

ABSTRACT

Aim: Variation in the management of fever and neutropenia (FN) in children is well described. The aim of this study is to explore the current management of FN across Australia and New Zealand and highlight areas for improvement.

Methods: A practice survey was administered to paediatric healthcare providers via four clinical and research networks. Using three clinical case vignettes we explored risk stratification, empiric antibiotics, initial investigations, intravenous-oral switch, ambulatory management and antibiotic duration in children with cancer and FN.

Results: A response was received from 104 participants from 16 different hospitals. FN guideline compliance was rated as moderate or poor by 24% of respondents and seven different fever definitions were described. There was little variation in selected empiric monotherapy and dual-therapy regimens and almost all respondents recommended first-dose antibiotics within one hour. However, twenty-seven different empiric antibiotic combinations were selected for beta-lactam allergy. An incorrect risk status was assigned to the low-risk case by 27% of respondents and to the high-risk case by 41%. Compared to current practice, significantly more respondents would manage the low-risk case in the ambulatory setting provided adequate resources were in place (43% versus 85%, $p < 0.0001$). There was variation in the use of empiric glycopeptides as well as use of aminoglycosides beyond 48 hours.

Conclusions: Although the antibiotics selected for empiric management of FN are appropriate and consistent, variation and inaccuracies exist in risk stratification, the selection of monotherapy over dual therapy, empiric antibiotics chosen for beta-lactam allergy, use of glycopeptides and duration of aminoglycosides.

Key words: febrile neutropenia, cancer, children, management, practice survey

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/jpc.13899](https://doi.org/10.1111/jpc.13899)

What is already known on this topic

- Fever and neutropenia (FN) is one of the most common complications of the treatment of childhood cancer
- Variation in the assessment and empiric and ongoing management of FN across Australia and New Zealand has been described
- Risk stratification is rarely used and formal low-risk FN ambulatory programs in Australia and New Zealand do not exist

What this paper adds

- Variation in the definition of fever used, empiric prescribing and duration of aminoglycoside treatment for FN continues to exist
- There are differences in clinicians' perception of low and high-risk FN
- Opportunities exist to improve the assessment, risk stratification and empiric and ongoing management of FN across Australia and New Zealand. This has potential to reduce unwanted variation, improve patient safety and increase ambulatory management of low-risk FN

INTRODUCTION

In children with cancer, fever and neutropenia (FN) is a common complication of treatment and a leading cause of emergency department presentations.^{1,2} Despite this, considerable variation in the approach to management, including empiric antibiotic choice and duration, risk stratification and treatment location, is described.³⁻⁵

Although some differences in practice are due to geography and local microbiology, unwarranted variation can lead to incorrect prescribing, poor patient outcomes and increased healthcare expenditures.⁶⁻⁸

In Australia, there has been a move toward the publication of state-based guidelines for FN in children.⁹⁻¹¹ Each guideline focuses on empiric antibiotics with some subtle differences depending on local antibiotic resistance patterns.¹² However, despite international recommendations for centres to incorporate a validated risk-stratification strategy into routine management, no state-based guideline describes a framework for this.¹³ This is perhaps not surprising, given the absence of a nationally validated clinical decision rule (CDR) to assist clinicians in identifying low-risk patients suitable for oral antibiotics or ambulatory care.

Contemporary management of FN across Australia and New Zealand remains unknown. A local audit of FN at nine paediatric cancer treatment centres in 2002 identified that 18 different empiric antibiotic combinations were used.³ The aim of this study is to explore current management of paediatric FN across Australia and New Zealand and to highlight potential areas for improvement. Using three clinical case vignettes we explored risk stratification, empiric antibiotic prescribing and ongoing antibiotic management of FN in children with cancer.

METHODS

A clinical practice survey was used to explore current approaches to management of FN in children. The survey was developed by the steering group (comprising

haematology/oncology, infectious diseases and emergency medicine clinicians) in consultation with senior haematology/oncology, infectious diseases, emergency medicine and general paediatric clinicians identified from the Australian Predicting Infectious Complications in Children with Cancer (PICNICC) research group (ACTRN12616001440415). The survey was administered electronically to paediatric health-care providers via relevant clinical/research networks: Australian and New Zealand Haematology/Oncology Group (ANZCHOG), Australia and New Zealand Paediatric Infectious Diseases (ANZPID) Group of Australasian Society for Infectious Diseases (ASID), Paediatric Research in Emergency Departments International Collaborative (PREDICT) and Children's Healthcare Australasia (CHA).¹⁴

The survey was distributed to CHA (unknown number) in June 2015 and ANZCHOG (185 members), ANZPID (77 members) PREDICT (8 members) in December 2015.

Survey

Three clinical case vignettes were described and questions were asked about various aspects of FN management including investigations, risk assessment and empiric and ongoing antibiotics. Anonymous demographic and hospital resource data as well as details of local hospital FN guidelines were also collected. The three cases and pre-allocated risk status are described in Table 1. In the absence of a locally validated CDR, risk status was assigned based on expert opinion and recognised paediatric sepsis criteria.¹⁰ In case 2, aminoglycoside duration beyond 48 hours was assessed using three different scenarios outlined in Table 1.

Partial responses were included if the demographic and general FN management details were completed. Where respondents indicated affiliation with more than one organisation, preference was given to ANZCHOG or ANZPID for the calculation of response rate. Responses to the cases were presented according to the themes: risk assessment, empiric antibiotic choice and timing, initial investigations, intravenous-

oral switch, ambulatory management and aminoglycoside duration. Unless otherwise stated, data was presented according to the risk status selected by the respondent. Factors guiding decision making in four key areas of management (dual therapy versus monotherapy, glycopeptide use, intravenous-to-oral antibiotic switch and management in the ambulatory setting) were assessed using a four-point likert scale. Given the range of expertise and experience of those surveyed, the options of 'unsure' and 'not applicable to my area of expertise' were provided.

Fisher's exact test was used to estimate P-values for categorical data. All tests were 2-tailed, and a P-value <0.05 was considered statistically significant.

Study design and protocol were in accordance with a low-risk quality improvement exercise, as defined by the NHMRC, and ethics approval was therefore not required.

RESULTS

A response was received from 104 healthcare providers (complete 79 and partial 25) from 16 different hospitals across Australia and New Zealand, with at least one response from all eight tertiary paediatric sites. The overall response rate was 38% (excluding CHA) (ANZCHOG 38%, ANZPID 25% and PREDICT 50%). All respondents worked in centres where chemotherapy is administered to paediatric patients, with 92 (88%) working in centres providing dose-intensive chemotherapy for haematological malignancies and solid tumours. Participant demographic data is available in Table 2.

A hospital or statewide guideline was available to 103 respondents (99%) with clinician compliance reported as good, moderate and poor in 64%, 23% and 1%, respectively (12% unsure). Seven different fever definitions were described (Table 3).

Forty-three (41%) respondents, across nine hospitals, indicated their institute had a CDR to distinguish low and high-risk FN. Responses were inconsistent, with several

respondents from four of these nine hospitals responding that they did not have a CDR. Of those that answered 'no' or 'unsure,' 48 (79%) would consider using a CDR to assist with FN decision-making. A policy or guideline for nurse-initiated FN antibiotics was infrequent, described by 11 respondents across 5 hospitals.

The response rate for cases 1, 2 and 3 was 89%, 80% and 76%, respectively (Table 4).

Risk assessment

In Case 1, 68 (74%) respondents correctly identified the patient as low risk. In case 2, 83 (99%) identified the patient as high risk. In case 3, 47 (59%) correctly identified this patient as high risk. Risk assessment according to clinical specialty is available in Table 4.

Empiric antibiotic choice

For cases 1 and 2, respondents were asked about empiric antibiotic choice (Table 5). Of those assigning case 1 as low risk, significantly more would choose monotherapy (74% versus 38%) over dual therapy (26% versus 63%) compared to those identifying the case as high-risk ($p=0.0085$). In case 1, piperacillin-tazobactam was the monotherapy chosen by all respondents, while piperacillin-tazobactam and gentamicin was most commonly selected for dual therapy ($n=24$), followed by piperacillin-tazobactam and amikacin ($n=3$), ceftriaxone and gentamicin ($n=1$) and ciprofloxacin and gentamicin ($n=1$). One respondent who assessed case 1 as high risk added empiric vancomycin.

All respondents assigned case 2 as high risk. Piperacillin-tazobactam and gentamicin was most commonly selected for dual therapy ($n=31$), followed by piperacillin-tazobactam and amikacin ($n=25$) and piperacillin-tazobactam and vancomycin ($n=10$). For those selecting monotherapy, piperacillin-tazobactam was the most common choice ($n=12$) with one respondent opting for meropenem. Empiric vancomycin was added by 43 (52%) respondents. Factors guiding decision to use dual

therapy over monotherapy and to add empiric glycopeptide, are presented in Figures 1 and 2. Additional factors considered very important in opting for dual therapy (with aminoglycoside) included renal impairment (n=3), degree of immune suppression (n=2), recent central venous access device (CVAD) access (n=1), mucositis (n=1) and presence of localizing infective signs (n=1).

In case 2 antibiotic allergy was addressed. Twenty-seven different antibiotic combinations were selected for non-life threatening penicillin allergy, with cefepime the most common (n=10), followed by meropenem (n=7), cefepime and gentamicin (n=7) and cefepime and amikacin (n=7). For life-threatening penicillin allergy there were 22 different antibiotic combinations, including seven (selected by 9 respondents) that included a cephalosporin and six (selected by 37 respondents) that included a carbapenem.

Empiric antibiotic timing

Recommended timing of first-dose antibiotic was addressed in cases 1 and 2 (Figure 3). Combining data from each case, there was a significant difference in the recommended time to first dose antibiotic depending on allocated risk status ($P<0.0001$). For high-risk patients, 30 minutes was preferred over 60 minutes (64% versus 34% respondents) while for low risk patients, 60 minutes was preferred over 30 minutes (72% versus 21% respondents).

Beyond risk status, factors influencing time to first dose antibiotic was addressed in case 3. Only 6 respondents (8%) would await confirmation of neutropenia and, of the 47 non-haematology/oncology respondents, 14 (30%) would discuss the case with the treating haematology/oncology team before starting antibiotics. Factors most frequently identified as contributing to delayed first-dose antibiotic included arriving without anesthetic cream on implantable port (n=28), bypassing local hospital to attend tertiary facility (n=27), waiting for 'business hours' to attend (n=24), availability of staff trained to access paediatric CVADs (n=21) and patient/family

requesting specific nurse to access CVAD (n=20).

Initial FN investigations

The recommended number, type and site of initial blood cultures is presented in Figure 4. Serum biomarkers are routinely used by 23 (22%) respondents with C-reactive protein (CRP) (n=18) used most frequently.

Intravenous-oral antibiotic switch

For case 1, respondents were asked about switching from intravenous to oral antibiotics. Provided the patient's course was uneventful, 3 (17%) and 13 (20%) would switch intravenous antibiotics to oral during this patient's FN episode for those assigning high and low-risk status, respectively. Factors guiding this decision are presented in Figure 5. Other factors identified as very important included the identification of an infective focus requiring intravenous antibiotics (n=7), reliability of the caregiver to administer oral antibiotics (n=8), previous infection history (n=2), declining CRP (n=1) and presence of a CVAD (n=1).

Ambulatory management

Of those that identified case 1 as low-risk (n=68), 29 (43%) would currently manage this patient with home-based care (Figure 6). In an ideal setting where ambulatory services and infrastructure were adequate, significantly more (n=58, 85%) would use home-based care (RR 2.5, p<0.0001). Factors guiding this decision are presented in Figure 7. Other factors identified as very important included proximity to hospital and ability to return (n=6), presence of an infection (n=2), language barrier (n=1) and reliability of caregiver (n=1).

Aminoglycoside duration

In case 2 the number of the haematology/oncology respondents that would cease the aminoglycoside for scenarios a, b and c (as outlined in Table 1) was 34 (61%), 20 (36%) and 46 (82%), respectively. Compared with the haematology/oncology group,

the infectious diseases respondents were significantly more likely to cease the aminoglycoside and continue single agent piperacillin-tazobactam for scenario a and b, with 17 (100%) of the ID respondents ceasing aminoglycoside for all three scenarios (Scenario a, $p=0.0016$; scenario b, $p<0.0001$)

DISCUSSION

This is the first survey to explore paediatric FN management practices across Australia and New Zealand and across different craft groups. Variation exists in risk stratification, the definition of fever, empiric prescribing of antibiotics including for antibiotic allergy and duration of aminoglycoside treatment, both among and between specialty craft groups. We also highlight the potential for a significant increase in ambulatory management of low-risk FN provided appropriate resources are in place.

In Australia and New Zealand, a prospectively validated CDR to distinguish high and low-risk FN has not been incorporated into routine practice and likely explains some of the inconsistencies in risk stratification in our survey. A typically low-risk FN episode was identified as high risk by a quarter of respondents and conversely, a high-risk case was perceived as low risk by over one third. Failure to categorize low-risk patients represents missed opportunity for use of empiric monotherapy over dual therapy, early intravenous-oral switch and entry into ambulatory management programs.^{13, 15} Similarly, accurate identification of high-risk patients may facilitate enhanced monitoring, early treatment and prevention of sepsis and other adverse events. A similar knowledge gap was evident in an Australian survey of risk-stratification practices in the adult haematology/oncology population.¹⁶

In keeping with evidenced-based FN guidelines, the most commonly selected empiric monotherapy and dual-therapy regimens were piperacillin-tazobactam and piperacillin-tazobactam plus aminoglycoside, respectively.^{9, 10, 13} This is in contrast to a 2002 Australian audit, where 18 different empiric combinations were used.³ However, as many as 27 different empiric antibiotic combinations were selected for

high-risk FN in the setting of beta-lactam allergy. Notably, a cephalosporin-containing regimen was selected by 11% for beta-lactam anaphylaxis despite the potential for 5% cross-reactivity with these agents.¹⁷ Antibiotic allergy in the adult cancer population is associated with increased antibiotic duration, inappropriate prescribing and higher readmission rates, suggesting that guidelines should address allergy recommendations and antibiotic allergy de-labeling strategies are employed.¹⁸

The majority of respondents appropriately identified severe sepsis as an important factor in guiding decision to use aminoglycoside-containing dual therapy. Despite this, 16% still selected monotherapy for the high-risk example with severe sepsis despite an aminoglycoside being recommended for this indication.^{9, 10, 13} Conversely, for the low-risk example without sepsis, 25% would still use aminoglycoside-containing dual therapy. Double gram-negative cover should be reserved for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens.¹³ This is supported by robust data that showed no difference in failure rate or mortality in patients with high-risk FN treated with monotherapy over dual therapy.¹⁹

Deviations for evidence-based guidelines were also evident in the use and duration of aminoglycoside and glycopeptides beyond the first 48 hours.¹³ In particular, over half of the haematology-oncology respondents would continue the aminoglycoside for ongoing fever despite negative blood cultures and clinical stability. In addition, remaining febrile at 48 hours was considered a very important factor guiding decision to use empiric vancomycin by 30%, despite placebo controlled trial data indicating no benefit on time to defervescence and all cause mortality.²⁰ Together these data suggest clinically important knowledge gaps in the assessment and management of severe sepsis, use of empiric monotherapy over dual therapy and duration of additional antibiotics with potential for toxicity. Guideline deviations may also represent a lack of confidence in clinical-trial data and the applicability of the results from FN antibiotic trials to the clinicians' patient population.

Provided adequate resources were in place, significantly more respondents would manage the low-risk FN example at home compared to their current practice. In contrast to a 2002 practice audit, more respondents would now also consider step down to oral antibiotics (20% versus 9%).³ These data suggest that with structured low-risk programs incorporating risk-assessment, regular observation and appropriate safeguards, many more low-risk patients would benefit from reduced intensity home-based care. Such treatment has been shown to be safe, improve quality of life and is significantly less expensive than routine inpatient care.²¹⁻²³

Seven different definitions of fever were selected, with two used by 86% of respondents. This variability is not surprising as a consensus fever definition was unable to be achieved by an international panel of FN experts.²⁴ Few studies have explored the clinical impact of different fever definitions, with one study concluding that a higher temperature definition was not associated with a lower FN rate, nor with an increased rate of bacteraemia.²⁵ Regarding the use of biomarkers in the assessment of FN, CRP continues to be most frequently used despite underwhelming evidence for its ability to accurately predict infection or adverse outcome.²⁶ Further translational research is required to identify novel biomarkers that can assist in risk stratification and guide antibiotic duration.

Although we provide a contemporary overview of paediatric FN management across Australia and New Zealand the results can only be considered reflective of those that participated in the survey. However, while response rate across the clinical research groups was less than 50%, there was representation from all tertiary paediatric hospitals with almost 90% working in centres providing dose-intensive chemotherapy and therefore likely to see many children with FN. Clinical responsibilities and survey fatigue is likely to have contributed to this low response rate. The survey was also administered over a six-month period due to intercurrent survey activity within the research groups. As the principles of FN management have not changed, this is

unlikely to have had a significant impact. In the absence of locally validated risk prediction rules, we relied on expert opinion and recognised sepsis criteria to develop low and high-risk case examples.¹⁰ This likely explains some of the variation in risk allocation.

We provide an overview of the assessment and management of FN across different craft groups in Australia and New Zealand. While the antibiotics selected for empiric FN management are consistent with evidenced-based guidelines, variation and knowledge gaps exist in risk stratification, identification and management of severe sepsis, use of dual therapy and glycopeptides, selection of antibiotics for beta-lactam allergy and antibiotic de-escalation. Our study adds insight into factors guiding decision making for empiric and ongoing prescribing and highlights potential for a significant increase in the utilization of ambulatory management of low-risk patients provided a structured program is in place. National guidelines and targeted education addressing the barriers to best practice as identified in this survey, together with collaborative research efforts, have the potential to reduce unwanted variation, improve patient safety and increase ambulatory management of low-risk FN in Australia and New Zealand.

REFERENCES

- [1] Haeusler GM, Thursky KA, Mechinaud F, et al. Predicting Infectious ComplicationNs In Children with Cancer: an external validation study. *Brit J Cancer*. 2017; **117**: 171-178.
- [2] Mueller E, Sabbatini A, Gebremariam A, Mody R, Sung L, Macy M. Why Pediatric Patients with Cancer Visit the Emergency Department: United States, 2006–2010. *Pediatr Blood Cancer*. 2015; **62**: 490-495.
- [3] Chamberlain JD, Smibert E, Skeen J, Alvaro F. Prospective audit of treatment of paediatric febrile neutropenia in Australasia. *J Paediatr Child Health*. 2005; **41**: 598-603.
- [4] Mueller E, Walkovich K, Yanik G, Clark S. Variation in Management of Fever and Neutropenia Among Pediatric Patients With Cancer: A Survey of Providers in Michigan. *Pediatr Hematol Oncol*. 2015; **32**: 331-340.
- [5] Herd F, Bate J, Chisholm J, Johnson E, Phillips B. Variation in practice remains in the UK management of pediatric febrile neutropenia. *Arch Dis Child*. 2016; **101**: 410-411.
- [6] Karnon J, Partington A, Horsfall M, Chew D. Variation in Clinical Practice: A Priority Setting Approach to the Staged Funding of Quality Improvement. *Appl Health Econ Health Policy*. 2016; **14**: 21-27.
- [7] Duggan A, Koff E, Marshall V. Clinical variation: why it matters. *Med J Aust*. 2016; **295**: 3-4.
- [8] Burrell A, McLaws M, Fullick M, Sullivan R, Sindhusake D. Sepsis Kills: early intervention saves lives. *Med J Aust*. 2016; **204**: e1-7.

- [9] Clinical practice guideline on fever and suspected or confirmed neutropenia. Royal Children's Hospital, Melbourne, Australia, 2016.
- [10] Infants and Children: Initial Management of Fever/Suspected Sepsis in Oncology /Transplant Patients. Ministry of Health, NSW, North Sydney, 2015; 1-31.
- [11] Network QPHO. Management of fever in the neutropenic paediatric oncology patients. In: Service CsHQHaH, ed. Children's Health Queensland Hospital and Health Service, 2012.
- [12] Haeusler GM, Mechinaud F, Daley A, et al. Antibiotic resistant Gram-negative bacteraemia in paediatric oncology patients – risk factors and outcome *Paediatr Infect Dis J.* 2013; **32**: 723-726.
- [13] Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. *J Clin Oncol.* 2017; **35**: 2082-2094.
- [14] Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; **42**: 377-381.
- [15] Haeusler G, Sung L, Ammann R, Phillips B. Management of fever and neutropenia in paediatric cancer patients: room for improvement? *Curr Opin Infect Dis.* 2015; **28**: 532-538.
- [16] Lingaratnam S, Slavin MA, Mileschkin L, et al. An Australian survey of clinical practices in management of neutropenic fever in adult cancer patients 2009. *Int Med J.* 2011; **41**: 110-120.
- [17] Terico A, Gallagher J. Beta-lactam hypersensitivity and cross-reactivity. *J Pharm Pract.* 2014; **27**: 530-544.
- [18] Trubiano J, Leung V, Chu M, Worth L, Slavin M, Thursky K. The impact of antimicrobial allergy labels on antimicrobial usage in cancer patients. *Antimicrob Resist Infect Control.* 2015; **4**.
- [19] Robinson PD, T. L, Phillips R, Dupuis LL, Sung L. Strategies for empiric management of pediatric fever and neutropenia in patients with cancer and

hematopoietic stem-cell transplantation recipients: A systematic review of randomized trials. *J Clin Oncol*. 2016; **34**: 2054-2060.

[20] Cometta A, Kern W, De Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis*. 2003; **37**: 382-389.

[21] Morgan J, Cleminson J, Atkin K, Stewart L, Phillips R. Systematic review of reduced therapy regimens for children with low risk febrile neutropenia. *Support Care Cancer*. 2016; **24**: 2651-2660.

[22] Teuffel O, Amir E, Alibhai SMH, Beyene J, Sung L. Cost-effectiveness of outpatient management for febrile neutropenia in children with cancer. *Pediatrics*. 2011; **127**: e279-286.

[23] Orme L, Babl F, Barnes C, Barnett P, Donath S, Ashley D. Outpatient versus inpatient IV antibiotic management for pediatric oncology patients with low risk febrile neutropenia: a randomised trial. *Pediatr Blood Cancer*. 2014; **61**: 1427-1433.

[24] Haeusler G, Phillips R, Lehrnbecher T, Thursky K, Sung L, Ammann R. Core Outcomes and Definitions for Pediatric Fever and Neutropenia Research: A Consensus Statement From an International Panel. *Pediatr Blood Cancer*. 2015; **62**: 483-489.

[25] Binz P, Bodmer N, Leibundgut K, Teuffel O, Niggli FK, Ammann RA. Different Fever Definitions and the Rate of Fever and Neutropenia Diagnosed in Children With Cancer: A Retrospective Two-Center Cohort Study. *Pediatr Blood Cancer*. 2012; **60**: 799-805.

[26] Haeusler G, Carlesse F, Phillips R. An updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment of fever during neutropenia in children with cancer. *Pediatr Infect Dis J*. 2013; **32**: e390-396.

Table 1. Clinical scenario, specific management areas explored and risk status allocated by the steering group for each case

Case 1	Clinical scenario: A 10 year old girl with standard-risk ALL presents with fever. She is receiving maintenance chemotherapy (daily 6-mercaptopurine, weekly methotrexate and monthly vincristine and steroid). On day 9 post vincristine and steroid her absolute neutrophil count is $0.3 \times 10^9/L$ (normal haemoglobin and platelet count) and she has a tympanic temperature measurements of $38.6^\circ C$. She is not clinically septic, has no history of rigors and no focal signs or symptoms of infection. She has a portacath in situ and no history of drug allergies
	Areas explored: risk-status, treatment setting (inpatient versus ambulatory), empiric antibiotics (type and timing) and antibiotic duration including intravenous-oral switch.
	Risk allocation by steering group: Low risk
Case 2	Clinical scenario: A 14 year old boy with relapsed AML and recent re-induction treatment with IDA-FLAG (UK MRC protocol: idarubicin, fludarabine, cytarabine, G-CSF) presents to the emergency department with a temperature of $38.9^\circ C$. On examination he is drowsy and has a heart rate of 130 bpm (normal 70-100 bpm) and a systolic blood pressure of 110 mmHg. He has oral mucositis but no other focus for infection. A total white cell count from earlier that day is $0.1 \times 10^9/L$. He has no drug allergies. At 48 hours you are notified: a) the patient has an <i>Escherichia coli</i> bacteraemia that is sensitive to piperacillin-tazobactam, is afebrile, clinically stable and repeat blood culture is negative; or (b) the patient has a negative blood culture, is febrile but clinically stable; or (c) the patient has a negative blood culture, is afebrile and clinically stable.
	Areas explored: risk status, empiric antibiotics (type and timing), antibiotic allergy, indications for dual empiric therapy and glycopeptide and aminoglycoside duration beyond 48 hours.
	Risk allocation by steering group: High risk
Case 3	Clinical scenario: A four-year-old girl with stage 4 neuroblastoma presents to the emergency department with fever and vomiting. She completed vincristine, doxorubicin and cyclophosphamide 10 days previously. On examination she has a temperature of $39^\circ C$, heart rate of 125 bpm (normal 80-130 bpm), normal blood pressure, oxygen saturations 98% and no clear focus for infection. Her full blood

	count is pending. She has a double lumen Broviac in situ.
	Areas explored: risk status, empiric antibiotics (timing), FN investigations and factors contributing to delayed first dose antibiotic
	Risk allocation by steering group: High risk

Table 2. Participant demographics

	No. of respondents (%) N=104
Specialty	
Haematology/Oncology	45 (43.3)
Haematology	3 (2.9)
Oncology	21 (20.2)
Infectious diseases	18 (17.3)
Emergency medicine	5 (4.8)
General paediatrics	8 (7.7)
Pharmacy	3 (2.9)
Other	1 (1.0)
Clinical role	
Head of unit	6 (5.8)
Consultant	49 (47.1)
Fellow/Registrar	18 (17.3)
Resident/Intern	1 (1.0)
Nurse practitioner	1 (1.0)
Registered nurse	19 (18.3)
Pharmacist	4 (3.8)
Other	6 (5.8)
Region	
Victoria	28 (26.9)
New South Wales	41 (39.4)
Queensland	15 (14.4)
Northern Territory	2 (1.9)
Western Australia	5 (4.8)
South Australia	1 (1.0)
Tasmania	1 (1.0)
New Zealand	11 (10.6)

Affiliation†	
ANZCHOG	70
ANZPID	19
CHA	9
PREDICT	4
Unknown	10

† 7 people had more than 1 affiliation (PREDICT/CHA, 3; ANZPID/CHA, 1; ANZCHOG/ANZPID, 1; ANZCHOG/CHA, 1; ANZCHOG/ANZPID/CHA, 1)

Table 3. Definition of fever used by each respondent

	No. of respondents (%) N=104
Greater than or equal to 38.5°C once or greater than or equal to 38.0°C sustained over a 1 hour period	46 (44.2)
Greater than or equal to 38.0°C once	44 (42.3)
Greater than or equal to 38.5°C once	9 (8.6)
Greater than or equal to 38.3°C once or greater than or equal to 38.0°C sustained over a 1 hour period	2 (1.9)
Greater than 38.5°C or Temp > 38.0°C on two sequential occasions in a 12 hour period	1 (1)
Greater than 38.5°C or Temp > 38.0°C on two sequential occasions in a 12 hour period	1 (1)
Greater than 37.5 °C	1 (1)

Table 4. Proportion of respondents completing each case and risk assessment according to clinical specialty

	Haem/ onc	Infect dis	Emerg med	General paeds	Pharm/ other	Total, n (%†)
Case 1						
Respondents, n (%)	62 (66.7)	17 (18.3)	4 (4.3)	7 (7.5)	3 (3.2)	93 (89.4)
High risk, n	14	1	1	5	1	22
Low risk, n	46	16	3	2	1	68
Unsure, n	2	0	0	0	1	3
Case 2						
Respondents, n (%)	56 (67.5)	17 (20.5)	4 (4.8)	5 (6.0)	1 (1.2)	83 (79.8)
High risk, n	55	17	4	5	1	82
Low risk, n	0	0	0	0	0	0
Unsure, n	1	0	0	0	0	1
Case 3						
Respondents, n (%)	52 (65.8)	17 (21.5)	4 (5.1)	5 (6.3)	1 (1.3)	79 (76)
High risk, n	36	7	2	2	0	47
Low risk, n	14	9	1	3	1	28
Unsure, n	2	1	1	0	0	4

†Expressed as a percentage of the number of partial or complete responses received (n=104)

Table 5. Type of empiric antibiotic according to risk status

	Intravenous Antibiotic, n			Oral antibiotic, n	Type of antibiotic - Unsure, n
	Mono therapy	Dual therapy	Unsure		
Case 1 †					
High risk (n=22)	6	10	2	0	4
Low risk (n=68)	48	17	1	2	0
Unsure risk status (n=3)	0	2	0	0	1
Case 2 †					
High risk (n=82)	13	66	3	0	0
Unsure risk status (n=1)	0	0	0	0	1

†0 respondents assigned this case as low risk.

FIGURE LEGENDS

Figure 1. Factors guiding decision to use empiric antibiotic dual therapy over monotherapy

Figure 2. Factors guiding decision to add a glycopeptide to empiric antibiotic therapy (BC, blood culture; MRSA, methicillin-resistant *Staphylococcus aureus*; CVAD, central venous access device)

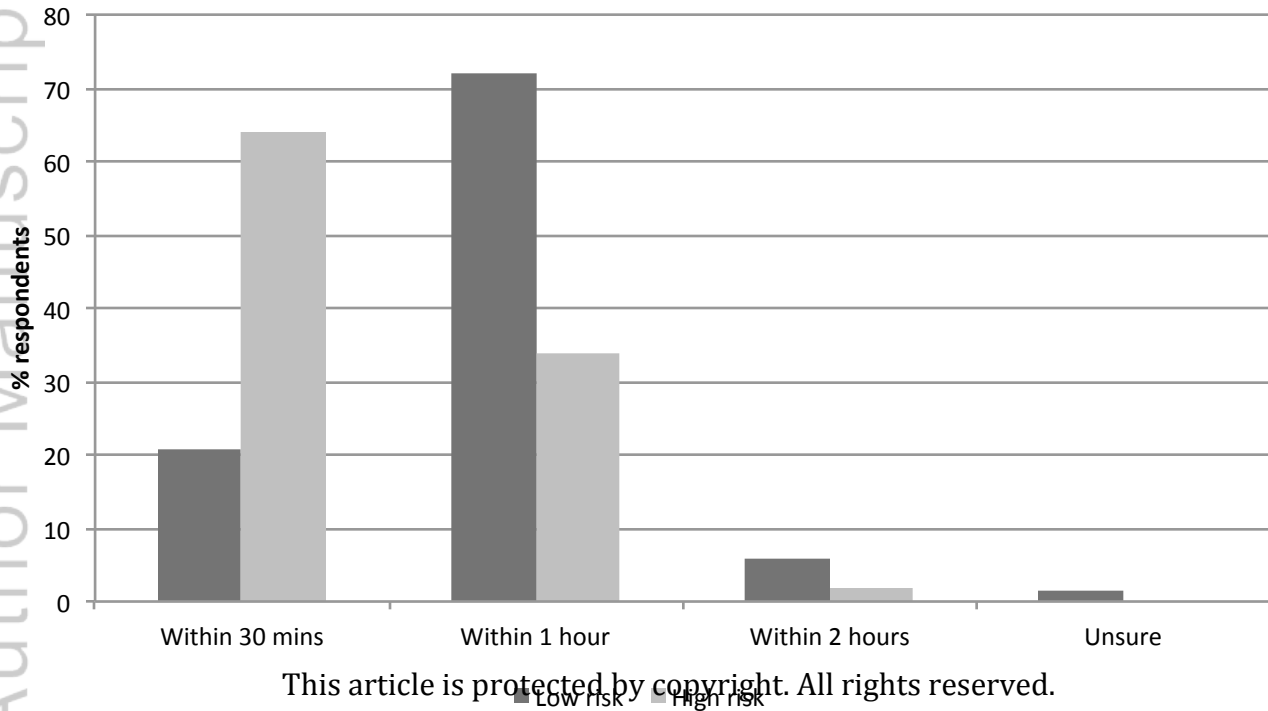
Figure 3. Recommended timing of first dose antibiotic according to allocated risk status for cases 1 and 2.

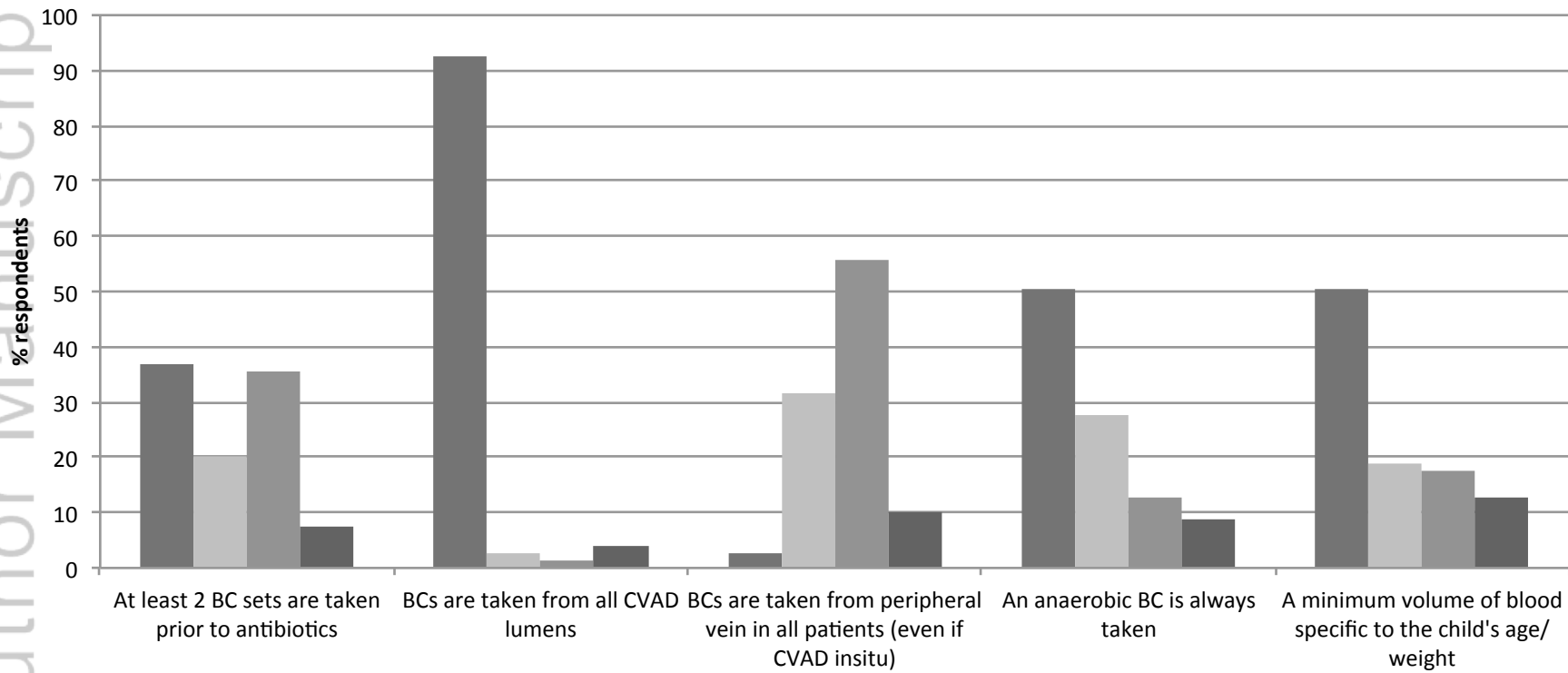
Figure 4. Recommended number, type and site of blood cultures taken as part of initial diagnostic workup of FN (BC, blood culture; CVAD, central venous access device)

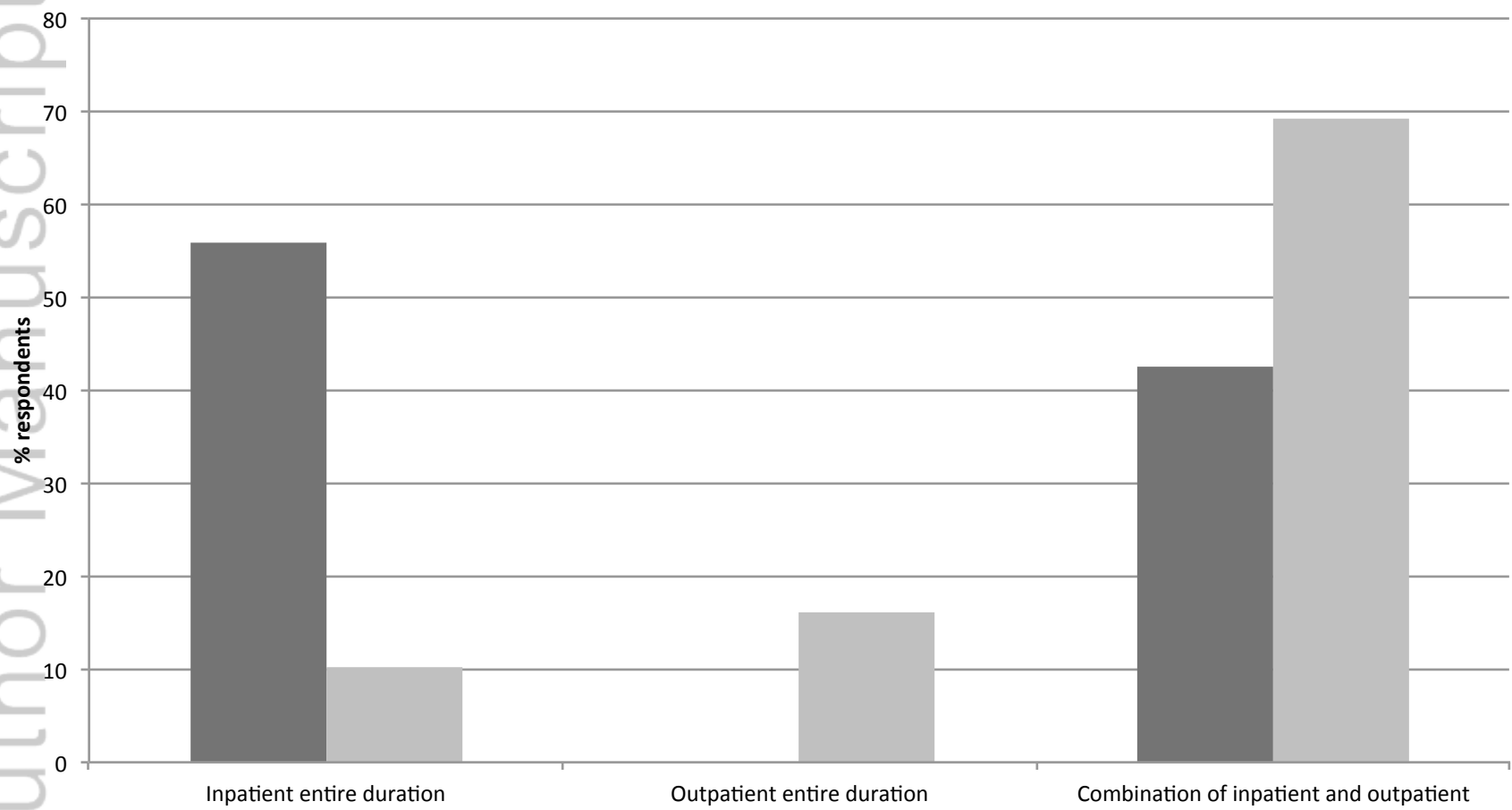
Figure 5. Factors guiding decision to switch patients with FN from intravenous to oral antibiotics

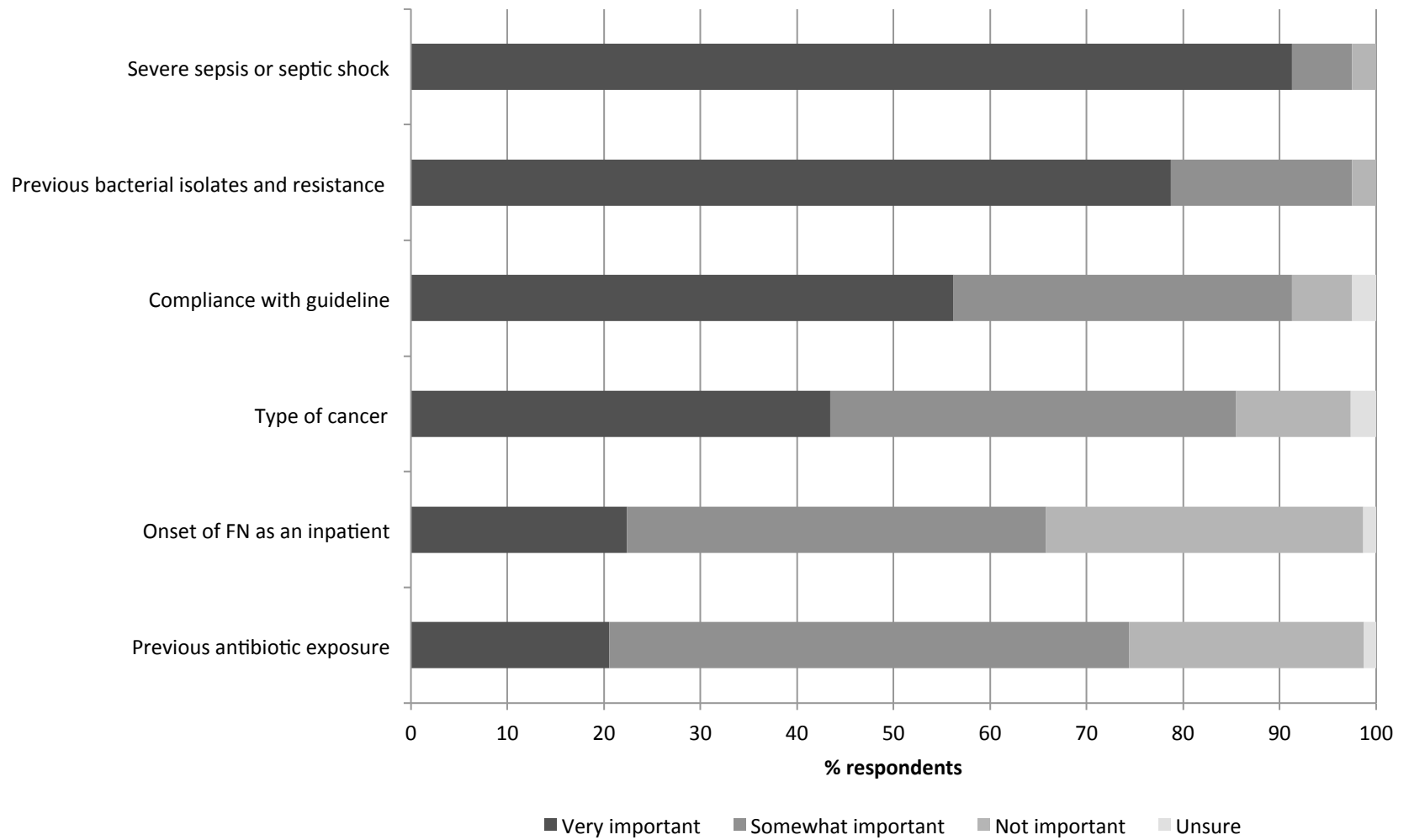
Figure 6. Clinician preference for treatment setting for patients identified as low risk in case 1

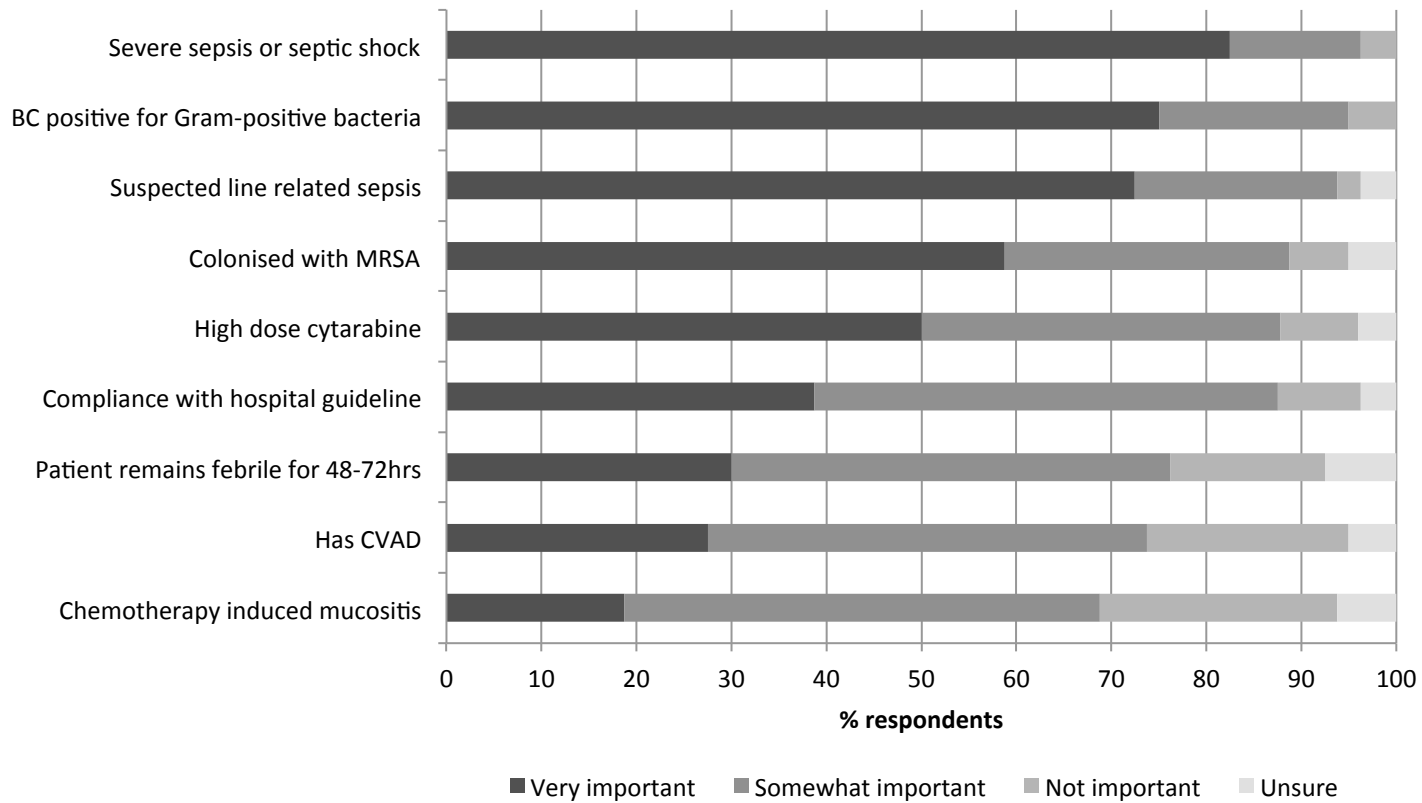
Figure 7. Factors guiding decision to manage patients with FN in ambulatory setting. (CDR, clinical decision rule)

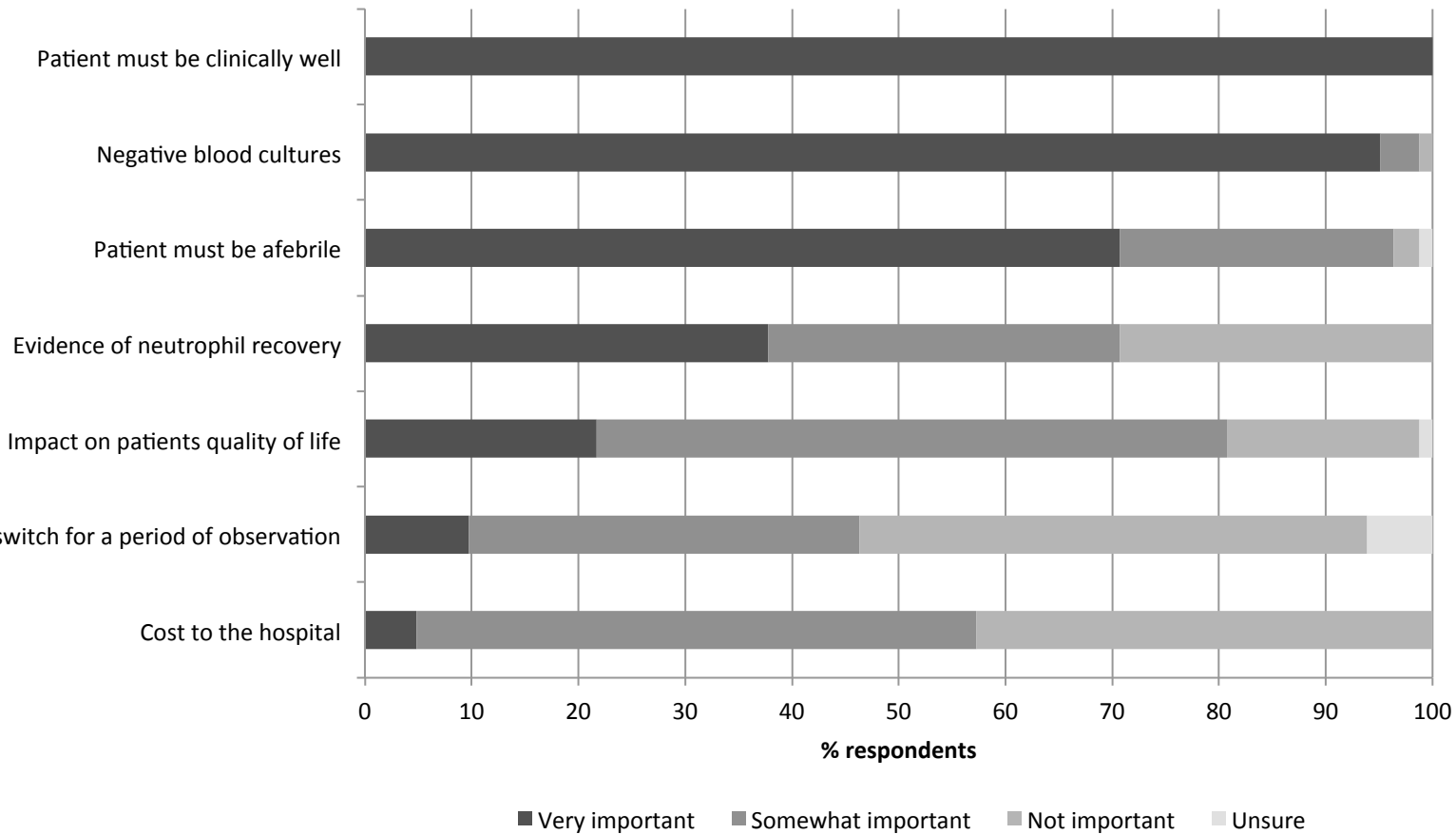


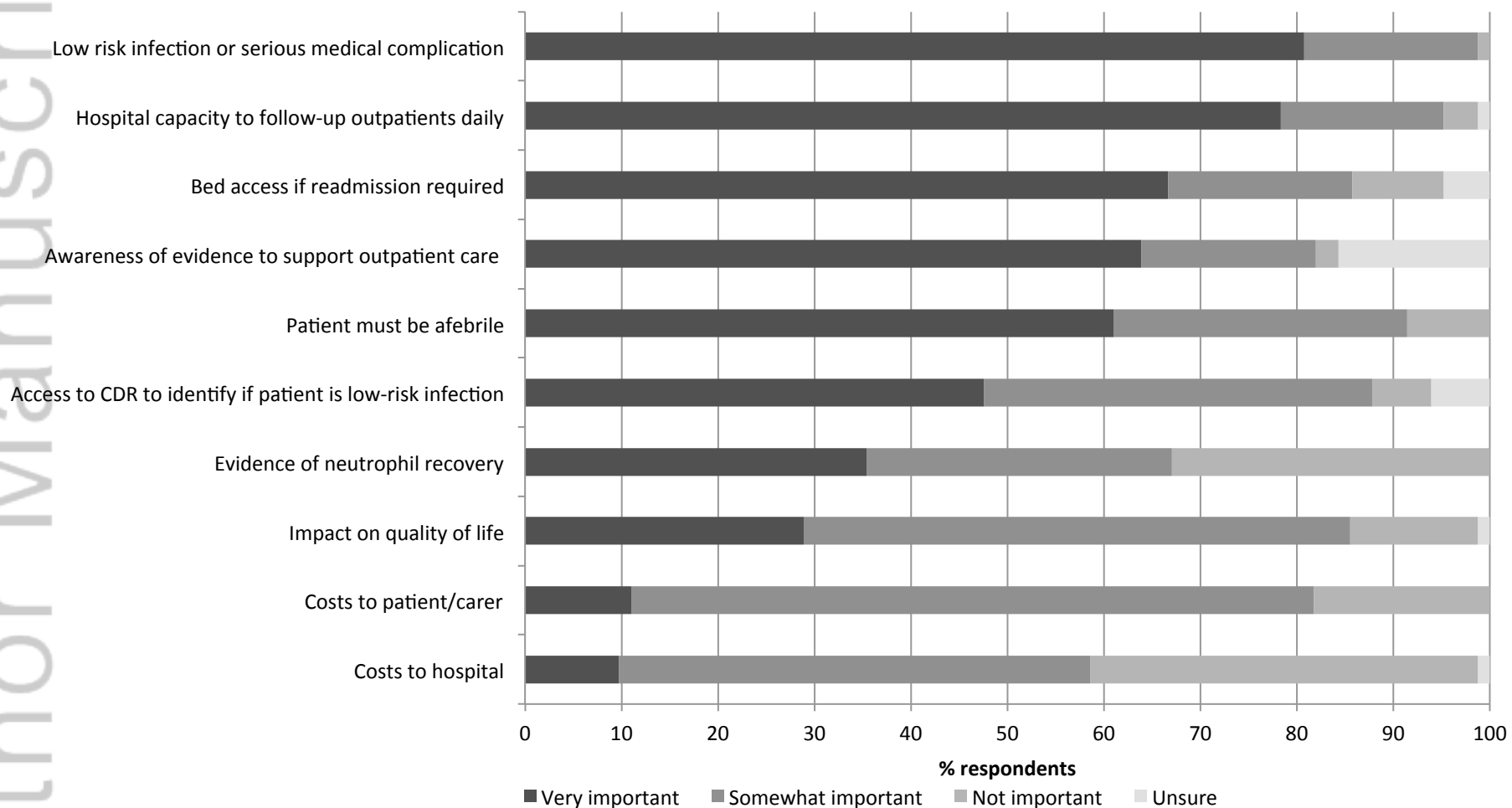












Management of fever and neutropenia in children with cancer: a survey of Australian and New Zealand practice

Original article

Gabrielle M Haeusler,¹⁻⁵ Monica A Slavin,^{1-3,6,7} Penelope A Bryant,⁸⁻¹⁰ Franz E Babl,^{8,9,11} Françoise Mechinaud^{8,12} and Karin A Thursky^{1-3,6,7,13}

1. Department of Infectious Diseases, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, Melbourne, Victoria, Australia, 3000

2. NHMRC National Centre for Infections in Cancer, Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia, 3010

3. Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia, 3010

4. The Paediatric Integrated Cancer Service, Parkville, Victoria, Australia, 3052

5. Department of Infection and Immunity, Monash Children's Hospital, Department of Paediatrics, Monash University, Clayton, Victoria, Australia, 3168

6. Department of Medicine, University of Melbourne, Parkville, Victoria, Australia, 3010

7. Victorian Infectious Diseases Service, The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia, 3000

8. Murdoch Children's Research Institute, Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia, 3052

9. Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Victoria, Australia, 3010

10. Infectious Diseases Unit, Royal Children's Hospital, Parkville, Victoria, Australia, 3052

11. Department of Emergency Medicine, Royal Children's Hospital, Parkville, Victoria, Australia, 3052

12. Children's Cancer Centre, Royal Children's Hospital, Parkville, Victoria, Australia, 3052

13. NHMRC National Centre for Antimicrobial Stewardship, The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia, 3000

Corresponding author: Dr Gabrielle M. Haeusler, Department of Infectious Diseases, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Australia, 3000, P: +61 3 9656 5853 F: +61 3 9656 1185, E: gabrielle.haeusler@petermac.org

Acknowledgments: We gratefully acknowledge following people for their helpful suggestions with survey content: Janelle Jones, David Ziegler, Thomas Walwyn, Frank Alvaro, Julia Clark, Heather Tapp, Luciano Dalla-Pozza, Peter Bradbeer and David Tickell. GMH was supported by a National Health and Medical Research Council post-graduate scholarship (GNT1056158). FEB was part funded by a grant from the Royal Children's Hospital Foundation, Melbourne, Australia and an NHMRC Practitioner Fellowship. There are no conflicts of interest to declare.