, Dawn Stacey Funded by Canadian Partnership Against Cancer Program details: Remote symptom protocols for patients receiving cancer treatment were developed for 13 symptoms including febrile neutropenia. Protocols include series of questions for nurse to ask patient and include recommendations for assessing symptom severity, triaging, review of medications being used for the symptom, review of self-management strategies, and summarizing and documenting the plan agreed on with the patient. Recommendations are supported by evidence-based clinical practice guidelines. Published evaluation studies: Study to develop and evaluate a template for evidence-informed symptom protocols for use by nurses over the telephone for the assessment, triage, and management

of patients experiencing cancer treatment-related symptoms (65). Usability of the protocol tested in 12 nurses indicated the protocols had just the right amount of information, used appropriate terms, good presentation, and good fit with the clinical work flow. Improvements were suggested for the areas of assessment, documentation, and triage. Implementation: Available for use in routine remote support practices http://www.cano-acio.ca/triage-remote-protocols
System: Electronic patient self-reporting of adverse events: patient information and advice (eRAPID) Developer: Leeds Institute of Cancer and Pathology Lead, Galina Velikova Core funded by: Cancer Research UK 1999-2013; National Institute for Health Research 2013-2018 Program details: eRAPID is a program of research that aims to develop, introduce and evaluate in cancer care a system for cancer patients to self-report their adverse effects (toxicity and symptoms) during and after cancer treatments. This system will be electronic and will be integrated into routine care by documenting patient-reported adverse effects in existing electronic patient records. Published evaluation studies: Description of the development of patient interface and care pathways in conference abstract (23). Ongoing/unpublished evaluation studies: National Institute for Health Research (NIHR): eRAPID Towards safer delivery and monitoring of cancer treatments. Expected completion 2018. Development components include a secure flexible electronic platform for patients to report adverse events from home and clinic, patient-reported adverse event items and evidence-based advice and alerts, and professionals and care pathways. Evaluation components include feasibility and pilot testing and a large scale RCT of eRAPID in systemic treatment. (http://www.pogweb.org/index.php/erapid/). Implementation: Not commercially available. The system is being tested in 3 hospitals in the UK in patients receiving systemic therapy, radiotherapy (for pelvic malignancies), and surgery (for upper gastrointestinal cancer).
System: PatientViewpoint Developer: Developed at Johns Hopkins School of Medicine. Funded by US National Cancer Institute. Program details: Patients receive an email reminder to complete a patient-reported outcome questionnaire from their healthcare provider with a link to the website. The results from this and previous questionnaires are shown in graphical format. Poor scores are highlighted in yellow to alert clinicians to potential issues. Free-text boxes ask patients to report the issue they are most interested in discussing with their clinician and any other feedback. The system is linked to the electronic health record. Published evaluation studies: Development of the prototype (66). Pilot test in 52 patients and 11 clinicians (67). Physicians reported using the questionnaire results for more than three-quarters of patients. Patients reported the system was easy to use, served as a memory aid for symptoms and side effects, enabled them in control of their care, and facilitated discussions with their healthcare provider. Included in narrative review (62). Implementation: Being used at Sidney Kimmel Comprehensive Cancer Centre at Johns Hopkins, Baltimore.
System: WebChoice Developer: The Centre for Shared Decision Making and Collaborative Care Research at Oslo University Hospital Lead investigator, Cornelia Ruland. Program details: A web-based, interactive health communication application that allows cancer patients to monitor their symptoms and problems, provides individually tailored information and self-management support, e-communication with expert cancer nurses, and an e-forum for group discussion with other patients. Published evaluation studies: Review of patient use patterns. The email exchange with nurses was valued the highest by patients (68).

RCT to evaluate the effects of WebChoice on primary outcomes of symptom distress, quality of life, depression and health service use, and secondary outcomes of self-efficacy, social support in 325 cancer patients (69). Patients using WebChoice had significantly better scores in symptom distress. RCT comparing an Internet-based patient provider communication service, WebChoice, and usual care on symptom distress, anxiety, depression. The WebChoice group reported significantly lower symptom distress, anxiety, and depression than the usual care group (70) Ongoing/unpublished evaluation studies: Improving Symptom Management for Cancer Patients and Their Caregivers Through Internet Support: A Randomized Clinical Trial (http://clinicaltrials.gov/ct2/show/NCT01867723?term=WebChoice&rank=3) Implementation: Not commercially available. Undergoing testing in Norway. WebChoice now called CONNECT (**C**are **O**nline: **N**ovel **N**etworks to **E**nhance **C**ommunication and **T**reatment).
System: Electronic Self-Report Assessment for Cancer (ESRA-C) Developer: Dana-Farber Cancer Institute, Boston and University of Washington, Seattle Lead investigator, Donna Berry Program details: Web-based self-monitoring of cancer symptoms and quality of life measures and self-care instruction available to patients at home or on a tablet in clinic. Graphical summaries provided to the healthcare providers. Published evaluation studies: RCT in 660 patients conducted in waiting rooms before clinic (71). RCT in 779 patients. The program was available to patients at home and in the clinic. Intervention enhanced to offer tailored education, communication coaching, and symptom & quality of life tracking; accessible from home (72,73). The patients using ESRA-C had lower symptom distress. Ongoing/unpublished evaluation studies: Computerized Assessment for Patients With Cancer-ESRA-C II (http://clinicaltrials.gov/ct2/show/NCT00852852?term=ESRA&rank=1) The computer program is being tested to see whether it can improve communications between patients and their care team and if it can improve patients' experiences during and after treatment. Implementation: Not commercially available. Still undergoing testing.
System: Cancer Emergency Response Tool (CERT) Developer: UK Oncology Nursing Society Program details: A mobile app for Android or iPhone that covers 7 medical complications and toxicities encountered by cancer patients (fever, nausea, vomiting, sore mouth, diarrhea, bleeding/bruising, leg weakness/loss of sensation). It assists appropriate decision making about when to seek medical advice, and speeds direct access to the local cancer centre when potentially life-threatening or urgent symptoms are present. It includes a button for direct phone access to the local cancer centre when urgent symptoms are present. The app is modeled on the UK Oncology Nursing Society Acute Oncology triage tool and uses stoplight colours (green, amber, red) to indicate the urgency of the problem. Implementation: Commercially available (iTunes, Android)

Appendix 8. Recommendations submitted for external review June 30, 2015.

DRAFT RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

- **Cancer patients in the community receiving chemotherapy who experience a fever should be assessed. While 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 a body temperature of 38.3˚C or sustained temperature of 38.0˚C lasting more than one hour. Tympanic temperature measurement is a viable option and should be measured according to manufacturers' specifications.**
- **Patients with fever should seek urgent assessment. Insufficient evidence exists 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 a reasonable option.**
- **Cancer patients in the community receiving chemotherapy should be provided with standardized information about fever and fever-associated infection. They should be informed about how to measure their temperature and how to recognize when assessment by a healthcare provider is recommended. This information should be delivered at the time of chemotherapy initiation and may be provided in conjunction with other self-assessment education, and reinforced with take-home written material and communication with healthcare providers.**

Qualifying statements

- *There is a lack of quality primary evidence to inform the definition of fever; thus, the consensus definition from existing guidelines on febrile neutropenia was recommended.*
- *There is wide variation in temperature readings across thermometer types.*
- *Some patients may be receiving growth factors to decrease the risk of febrile neutropenia. Their risk for poor outcome in the setting of fever may be lower, and fever may be a side effect of the growth factors themselves. The management of fever in chemotherapy patients who also receive growth factors to prevent febrile neutropenia was outside the scope of this guideline, but no obvious citations that address this issue were identified during the literature review to inform management of this subgroup.*

Key Evidence

Temperature

The key evidence for this recommendation is based on existing guidelines and consensus. Most existing related clinical practice guidelines focus on the management of febrile neutropenia and define fever as a one-time temperature measurement of 38.3˚C or two readings of 38.0˚C one hour apart (2,4-8). Slight variations in definition were noted in two guidelines (1,3). Evidence from a primary literature review found six studies addressing the predictive value of body temperature. Patients were already diagnosed with febrile neutropenia, and the cut-off used in five studies was 39˚C (9-13). In these studies, temperature was an unreliable predictor of poor outcome. A blinded diagnostic test study in neutropenic patients reported sensitivity, specificity, positive predictive value and negative predictive value in detecting rectal fever (≥38˚C) with tympanic membrane thermometry of 68%, 98%, 90%, and 92%, respectively. The sensitivity, specificity, positive predictive value and negative predictive value for oral thermometry were 56%, 98%, 90%, and 89%, respectively (14).

Assessment

No evidence was found that directly pertained to the assessment of fever before a diagnosis of febrile neutropenia was made. Fever was included as one among several symptoms (e.g., fatigue, pain, nausea, and vomiting) in some studies of symptom management and the adverse effects of chemotherapy. Protocols for symptom management included patient-initiated drop-in clinics (15,16), healthcare provider-initiated case management (17,18), and various remote monitoring strategies using cell phone applications, web-based and touch-tone phone interfaces, and automated programs (19-23). A number of studies are currently being conducted in the area of symptom management systems.

Education

There is very little primary evidence directly addressing information resources for managing fever in cancer patients. Improvement in symptoms was seen with interventions such as cognitive behavioural therapy provided by nurses (24); pre-chemotherapy education class supplemented with take-home reading materials and instructions on how and when to report symptoms (25); a symptom management toolkit describing self-assessment activities (19); and education, fever management algorithm, and thermometer (26).