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ORIGINAL PAPER

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Prevention and management of febrile neutropenia in acute myeloid leukaemia and higher risk myelodysplastic syndrome: An international survey of current practice

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Summary

Febrile neutropenia causes substantial morbidity in acute myeloid leukaemia and higher risk myelodysplastic syndrome. We aimed to describe current practice and priorities for clinical trials in the prevention and management of febrile neutropenia across Australia/New Zealand (ANZ), the United Kingdom (UK), Canada and Europe. We performed an international survey of haematologists recruited via professional networks. Eighty-five unique hospitals were represented (ANZ = 20; Canada = 14; UK = 30; Europe = 21). Antibacterial prophylaxis was more commonly prescribed in Canada (79%) and the UK (83%) than in ANZ (30%) and Europe (48%, $p < 0.001$), and was prescribed more frequently to outpatients than inpatients. The most common empiric treatment was piperacillin–tazobactam monotherapy (66/84, 79%), with nurse-initiated antibiotic orders used in 35/84 (42%). Screening for multidrug-resistant organisms varied and was not usually used to direct antibiotic treatment. Antibiotic de-escalation was attempted in most institutions; for uncomplicated short-lived fever of unknown source, 39/85 (46%) reported ceasing antibiotics at 72 h and 68/85 (80%) within 7 days. For patients with bacteraemia, de-escalation strategies included narrowing spectrum, oral switch and cessation after defined duration. Most respondents (79/85, 93%) reported interest in recruiting for clinical trials. Clinical trials addressing practice variability in febrile neutropenia are needed, and are supported by haematologists.

KEYWORDS
antibiotics, febrile neutropenia, infection, prophylaxis, survey of practice

For affiliations refer to page 9.

BACKGROUND

Febrile neutropenia is a common complication of acute myeloid leukaemia (AML) and higher risk myelodysplastic syndrome (HR-MDS), contributing to induction-related mortality of 5%–10%.[1–5] Patients who survive infections experience delays in chemotherapy, side effects of antibiotics including antimicrobial resistance (AMR), hospital readmission, prolonged length of stay, increased healthcare costs, and reduced health-related quality of life.[6–8]

Considerable effort and resources are dedicated to managing febrile neutropenia, but uncertainty remains regarding best practice for prevention and treatment.[5,9–11] Key areas of uncertainty relate to antimicrobial use, including febrile neutropenia prophylaxis, initial empirical treatment, screening for multidrug-resistant organisms (MDROs) and antibiotic de-escalation. International guidelines differ in their recommendations; for example, antimicrobial prophylaxis is routinely recommended in high-risk groups in North America, but not Australia/New Zealand (ANZ).[5,9–11] Previous surveys of clinical practice, including a global study in allogeneic stem cell transplant (alloSCT) recipients, demonstrate variation between and within jurisdictions,[12,13] but a dedicated survey of practice in AML/HR-MDS is lacking.

In addition, many patients with AML/HR-MDS now receive lower intensity treatment via venetoclax-based regimens and targeted therapies, often as outpatients (i.e. home-based or through an infusion centre). These patients have typically not been included in randomised controlled trials (RCTs) of febrile neutropenia prevention and treatment, nor captured in previous surveys of practice.[12,13] They represent an important emerging population for whom best practice is yet to be defined.

Collaborative international clinical trials are needed to inform best practice in febrile neutropenia in patients with AML/HR-MDS, including in emerging groups, and these trials should be informed by current practice and clinician priorities. We therefore aimed to describe approaches to prevention and management of febrile neutropenia in patients with AML and HR-MDS among haematologists in ANZ, Canada, the United Kingdom (UK) and Europe, including prophylaxis, empiric therapy, de-escalation and management of outpatients.

METHODS

Survey

A survey of practice in prevention and management of febrile neutropenia was developed by a group of haematologists, infectious diseases physicians and researchers with expertise in survey development and qualitative research. The survey was delivered in English, piloted by nine clinicians at nine different healthcare centres and edited for clarity.

Survey domains included presence of local protocols, antibiotic prophylaxis, empirical antibiotic choice, screening for MDROs, antibiotic de-escalation, outpatient management and interest in future clinical trials (survey material: Appendix S1). Survey delivery was via the platform Qualtrics. No incentive to participate was provided for respondents. The study was approved by Monash University Human Research Ethics Boards (MUHREC, project ID 44764).

Population

Consultant haematologists delivering chemotherapy to patients with AML/HR-MDS were invited to participate. A single unique response per institution was sought, and respondents were asked to describe typical practice in their hospital.

Data collection took place in ANZ, Canada and the UK from November 2024 to July 2025. Invitations were sent through professional bodies (the Australasian Leukaemia Lymphoma Group, the United Kingdom AML Research Network, and Myelo-CAN), as well as via professional networks, invitations at scientific meetings and snowballing. Snowballing refers to the practice of encouraging participants to forward the invitation to colleagues who may be interested. For invitations sent via professional bodies, one reminder was sent after 4 weeks. Preliminary results were presented at an international conference (European Haematology Association, June 2025) in poster form, with display of a QR code (Quick Response code) to invite participation from conference attendees. If more than one response was received from the same institution, the first complete response was included. Incomplete survey responses, defined as <50% of questions answered, were excluded. Consent was implied by completing any part of the survey.

Statistical analysis

Descriptive analyses were performed. Absolute numbers, rates and missing data were reported for all variables. Denominator data were not collected due to the mechanism of survey distribution. Categorical variables were compared using chi-squared or Fisher's exact test, as appropriate. A p-value ≤0.05 was considered statistically significant.

RESULTS

Study participants

One hundred and five responses were received between November 2024 and July 2025. Twenty responses were excluded (jurisdiction not reported or not included in the study, $n = 2$; incomplete survey with insufficient response data, $n = 8$; duplicate responses from the same centre, $n = 10$).

TABLE 1 Respondent characteristics and neutropenic fever protocols.

	ANZ ($n=20$)	Canada ($n=14$)	UK ($n=30$)	Europe ($n=21$)	Total ($n=85$)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Institution characteristics					
High-intensity chemotherapy delivered to patients with AML/HR-MDS	19 (95%)	13 (93%)	27 (90%)	20 (95%)	79 (93%)
Allogeneic stem cell transplants performed	9 (45%)	9 (64%)	12 (40%)	12 (57%)	42 (49%)
High-intensity chemotherapy delivered to outpatients with AML/HR-MDS	14 (71%)	9 (64%)	19 (62%)	3 (12%)	43 (53%)
FN protocols					
FN protocol is present in this institution	20 (100%)	12 (86%)	30 (100%)	21 (100%)	83 (98%)
Respondent considers the FN protocol is easy to access and clinicians are aware of it	20 (100%)	8 (67%)	30 (100%)	20 (96%)	78 (94%)
FN protocol contains guidance on the following					
Prophylaxis	6 (30%)	4 (33%)	17 (57%)	14 (67%)	41 (48%)
Immediate management	20 (100%)	12 (100%)	30 (100%)	21 (100%)	83 (98%)
Antibiotic de-escalation	8 (40%)	4 (33%)	13 (43%)	11 (52%)	36 (42%)
Antibiotic cessation	10 (50%)	5 (42%)	10 (33%)	12 (57%)	37 (44%)
Other[a]	1 (5%)	0 (0%)	0 (0%)	1 (5%)	2 (2%)
Neutropenia threshold used to define 'febrile neutropenia'					
$<1.0\times10^9$ cells/L	17 (85%)	6 (50%)	23 (77%)	5 (24%)	52 (61%)
$<0.5\times10^9$ cells/L	2 (10%)	4 (33%)	5 (17%)	16 (76%)	28 (61%)
Other	1 (5%)	1 (8%)	2 (7%)	0 (0%)	4 (5%)
Don't know	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (1%)

Abbreviations: AML/HR-MDS, acute myeloid leukaemia/higher grade myelodysplastic syndrome; ANZ, Australia and New Zealand; FN, febrile neutropenia; UK, United Kingdom.

[a]Other: Two respondents reported their institutional protocol included guidance on diagnostics and escalation for patients with persistent fever.

Responses from 85 unique institutions were included in the final analysis, located in ANZ ($n=20$), Canada ($n=14$), the UK ($n=30$) and Europe ($n=21$). European respondents were from institutions in Germany ($n=10$), Belgium ($n=2$), France ($n=2$) and one institution each from the Czech Republic, Finland, Italy, Lithuania, the Netherlands, Sweden and Switzerland.

Among participating institutions, 79/85 (93%) reported delivering high-intensity chemotherapy, such as 7 + 3 induction or high-dose cytarabine consolidation, including 45/85 (53%) that delivered high-intensity chemotherapy to outpatients. 42/85 (49%) were alloSCT centres (Table 1).

Febrile neutropenia protocols

Febrile neutropenia protocols were present in 83/85 (98%) of represented institutions (Table 1). Almost all respondents who had an institutional protocol reported that it was easy to access and had good institutional awareness (94%; 78/83). Reported awareness of protocols was 100% in ANZ and the UK and 96% in Europe. In Canada, 10/12 (83%) reported that there was good awareness of the febrile neutropenia protocol in their institution, in addition to two respondents who reported no protocol present.

Neutropenia definitions in local protocols were reported as $<1.0\times10^9$ cells/L (51/85, 61%) or $<0.5\times10^9$ cells/L (27/85, 33%), with the lower cut-off more frequently used in Europe (16/21, 76%) compared to ANZ, Canada or the UK. All institutional febrile neutropenia protocols included guidance on immediate management of febrile neutropenia (83/83, 100%), whereas fewer than half included guidance on prophylaxis (41/83, 49%), de-escalation (36/83, 43%) and antibiotic cessation (37/83, 45%).

Prophylaxis of febrile neutropenia

Use of antibacterial prophylaxis varied by country, chemotherapy intensity and inpatient/outpatient status (Figure 1). Prescription of prophylaxis for febrile neutropenia in one or more subgroups of patients was reported in 52/85 respondents (61%) and was more common in Canada (79%) and the UK (83%) compared to ANZ (30%) or Europe (48%, $p<0.001$).

For patients receiving high-intensity chemotherapy as inpatients, 30/85 (35%) of respondents reported routine antibacterial prophylaxis, while 41% (35/85) reported prescribing prophylaxis to outpatients receiving high-intensity therapy. For patients receiving reduced intensity chemotherapy, 25%

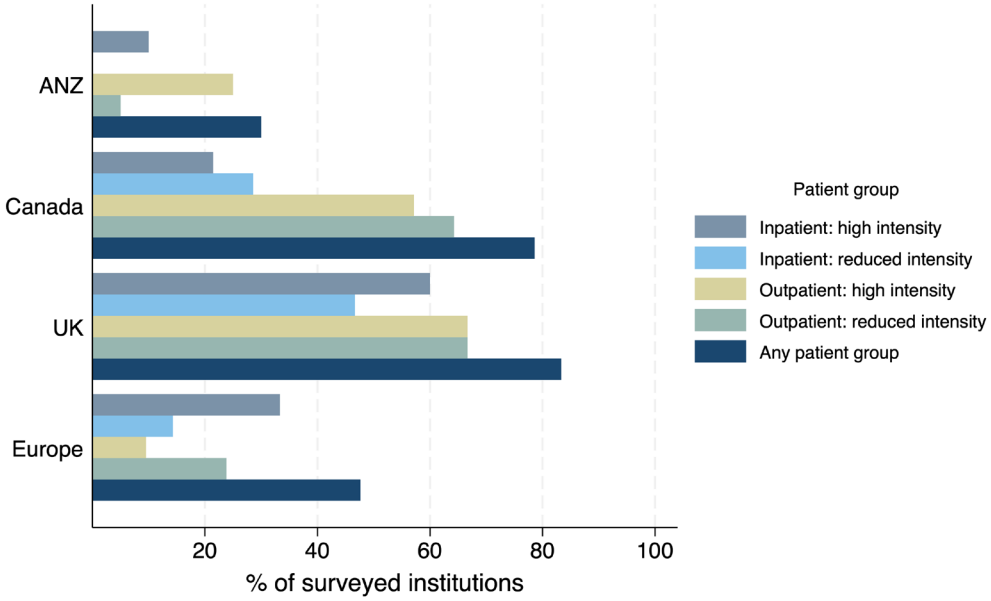

FIGURE 1 Routine prescription of antibiotic prophylaxis for febrile neutropenia in specific patient groups. ANZ, Australia and New Zealand; UK, United Kingdom.

of respondents (21/85) reported prescribing prophylaxis, compared to 41% (35/85) for outpatients (Table 2).

The prophylaxis agent used was a quinolone antibiotic in all but three centres (49/52, 94%). No centres reported use of non-absorbable antibiotics/oral decontamination.

Initial management of febrile neutropenia

In all regions, piperacillin–tazobactam monotherapy was the most common empiric antibiotic for febrile neutropenia without haemodynamic instability (66/84, 79%), followed by piperacillin–tazobactam plus aminoglycoside (7/84, 8%) and cefepime (7/84, 8%). Only 2% (2/84) of respondents reported prescribing empirical carbapenems. Empiric cefepime was more commonly reported in Europe ($n = 6$, 29% of all European centres, spread across six countries, $p = 0.03$).

A pre-documented 'fever plan' (i.e. a predetermined antibiotic plan specific to the patient, to be administered in the event of a fever) was reported in 43/84 (51%) of institutions and was more common in European centres (16/21 centres, 76%). In addition, 35/84 respondents (42%) reported using pre-prescribed antibiotics for febrile neutropenia, with antibiotics to be administered by nursing staff in the event of a fever, while awaiting medical review, with no difference between regions (Table 2).

Screening for MDRO colonisation varied between centres according to the specific organism(s) screened (Table 2). Overall, 56/85 (66%) of respondents reported screening for one or more MDRO. However, only 35/56 (63%) respondents reported that empiric antibiotic choices were adjusted based on screening, while 8/56 (14%) reported no adjustment and 11/56 (20%) reported variable practice depending on clinical status and advice from microbiology. Overall, screening was less common in ANZ with 11/20 (55%) respondents reporting no screening. In addition, a minority of respondents (26/85, 31%) reported receiving regular information about local resistance rates in their centre, and most were unable to estimate resistance rates for specific organisms (Table S1).

Antibiotic de-escalation and cessation

Overall, most respondents reported attempts at antibiotic de-escalation, such as narrowing of spectrum, oral switch or early antibiotic cessation at their institution (Table 3).

For patients with *resolved fever of unknown source and no positive cultures*, 39/79 (49%) respondents reported typically ceasing antibiotics within 72 h and 68/79 (86%) reported ceasing within 7 days.

For patients with *bloodstream infection* (*BSI*) *with positive blood cultures for a clinically significant organism*, who were clinically stable with resolved fever, 54/76 (71%) reported narrowing antibiotic spectrum, 4/76 (5%) switched to oral antibiotics and 18/76 (24%) continued broad-spectrum antibiotics until neutrophil recovery. For patients with *positive blood cultures for a skin or mouth commensal organism*, de-escalation was less common, with 39/74 (53%) continuing broad-spectrum therapy until neutrophil recovery.

For patients who *completed a 'standard' course of antibiotics for BSI* (e.g. *10–14 days*), with no concern for persistent source, but who remain neutropenic, most respondents reported ceasing antibiotics (41/79, 52%) or changing to prophylaxis (26/79, 33%), with 4/79 (5%) continuing to neutrophil count recovery.

There were statistically significant differences between regions in reported approaches to de-escalation, for example, with Canadian respondents more frequently reporting continued broad-spectrum antibiotics compared to other regions (Table 3).

TABLE 2 Prophylaxis and empiric treatment of febrile neutropenia.

	ANZ ($n=20$)	Canada ($n=14$)	UK ($n=30$)	Europe ($n=21$)	Total ($n=85$)	p
Prophylaxis						
Prophylaxis of FN is prescribed in the following scenarios						
Inpatients, high-intensity chemotherapy	2 (10%)	3 (21%)	18 (60%)	7 (33%)	30 (35%)	0.002
Inpatients, reduced intensity chemotherapy	0 (0%)	4 (29%)	14 (47%)	3 (14%)	21 (25%)	0.001
Outpatients, high-intensity chemotherapy	5 (25%)	8 (57%)	20 (67%)	2 (10%)	35 (41%)	<0.001
Outpatients, reduced intensity chemotherapy	1 (5%)	9 (64%)	20 (67%)	5 (24%)	35 (41%)	<0.001
Any (one or more) patient groups	6 (30%)	11 (79%)	25 (83%)	10 (48%)	52 (61%)	<0.001
Prophylaxis agent prescribed						<0.001
Levofloxacin	0 (0%)	7 (50%)	1 (3%)	1 (5%)	9 (11%)	
Ciprofloxacin	3 (50%)	2 (14%)	19 (63%)	8 (38%)	32 (38%)	
Other	3 (15%)	2 (21%)	3 (10%)	1 (5%)	9 (11%)	
Non-absorbable antibiotics/oral decontamination prescribed	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Initial treatment of FN						
First-line empiric antibiotics used for FN, in patients with no haemodynamic compromise						0.03
Piperacillin–tazobactam	17 (85%)	10 (71%)	24 (80%)	15 (71%)	66 (78%)	
Piperacillin–tazobactam plus aminoglycoside[a]	2 (10%)	1 (7%)	4 (13%)	0 (0%)	7 (8%)	
Cefepime	1 (5%)	0 (0%)	0 (0%)	6 (29%)	7 (8%)	
Carbapenem	0 (0%)	1 (7%)	0 (0%)	0 (0%)	1 (1%)	
Carbapenem plus aminoglycoside[a]	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (1%)	
Other/unknown	0 (0%)	2 (14%)	1 (3%)	0 (0%)	3 (3%)	
Use of predocumented fever plan for FN	10 (50%)	5 (36%)	12 (40%)	16 (76%)	43 (51%)	0.07
Use of pre-prescribed antibiotics for FN	7 (35%)	4 (29%)	14 (47%)	10 (48%)	35 (41%)	0.57
Routine MDRO screening performed						
MRSA	7 (35%)	13 (93%)	18 (60%)	14 (67%)	52 (61%)	0.01
ESBL	8 (40%)	5 (36%)	8 (27%)	15 (71%)	36 (42%)	0.01
CRO	7 (35%)	3 (21%)	13 (43%)	11 (52%)	34 (40%)	0.42
VRE	9 (45%)	10 (71%)	8 (27%)	14 (67%)	41 (48%)	0.01
No MDRO screening	11 (55%)	1 (7%)	7 (23%)	5 (24%)	24 (28%)	0.02
Other/unknown MDRO screening[b]	2 (11%)	0 (0%)	7 (24%)	1 (5%)	10 (12%)	
If screening is performed, is the empiric antibiotic choice adjusted in the event of FN? (n = centres where any screening is performed)	($n=9$)	($n=13$)	($n=18$)	($n=16$)	($n=56$)	0.08
Yes	4 (44%)	6 (46%)	11 (61%)	14 (88%)	35 (63%)	
Sometimes/it depends	1 (11%)	3 (23%)	5 (28%)	2 (13%)	11 (20%)	
No	3 (33%)	3 (23%)	2 (11%)	0 (0%)	8 (14%)	
Don't know	1 (11%)	1 (8%)	0 (0%)	0 (0%)	2 (4%)	
Regular information provided about local MDRO epidemiology in your institution	4 (20%)	3 (21%)	10 (33%)	9 (42%)	26 (31%)	0.59

Abbreviations: ANZ, Australia and New Zealand; CRO, carbapenem-resistant organism; ESBL, extended spectrum beta-lactamase; FN, febrile neutropenia; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; UK, United Kingdom; VRE, vancomycin resistant enterococci.

[a]Aminoglycoside choice with piperacillin–tazobactam: amikacin, $n=3$; gentamicin, $n=3$; tobramycin, $n=1$. Aminoglycoside with carbapenem: gentamicin ($n=1$).

[b]Includes targeted screening in select patient groups, for example, recent overseas travel.

Management of outpatients with febrile neutropenia

For patients with AML/HR-MDS managed in the community, a minority of respondents reported that providing emergency oral antibiotics to take in the event of a fever while awaiting medical review (Table 4). In total, 21% (18/85) prescribed emergency antibiotics for patients treated with high-intensity chemotherapy, 16/85 (19%) prescribed emergency antibiotics for patients receiving reduced intensity chemotherapy, 67% (57/85) did not prescribe emergency antibiotics to outpatients and 11 (13%) did not prescribe any outpatient chemotherapy. There were no significant differences in this practice between regions. Among those who

reported prescribing emergency antibiotics, the prescribed antibiotics included amoxycillin–clavulanate (5/18, 28%), a quinolone (5/18, 28%) or both (6/18, 33%).

For outpatients who develop febrile neutropenia and present to an emergency department, respondents reported a range of management strategies, ranging from direct discharge from the emergency department for home-based care to inpatient admission until neutrophil recovery, with no significant difference between regions (Table 4). Decision to discharge most frequently depended on specific circumstances (35/85, 41%), including patient comorbidities, living situation (e.g. rural or regional) and availability of outpatient services in services/programmes. It was uncommon to make these assessments using a risk score such as that from the Multinational Association for Supportive Care in Cancer (MASCC) (23%, 18/85) or the Clinical Index of Stable Febrile Neutropenia (1/85, 1%).

Interest in clinical trials

Respondents reported interest in recruiting patients for clinical trials of prophylaxis, empiric treatment and de-escalation, with 79/85 (93%) interested in recruiting patients for randomisation for one or more clinical trials (Table 5). Interest was highest for trials of antibiotic de-escalation (64/85, 75%) and outpatient prophylaxis (60/85, 71%). Interest in trials of inpatient prophylaxis was lower in regions where prophylaxis is currently less frequently used (ANZ and Europe, $p = 0.03$).

Differences in centres performing allogeneic stem cell transplantation

A sensitivity analysis was performed comparing responses from institutions performing alloSCT versus those that do not (non-alloSCT). Overall responses were similar between alloSCT and non-alloSCT centres (Table S2). There was no significant difference in the reported presence of febrile neutropenic protocols, choice of empiric antibiotics, use of pre-planned or precharted antibiotics or antibiotic de-escalation. Overall prescription of antibacterial prophylaxis in one or more patient groups was similar (alloSCT centres 25/42, 60% vs. non-alloSCT centres 27/43, 63%, $p = 0.76$). However, prescription of antibacterial prophylaxis to inpatients was more common in non-alloSCT (7/42, 17% vs. 23/43, 53%, $p < 0.01$). In addition, MDRO screening rates were higher in alloSCT centres, but adjustment of antibiotic prescribing in response to screening was not significantly different. There was no difference in respondent willingness to recruit patients to clinical trials.

DISCUSSION

This international survey of febrile neutropenia management in AML/HR-MDS included 85 unique healthcare organisations and identified wide variation in clinical practice, reflecting deficiencies of the current evidence base for management of febrile neutropenia and high interest in future clinical trials to address uncertainty.

Several areas of management require specific mention. Antibacterial prophylaxis use varied by country and was more commonly used in outpatients and those receiving lower intensity chemotherapy. This variation is likely driven by differences in international guidelines, and a lack of recent and targeted clinical trial evidence, particularly a lack of evidence specific to novel therapies and reduced intensity regimens.[5,14,15] The European Council for Infections in Leukaemia guidelines recommended a 'risk–benefit' assessment to guide use of prophylaxis,[16] while routine use is not recommended in ANZ.[15] In contrast, guidelines from the United States recommend routine antibacterial prophylaxis for patients with prolonged neutropenia.[14] Previous meta-analyses have reported a reduction in fevers and BSIs in patients receiving quinolone prophylaxis, but without mortality improvement[17]; however, the most recent large-scale RCT in AML in 2005 did not include contemporary patient groups such as outpatients and those receiving reduced intensity chemotherapy. We observed higher (though still variable) use of prophylaxis in these groups, likely reflecting this clinical uncertainty. However, our data do not capture differences in prophylaxis prescribing in specific subgroups of patients (e.g. specific chemotherapy regimens, or conditioning for alloSCTs). Importantly, in regions where antibiotic prophylaxis was less common, fewer respondents reported willingness to recruit patients for a randomised trial of prophylaxis for inpatients, whereas interest was higher for trials in outpatients. This may result from prioritisation of areas of clinical uncertainty and concerns around the potential to increase antimicrobial use. Finally, use of alternative prophylaxis such as narrower spectrum or topical/non-absorbable antibiotics was not reported, although this practice is occasionally reported in the United States and Europe.[18–21]

Regarding initial antibiotic choice for febrile neutropenia, piperacillin–tazobactam was reported in almost all centres in ANZ, UK and Canada. In contrast, cefepime was used in around a third of European centres and is the most frequently prescribed antibiotic for febrile neutropenia in the United States.[12,22] Both piperacillin–tazobactam and cefepime are listed as appropriate first-line treatment in international guidelines,[9,16,23] but debate remains as to which is optimal. Higher mortality in patients treated with cefepime was previously reported in meta-analyses, but may have been mediated through inadequate dosing,[24,25] while piperacillin–tazobactam has been associated with greater microbiome disruption, which itself is predictive of infection risk and overall mortality.[26–28] In addition, around half of surveyed haematologists reported using personalised febrile neutropenia treatment plans, such as preprescribed antibiotics, or directed therapy based on MDRO screening. However, these practices were inconsistent. Variation may reflect differences in local epidemiology (e.g. screening practices in jurisdictions where an outbreak has occurred), but there is also

TABLE 3 Antibiotic de-escalation and cessation.

	ANZ ($n=20$)	Canada ($n=14$)	UK ($n=30$)	Europe ($n=21$)	Total ($n=85$)	p
In a patient with isolated, short-lived fever (<24–48 h), with no positive microbiology results and no clear source of infection, who is otherwise well but remains neutropenic (ANC <1.0 × 10⁹ cells/L), how long are antibiotics continued after fever has resolved?						<0.001
≤72 h	11 (55%)	2 (14%)	16 (53%)	10 (48%)	39 (46%)	
≤7 days	8 (40%)	3 (21%)	11 (37%)	7 (33%)	29 (34%)	
>7 days	0 (0%)	1 (7%)	0 (0%)	2 (10%)	3 (4%)	
Until count recovery	0 (0%)	3 (21%)	0 (0%)	0 (0%)	3 (4%)	
Variable or unknown/missing	1 (5%)	3 (21%)	0 (0%)	1 (5%)	5 (6%)	
Missing	0 (0%)	2 (14%)	3 (10%)	1 (5%)	6 (7%)	
Scenario: a patient has febrile neutropenia (ANC <1.0 × 10⁹ cells/L) and is clinically stable. Vital signs are normal other than temperature. Blood cultures are positive for a clinically relevant bacterium other than mouth flora or skin flora and the organism is susceptible to a narrow(er) spectrum antibiotic (e.g. blood cultures are positive for Escherichia coli sensitive to ceftriaxone).						0.05
Change to narrower spectrum IV antibiotics (including if febrile and neutropenic)	3 (15%)	1 (7%)	14 (47%)	6 (29%)	24 (28%)	
Change to narrower spectrum IV antibiotics only once afebrile (including if neutropenic)	10 (50%)	9 (64%)	5 (17%)	6 (29%)	30 (35%)	
Change to oral antibiotics only once afebrile (including if neutropenic)	1 (5%)	0 (0%)	2 (7%)	1 (5%)	4 (5%)	
Continue broad spectrum antibiotics until neutrophil count recovery	6 (30%)	3 (21%)	4 (13%)	5 (24%)	18 (21%)	
Other	0 (0%)	0 (0%)	3 (10%)	2 (10%)	5 (6%)	
Missing	0 (0%)	1 (7%)	2 (7%)	1 (5%)	4 (5%)	
Scenario: a patient has febrile neutropenia (ANC <1.0 × 10⁹ cells/L) and is clinically stable. Vital signs are normal other than temperature. Blood cultures are positive for an organism that represents mouth flora (e.g. *Streptococcus mitis*) *or skin flora* (e.g. *Staphylococcus epidermidis*) *and no other organism.*						0.42
Change to narrower spectrum IV antibiotics (including if febrile and neutropenic)	2 (10%)	3 (21%)	5 (17%)	2 (10%)	12 (14%)	
Change to narrower spectrum IV antibiotics only once afebrile (including if neutropenic)	6 (30%)	6 (43%)	10 (33%)	5 (24%)	27 (32%)	
Change to oral antibiotics only once afebrile (including if neutropenic)	2 (10%)	0 (0%)	5 (17%)	1 (5%)	8 (9%)	
Continue broad-spectrum antibiotics until neutrophil count recovery	9 (45%)	4 (29%)	5 (19%)	9 (43%)	27 (32%)	
Other	1 (5%)	0 (0%)	3 (10%)	3 (14%)	7 (8%)	
Missing	0 (0%)	1 (7%)	2 (7%)	1 (5%)	4 (5%)	
Scenario: a neutropenic patient has recently had a positive blood culture and has completed a course of antibiotics that would generally be considered sufficient for this infection (e.g. *10–14 days*). *The patient remains clinically well and afebrile. They have no other indication to continue treatment (including no persistent source of infection), but they remain neutropenic (ANC <1.0 × 10⁹ cells/L). What is your usual course of action in this scenario?*						0.05
Cease antibiotics prior to neutrophil count recovery	14 (70%)	5 (36%)	11 (37%)	11 (52%)	41 (48%)	
Switch to oral antibiotics prior to neutrophil count recovery (if not usually on antibiotic prophylaxis)	3 (15%)	3 (21%)	1 (3%)	1 (5%)	8 (9%)	
Switch to prophylactic antibiotics prior to neutrophil count recovery (if usually on antibiotic prophylaxis)	1 (5%)	4 (29%)	14 (47%)	7 (33%)	26 (31%)	
Continue IV antibiotics until neutrophil count recovery	2 (10%)	1 (7%)	0 (0%)	1 (5%)	4 (5%)	
Other	0 (0%)	0 (0%)	2 (7%)	0 (0%)	2 (2%)	
Missing	0 (0%)	1 (7%)	2 (7%)	1 (5%)	4 (5%)	

Abbreviations: ANC, absolute neutrophil count; ANZ, Australia and New Zealand; UK, United Kingdom.

a lack of evidence to guide routine screening. Colonisation is known to increase the risk of MDRO BSIs, but routine screening-directed therapy lacks an evidence base and may be associated with increased antimicrobial exposure.[29]

Most respondents reported attempting antibiotic de-escalation in stable patients with febrile neutropenia, with only a minority continuing broad-spectrum intravenous antibiotics until neutrophil recovery. This was the case for patients with fever of unknown source and those with positive blood cultures for susceptible organisms. A range of strategies were reported, including oral switch, narrowing of spectrum and early cessation. Rates of antibiotic de-escalation

TABLE 4 Outpatient management of febrile neutropenia.

	ANZ (*n* = 20)	Canada (*n* = 14)	UK (*n* = 30)	Europe (*n* = 21)	Total (*n* = 85)	*p*
In which of the following, outpatient scenarios are emergency oral antibiotics prescribed to take in the event of a fever while awaiting medical review? (more than one answer possible)						
Patients receiving high-intensity outpatient chemotherapy	6 (30%)	1 (17%)	5 (29%)	6 (29%)	18 (21%)	0.30
Patients receiving reduced intensity outpatient chemotherapy	3 (15%)	1 (7%)	5 (17%)	7 (33%)	16 (19%)	0.22
No routine emergency antibiotics provided	11 (55%)	11 (79%)	22 (73%)	12 (57%)	57 (67%)	0.22
N/A, no outpatient chemotherapy prescribed	3 (15%)	2 (14%)	4 (13%)	2 (10%)	11 (13%)	0.96
Choice of emergency antibiotic agent						0.68
Amoxycillin–clavulanate monotherapy	1 (5%)	0 (0%)	2 (7%)	2 (10%)	5 (6%)	
Levofloxacin or ciprofloxacin monotherapy	3 (15%)	0 (0%)	1 (3%)	1 (5%)	5 (6%)	
Levofloxacin/ciprofloxacin plus amoxycillin–clavulanate	2 (10%)	1 (7%)	1 (3%)	2 (10%)	6 (7%)	
Other	0 (0%)	0 (0%)	0 (0%)	2 (10%)	2 (2%)	
NA/none prescribed	14 (70%)	13 (93%)	26 (87%)	14 (67%)	67 (79%)	
In patients who present to hospital with isolated FN, who are clinically stable with no identified source of infection, do you consider discharge for home-based management? (more than one answer possible)						
Consider discharge for home-based management, including direct from ED	1 (5%)	2 (14%)	3 (10%)	2 (10%)	8 (9%)	0.84
Consider discharge for home-based management, including prior to neutrophil recovery	7 (35%)	2 (14%)	7 (23%)	5 (24%)	21 (25%)	0.57
Discharge home only after neutrophil recovery	7 (35%)	5 (36%)	4 (13%)	8 (38%)	24 (28%)	0.16
Depends on other factors	8 (40%)	5 (36%)	15 (50%)	7 (33%)	35 (41%)	0.64
Use of dedicated risk score to guide discharge and home-based management of neutropenic fever[a]						0.04
MASCC	3 (15%)	3 (21%)	3 (10%)	9 (43%)	18 (23%)	
CISNE	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (1%)	
None	16 (80%)	6 (43%)	20 (67%)	9 (43%)	51 (65%)	
Don't know/other	0 (0%)	3 (21%)	4 (13%)	1 (5%)	8 (10%)	

Abbreviations: ANZ, Australia and New Zealand; CISNE, Clinical Index of Stable Febrile Neutropenia; ED, emergency department; FN, febrile neutropenia; MASCC, Multinational Association for Supportive Care in Cancer; UK, United Kingdom.

[a]Missing data excluded.

TABLE 5 Interest in future clinical trials.

	ANZ (*n* = 20)	Canada (*n* = 14)	UK (*n* = 30)	Europe (*n* = 21)	Total (*n* = 85)	*p*
Inpatient prophylaxis	9 (45%)	11 (79%)	23 (77%)	10 (48%)	53 (62%)	0.03
Outpatient prophylaxis	12 (60%)	12 (86%)	24 (80%)	12 (57%)	60 (71%)	0.13
Oral de-contamination (non-absorbable antibiotics)	7 (35%)	7 (50%)	20 (67%)	6 (29%)	40 (47%)	0.51
Empiric antibiotics	9 (45%)	6 (43%)	15 (50%)	9 (43%)	39 (46%)	0.95
De-escalation	17 (85%)	11 (79%)	20 (67%)	16 (76%)	64 (75%)	0.03
Outpatient management	10 (50%)	6 (43%)	17 (57%)	10 (48%)	43 (51%)	0.84
Other	3 (15%)	1 (7%)	5 (17%)	1 (5%)	10 (12%)	0.54

Note: Respondents were asked 'Would you be likely to recruit patients for a clinical trial investigating the following? (Tick all that apply)'.

Abbreviations: ANZ, Australia and New Zealand; UK, United Kingdom.

and cessation appear higher than previous studies and in other jurisdictions and patient groups. In a 2024 survey in the United States, 45% of respondents continued broad-spectrum antibiotics for patients with febrile neutropenia until neutrophil count recovery; in a European survey of alloSCT centres, only 36.6% discontinued antibiotics prior

to neutrophil recovery.[12,13] Areas of research uncertainty remain that might explain this variation. De-escalation aims to minimise antibiotic exposure and dose-dependent adverse events, but supporting evidence in AML/HR-MDS is limited. The 2017 How Long RCT provided supporting evidence for early discontinuation for patients with fever of unknown source, but included only a minority of patients with high-grade malignancies such as AML and did not include patients with positive blood cultures.[30] Studies of antibiotic duration for patients with bacteraemia, such as the BALANCE trial, have excluded severely immunocompromised patients.[31] In addition, de-escalation was the most popular topic for a future RCT, with three quarters of respondents expressing interest in enrolling patients.

Finally, the management of outpatients, and patients receiving novel therapies, emerged as areas of research need. A growing population of patients, including older individuals with multiple comorbidities, are now managed with reduced intensity venetoclax-based regimens, demethylating agents and targeted therapies.[32] Many receive treatment in the outpatient setting, while outpatient delivery of higher intensity regimens is also increasingly reported.[33] These groups have not been captured in previous surveys of practice and were not included in RCTs of antibacterial prophylaxis in AML, which themselves are all at least 20 years old.[12,13,34] Studies of outpatient febrile neutropenia including development of risk scores like MASCC have primarily focussed on patients with solid tumour malignancies, and scores were not derived or validated in high-risk patients with AML/HR-MDS.[35] This was reflected in low reported uptake of such scores in our survey. Patients with AML/HR-MDS who are managed as outpatients, including recipients of reduced intensity targeted therapies, represent important groups for whom best practice in febrile neutropenia prevention and management is not yet defined.

Overall, variation in practice regarding febrile neutropenia was reported both between and within regions. The pattern of responses were similar in both alloSCT centres and non-alloSCT centres, indicating that variation is unlikely to be explained solely by the patient mix and therapies offered in a given institution. Importantly, interest in clinical trials was high across all surveyed jurisdictions, including clinicians working in alloSCT centres.

This survey has several limitations. Our distribution strategy was intended to maximise participation through email invitation, snowballing and wide promotion, and we were therefore unable to collect denominator data and cannot report a response rate; as such, responses may be subject to bias. Specifically, individuals and institutions with an interest in antimicrobial stewardship may have been more likely to respond, resulting in biased reporting of antimicrobial use. Responses from Europe primarily represent Northern European countries where overall rates of AMR are low. Reported practice in these countries is not generalisable to Southern and Eastern Europe, due to differences in local epidemiology and microbiology.[13] Furthermore, we sought a single response from each institution, which limits capture of variation between clinicians within centres. Responses are subject to individuals' familiarity with, and interpretation of, their local protocols. Less protocolised elements of care, such as de-escalation and outpatient management, may be subject to individual judgement and responses do not necessarily indicate generalised institutional practice but represent a cross section of self-reported practice among consultant haematologists. In addition, some responses might reflect clinicians' 'ideal' course of action rather than actual practice, and our findings would be extended by a cross-sectional audit of prescribing. Finally, we specifically collected responses from consultant haematologists, aiming to characterise practice among the primary treating team. Other clinicians, including microbiologists, pharmacists, infectious diseases physicians and others, also advise on management of febrile neutropenia, and their input should also be explored in future studies. Strengths of the study include the piloting process, large number of responses and high completion rate. We achieved broad representation of 85 different healthcare services worldwide. To our knowledge, this is the most current survey of practice and the only one to specifically focus on AML/HR-MDS. The specific focus on high-risk patients with AML/HR-MDS is important to guide future clinical trials in this group.

CONCLUSION

Survey findings in febrile neutropenia management for patients with AML/HR-MDS highlight specific areas for further research, including outpatient antibiotic prophylaxis and antibiotic de-escalation, with practice variation, equipoise and enthusiasm for clinical trials in this area.

AUTHOR CONTRIBUTIONS

AM, JL, BLH, SJS and ZM were responsible for the study conception and plan. All authors were involved in refining and delivering the survey. AM was responsible for analysis of the results. All authors contributed in interpretation of results, drafting and revision of the manuscript.

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DATA AVAILABILITY STATEMENT

Access to survey data is restricted by the study's ethical approval. Requests for aggregate, de-identified data without site information may be considered on a case-by-case basis and can be addressed to the corresponding author.

ETHICS STATEMENT

This study was approved by Monash University Human Research Ethics Boards (MUHREC, project ID 44764).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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