Temperature management in haematology patients with febrile neutropenia: a practice survey

Robert Weinkove, Jennifer Clay, Catherine Wood

Abstract

Aim To assess the attitudes of clinicians to temperature management in haematology patients with febrile neutropenia.

Method An online scenario-based survey was circulated to consultant members of the New Zealand branch of the Haematology Society of Australia and New Zealand, to haematology advanced trainees, and to nursing representatives at each haematology department in New Zealand.

Results Eighty-eight responses were obtained, from 34 doctors and 54 nurses. Most respondents would advise a neutropenic patient to take paracetamol as needed for pain. Median temperature intervention threshold for an asymptomatic patient with febrile neutropenia was higher for doctors than for nurses (38.5 versus 38.0°C), despite considerable heterogeneity. Both groups indicated they would intervene at a median 38.0°C for a patient with rigors. Paracetamol was the preferred first-line cooling measure, with physical methods second-line, and pethidine third-line. All respondents favoured oral over intravenous or rectal paracetamol. Most believed a clinical trial of antipyretic treatment for febrile neutropenia was warranted, and indicated willingness to enrol their patients in such a study.

Conclusion This survey documents clinicians’ preferred temperature intervention thresholds and methods for haematology patients with neutropenic fever, and shows considerable variation in practice. Most respondents supported a trial of antipyretic management in febrile neutropenia.

Severe neutropenia is a risk factor for sepsis.¹ Febrile neutropenia is commonly defined as a single fever of ≥38.3°C or a temperature of ≥38°C for at least 1 hour, in the context of a neutrophil count of <0.5×10⁹/L, or <1.0×10⁹/L with the expectation of a decline to <0.5×10⁹/L in subsequent days.²

Febrile neutropenia occurs in the majority of patients undergoing acute leukaemia induction and autologous and allogeneic stem cell transplantation,³,⁴ and carries a high mortality without prompt antibiotic treatment.¹ Guidelines for the investigation and antimicrobial treatment of neutropenic fever have been published.²,⁵,⁶

Fever is a natural response to infection, and may be beneficial to the outcomes of sepsis: compared to 37°C, temperatures within the febrile physiological range inhibit in vitro growth of some bacteria,⁷ and enhance antimicrobial sensitivitiy.⁸

On the other hand, antipyretics such as paracetamol improve patient comfort,⁹ and may have favourable haemodynamic effects.¹⁰ The authors’ experience suggests that the attitudes of haematology clinicians to cooling measures in patients with
neutropenic fever vary, with some encouraging, and others discouraging, the use of cooling measures.

We aimed to assess the attitudes of haematology clinicians in New Zealand to the management of fever in patients with febrile neutropenia using a practice survey.

Method
A survey asking respondents about their management approach to three clinical vignettes was designed. The first scenario was of a neutropenic patient at home asking their clinician whether they could use paracetamol as an analgesic: respondents were asked to state whether they would advise the patient to take paracetamol regularly, as needed, or to avoid paracetamol.

The second and third scenarios related to a patient with severe neutropenia and fever who has already commenced first-line antimicrobials: respondents were asked at which temperature they would intervene with cooling measures (with options in 0.5°C bands) if the patient were asymptomatic, or symptomatic with rigors. Respondents were then asked which physical or pharmacological cooling measures they would use, and whether paracetamol would be administered as needed or regularly, and via which route.

Respondents were asked at what time point they would use fever as a determinant of empiric antimicrobial change in a patient with febrile neutropenia. Finally, respondents were asked whether they felt a clinical trial of antipyretic treatment in febrile neutropenia was warranted, and whether they would be willing to enrol their patients in such a trial. The survey is in Appendix 1.

The survey was piloted in the authors’ own haematology department, and changes made to improve clarity, and add to response options. A link to the online survey was then emailed to all current medical and nursing members of the New Zealand branch of the Haematology Society for Australia and New Zealand (HSANZ), to all haematology trainees in New Zealand, and to a nursing representative at each haematology centre in New Zealand, for distribution to other nursing staff.

Survey responses were collected using an online survey tool (SurveyMonkey.com, Palo Alto, California, USA), exported to an Excel spreadsheet (Version 12.3.0, Microsoft Corporation, Redmond, Washington, USA), and analysed using Prism statistical software (Version 5.0d, GraphPad Software, La Jolla, CA, USA). All data were analysed using non-parametric statistical tests. The a priori subgroups of doctor and nurse professionals were analysed separately. Temperature thresholds (in 0.5°C bands) were treated as continuous variables for analysis. A probability value of p < 0.05 was considered significant. This online practice survey was classified as low-risk, and did not require formal ethical review according to the guidelines of the Central Regional Ethics Committee of New Zealand.

Results
Eighty-eight responses were received, from 20 consultant haematologists, 14 haematology trainee doctors, 18 senior nurses (charge nurses, clinical nurse specialists or nurse educators), and 36 ward or day unit nurses. Approximately 45 consultant haematologists and 25 haematology registrars are practising in New Zealand (Dr Bart Baker, personal communication), giving an overall response rate of 48% among doctors. The total number of nurses practising in haematology in New Zealand is not known. The number of respondents from each professional group, and duration of practice in clinical haematology, is given in table 1.
Table 1. Survey respondents

<table>
<thead>
<tr>
<th>Professional group</th>
<th>Respondents (n)</th>
<th>Haematology experience (years); median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant Haematologists</td>
<td>20</td>
<td>14 (6–30)</td>
</tr>
<tr>
<td>Haematology trainee doctors</td>
<td>14</td>
<td>1 (0.33–5)</td>
</tr>
<tr>
<td>Charge nurses, Clinical nurse specialists, nurse educators</td>
<td>18</td>
<td>11.5 (5–27)</td>
</tr>
<tr>
<td>Ward and day unit nurses</td>
<td>36</td>
<td>5.5 (0.25–20)</td>
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Sixty-eight percent of doctors and 44% of nurses indicated that they would allow a neutropenic patient to take paracetamol as needed for pain, and a further 15% of doctors and 7% of nurses would allow a neutropenic outpatient to take regular paracetamol. Nurses were significantly more likely than doctors to advise a neutropenic patient to avoid paracetamol (p < 0.05, Fisher’s exact test).

Figures 1A and 1B show the temperature thresholds at which respondents would intervene to lower temperature in an asymptomatic and a symptomatic patient with febrile neutropenia, respectively.

For asymptomatic patients, the temperature threshold for intervention varied widely between respondents, but the threshold was significantly higher for doctors than for nurses (median 39°C for doctors, 38.5°C for nurses; p<0.01, Mann Whitney test).

For symptomatic patients, the median intervention threshold was 38°C for both doctors and nurses (difference not significant). Considering all survey respondents, there was no significant correlation between years of experience in haematology and temperature intervention threshold for either symptomatic or asymptomatic patients (data not shown).

Figure 1. Reported temperature intervention thresholds in severe neutropenia
Fifty-five percent of respondents favoured paracetamol as the first line intervention to reduce temperature, with a further 44% selecting physical cooling measures. Forty-five percent of respondents favoured physical cooling as the second line intervention, with 30% selecting paracetamol. Sixty-eight percent of respondents selected pethidine as the third line intervention. Other measures, such as non-steroidal anti-inflammatory drugs (NSAIDS), cyclo-oxygenase 2 (COX-2) inhibitors, and other opiates, were favoured by fewer respondents. These data are presented in Figure 2.

Figure 2. Preferred temperature-lowering interventions in febrile neutropenia

Eighty-three respondents answered the question about frequency of paracetamol administration in inpatients with febrile neutropenia. Of these, seventy-two (87%) reported that they would administer or prescribe paracetamol only as needed, and three (4%) would prescribe or administer paracetamol regularly. Eight (10%) reported that they would never use paracetamol in this setting.

Regarding the route of paracetamol use in patients with febrile neutropenia, all 85 respondents to this question reported that they would use oral paracetamol as the first choice. Forty-nine respondents selected an alternative route of administration in case oral paracetamol could not be given, of which 39 respondents favoured intravenous paracetamol and ten favoured rectal paracetamol. Sixty-four percent of respondents to this question (54/85) reported that they would avoid rectal paracetamol in patients with neutropenic fever.

Among the 83 respondents who selected at least one choice of physical cooling method, the most frequently selected options were removal of clothes (83% of
respondents), provision of a fan (81%), tepid sponging (58%), and provision of a wet
towel or flannel (53%). Fewer than ten percent of respondents selected the use of ice
packs, cooling blankets or intravenous fluids for physical cooling.

Seventy-five respondents answered the question about time to change of
antimicrobials. Of these, the majority stated that they would consider an antibiotic
change at either 48 or 72 hours, with 39% (29 respondents) selecting each of these
time points. A further 9% would change at 24 hours, 4% at 36 hours and 1% at 96
hours. Eight percent (6/75) indicated that they had no fixed time for antimicrobial
change in this situation.

Sixty-nine percent of respondents (51/74) stated that they would be willing to enter
their patients into a randomised study of antipyretic management in febrile
neutropenia. A further 27% (20/74) were unsure. Three respondents to this question
(4%) stated that they would not be willing to enter their patients in such a study.

Discussion

This practice survey reports the attitudes of haematology doctors and nurses to
antipyretic treatment for patients with neutropenic fever.

The survey indicates that overall, most respondents would advise a neutropenic
patient to take paracetamol as needed for pain, but that nurses were significantly more
likely than doctors to advise patients to avoid paracetamol. In febrile neutropenia,
thresholds for temperature-lowering interventions varied widely, but nurses reported
they would intervene at a significantly lower temperature than doctors in a patient
without rigors.

In a symptomatic patient, both professional groups would intervene at a median of
38.0°C. Most clinicians would use either paracetamol or physical measures as a first-
line intervention, with a narrow preference for paracetamol. Physical measures were
the favoured second-line, and pethidine was the favoured third-line, cooling
intervention.

Oral paracetamol was preferred over the intravenous route, and most respondents
would avoid the rectal route. Finally, the majority of respondents believed a clinical
study of antipyretic treatment in febrile neutropenia was warranted, and would
consider entering their patients in such a study.

To the authors’ knowledge, this is the first survey of temperature management in
febrile neutropenia. In collaboration with the New Zealand branch of the HSANZ, we
were able to survey nearly half of all haematology doctors working in New Zealand.
The majority of respondents who commenced the online survey completed it, with
95% and 84% response rates to the penultimate and final survey questions,
respectively. This study employed scenarios to assess clinical practice, an approach
that has been validated in a variety of settings.11,12
Although we were able to calculate a response rate for doctors, the survey response rate among nurses is unknown due to a lack of a central register of haematology nurses in New Zealand, and a large number of haematology patients being cared for in mixed-specialty wards. Nonetheless, we believe the response rate among nurses to be lower than that among doctors.

Among both doctors and nurses, the voluntary nature of survey participation may result in bias, so the current findings may not be representative of all clinicians. Finally, reported preferences in a survey may not reflect actual clinical practice. We intend to address some of these points by undertaking an observational study of paracetamol usage among inpatients with febrile neutropenia.

The authors are not aware of any published surveys of fever management in neutropenic fever, but clinicians’ attitudes to fever have been investigated in other infection scenarios. In a review of fever management among critical care clinicians in Australia and New Zealand, doctors reported a significantly higher mean temperature intervention threshold than nurses (39.0°C vs 38.5°C), similarly to this study. The temperature intervention thresholds in the critical care study were higher than in the current study, possibly because many intensive care patients are sedated, so fever-related symptoms are less of a concern.

A study of fever management by paediatric junior doctors indicated a mean antipyretic treatment threshold of 38.6°C, with alternating aspirin and paracetamol as the favoured intervention. Very few respondents favoured non-steroidal anti-inflammatory drugs in the current study, possibly due to concerns about impairing platelet function in neutropenic patients, many of whom are also thrombocytopenic.

In a survey of fever management among Swiss paediatricians, a temperature threshold of 38.5°C was identified as a threshold for treatment, with the vast majority favouring paracetamol; in this study, the favoured routes of paracetamol administration were rectal for 18 month olds, and oral for older children. The widespread reluctance to use rectal paracetamol in the current study is likely to reflect concern about inducing bacteraemia in the neutropenic patient.

The role of antipyretics in the management of infection remains unclear. Observational studies have found that the absence of fever is associated with increased mortality in patients admitted to intensive care units with infection, and that the use of antipyretics is associated with increased mortality in septic, but not in non-septic patients.

A number of interventional studies support the notion that fever is an important physiological response to infection: in children with falciparum malaria, the administration of regular paracetamol was associated with delayed resolution of parasitaemia, and in healthy volunteers infected with rhinovirus, regular paracetamol administration was associated with a reduced antibody response and a prolongation of symptoms.

A single randomised trial comparing aggressive temperature control to permissive hyperthermia in patients with sepsis in intensive care found a trend towards reduced mortality in the permissive hyperthermia group. This finding is yet to be replicated.
The present study assesses clinician preferences regarding antipyretic treatment in febrile neutropenia using a scenario-based survey. This survey demonstrates a lack of clear consensus on thresholds for, and methods of, lowering temperature, which is understandable given the lack of evidence. Establishing the role of antipyretics in neutropenic fever would require a prospective randomised controlled trial, for which the majority of respondents to this survey indicate support.

**Competing interests:** Nil.

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**References:**


Appendix 1: Survey questions

1. What is your role in the management of haematology patients?
   - Consultant Haematologist (doctor)
   - Haematology Registrar
   - Other doctor in training
   - Clinical Nurse Specialist (in haematology and/or oncology)
   - Ward Nurse (in haematology or oncology)
   - Day Unit Nurse (in haematology or Oncology)
   - Other (please specify)

2. For how many years have you practised in haematology?

The following questions relate to clinical scenarios. Please indicate what your clinical practice would be.

3. A patient has just received chemotherapy which is expected to cause severe neutropenia, and is to be discharged from hospital. They ask if they can use paracetamol at home, for joint pain. What do you advise?
   - Yes, take paracetamol regularly for pain
   - Yes, take paracetamol as needed for pain, but avoid taking it regularly
   - No, do not take paracetamol
   - Other, please specify

4. A patient with fever and severe neutropenia following chemotherapy has already started first-line antibiotics. The patient is currently ASYMPTOMATIC. At what temperature would you intervene with medications or physical cooling measures?
   - 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5°C
   - I would not intervene at any temperature
   - Other (please specify)

5. A patient with fever and severe neutropenia following chemotherapy has already started first-line antibiotics. The patient complains of RIGORS and SWEATS. At what temperature would you intervene with medications or physical cooling measures?
   - 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5°C
   - I would not intervene at any temperature
   - Other (please specify)
6. You have decided to reduce the temperature of a patient with febrile neutropenia. What would be your first, second and third-line method(s) of reducing body temperature? If you would use more than one method at a time, please select all that apply.

<table>
<thead>
<tr>
<th>Variables</th>
<th>First line</th>
<th>Second line</th>
<th>Third line</th>
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<tbody>
<tr>
<td>Paracetamol</td>
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<td></td>
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<tr>
<td>Physical cooling measures (e.g. fan, sponging, cooling blanket)</td>
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<td></td>
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<tr>
<td>Non-steroidal anti-inflammatory drug (e.g. ibuprofen, diclofenac)</td>
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<tr>
<td>COX-2 selective inhibitor (e.g. celecoxib, paracoxib)</td>
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<tr>
<td>Pethidine</td>
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<tr>
<td>• Other (please specify)</td>
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</table>

7. If you ever prescribe or administer paracetamol in febrile neutropenia, do you usually provide it regularly or as needed (PRN)?

• Regular paracetamol
• As needed (PRN)
• I never prescribe or administer paracetamol for febrile neutropenia

8. If you ever prescribe or administer paracetamol in febrile neutropenia, what route of administration do you prefer?

<table>
<thead>
<tr>
<th>Variables</th>
<th>First choice</th>
<th>Second choice</th>
<th>Third choice</th>
<th>I avoid this route</th>
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</thead>
<tbody>
<tr>
<td>Oral paracetamol</td>
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<tr>
<td>Intravenous paracetamol</td>
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<tr>
<td>Rectal paracetamol</td>
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• Comments:

If you ever recommend or apply physical cooling methods, which do you use (select all that apply)?

• Removal of clothes or coverings
• Tepid sponging
• Wet towel or blanket
• Fan
• Ice packs
In the planned clinical trial, we anticipate randomising patients with febrile neutropenia to receive paracetamol or placebo. Patients will start first-line antimicrobial therapy before paracetamol/placebo treatment. Patients will stop paracetamol/placebo before assessing the need for second-line antimicrobials. Antimicrobials can be changed at any time if culture results/antibiotic sensitivities or clinical features (e.g. hypotension, clinical deterioration) demand.

9. In the trial, patients would stop receiving paracetamol/placebo before a planned assessment of the need for second-line antimicrobials. At what time point would you empirically change to second-line antimicrobials in a patient with neutropenic sepsis and ongoing fever?

   - After 24 hours (1 day)
   - After 36 hours (1.5 days)
   - After 48 hours (2 days)
   - After 72 hours (3 days)
   - After 96 hours (4 days)
   - I do not have a fixed time before antimicrobial review
   - Other (please specify)

10. Are there any groups of patients who you would NOT want to include in a randomized trial of paracetamol in febrile neutropenia? If not, why not (use comments box)?

   - Elderly patients
   - Autologous stem cell transplant recipients
   - Patients having stem cell harvest
   - Allogeneic stem cell transplant recipients
   - Other patient groups / comments

11. Do you believe a clinical trial of antipyretic (paracetamol) use in febrile neutropenia is warranted?

   - Yes
   - No
   - Unsure
12. Would you be willing to randomise your patients in a randomised trial of paracetamol for febrile neutropenia?

- Yes
- No
- Maybe

14. Would you like to add any further comments?