[18F]FDG-PET-CT compared with CT for persistent or recurrent neutropenic fever in high-risk patients (PIPPIN): a multicentre, open-label, phase 3, randomised, controlled trial

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Summary

Background Management of neutropenic fever in high-risk haematology patients is challenging; there are often few localising clinical features, and diagnostic tests have poor sensitivity and specificity. We aimed to compare how [18F]flurodeoxyglucose ([18F]FDG)-PET-CT scans and conventional CT scans affected the guidance of antimicrobial management and the outcomes of patients with persistent or recurrent neutropenic fever.

Methods We did a multicentre, open-label, phase 3, randomised, controlled trial in two tertiary referral hospitals in Australia. We recruited adults aged 18 years or older who were receiving conditioning chemotherapy for haematopoietic stem-cell transplantation or chemotherapy for acute leukaemia and had persistent (>72 h) or recurrent (new fever beyond 72 h of initial onset interspersed with >48 h defervescence) neutropenic fever. Exclusion criteria were pregnancy, allergy to iodinated contrast, or estimated glomerular filtration rate of less than 30 mL/min. Patients were randomly assigned by computer-generated randomisation chart (1:1) to [18F]FDG-PET-CT or conventional CT. Masking was not possible because of the nature of the investigation. Scans were done within 3 days of random assignment. The primary endpoint was a composite of starting, stopping, or changing the spectrum (broadening or narrowing) of antimicrobial therapy—referred to here as antimicrobial rationalisation—within 96 h of the assigned scan, analysed per protocol. This trial is registered with clinicaltrials.gov, NCT03429387, and is complete.

Findings Between Jan 8, 2018, and July 23, 2020, we assessed 316 patients for eligibility. 169 patients were excluded and 147 patients were randomly assigned to either [18F]FDG-PET-CT (n=73) or CT (n=74). Nine patients did not receive a scan per protocol, and two participants in each group were excluded for repeat entry into the study. 65 patients received [18F]FDG-PET-CT (38 [58%] male; 53 [82%] White) and 69 patients received CT (50 [72%] male; 58 [84%] White) per protocol. Median follow up was 6 months (IQR 6–6). Antimicrobial rationalisation occurred in 53 (82%) of 65 patients in the [18F]FDG-PET-CT group and 45 (65%) of 69 patients in the CT group (OR 2·36, 95% CI 1·06–5·24; p=0·033). The most frequent component of antimicrobial rationalisation was narrowing spectrum of therapy, in 28 (43%) of 65 patients in the [18F]FDG-PET-CT group compared with 17 (25%) of 69 patients in the CT group (OR 2·31, 95% CI 1·11–4·83; p=0·024).

Interpretation [18F]FDG-PET-CT was associated with more frequent antimicrobial rationalisation than conventional CT. [18F]FDG-PET-CT can support decision making regarding antimicrobial cessation or de-escalation and should be considered in the management of patients with haematological diseases and persistent or recurrent high-risk neutropenic fever after chemotherapy or transplant conditioning.

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Introduction

Conditioning chemotherapy for allogeneic and autologous haematopoietic stem-cell transplantation (HSCT) and intensive chemotherapy for acute leukaemia are complicated by prolonged neutropenia, and high rates of neutropenic fever; sepsis; and infection.[1,2] Diagnostic approaches for neutropenic fever, including sample cultures and chest X-ray imaging, often fail to identify a cause, with persistent and recurrent neutropenic fever remaining common clinical scenarios (occurring in 15–50%).[3,4] Conventional CT is often used to localise a source of fever and rule out key diagnoses, such as invasive fungal disease, but has poor sensitivity and specificity.[5,6] Given the substantial risk of deterioration in the setting of untreated infection,[7,8] there is high reliance on empirical and often protracted antimicrobial therapy,[9] which is not aligned with best practice antimicrobial stewardship. Markers to guide antimicrobial therapy escalation and de-escalation in persistent neutropenic fever are urgently needed to avoid prolonged exposure,

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Research in context

Evidence before this study

One randomised trial has reported the safety of early cessation of antimicrobial therapy in the setting of resolved neutropenic fever, but this approach does not apply to patients with persistent or recurrent neutropenic fever of unclear cause. We reviewed original articles relating to [^{18}F] fluorodeoxyglucose (FDG)-PET-CT in detecting the cause and guiding management of neutropenic fever. We searched PubMed and Scopus using the terms "febrile neutropenia", "neutropenic fever", "Positron emission tomography", "PET", "FDG-PET-CT", "hematologic" and "hematology". Studies in English published until Jan 31, 2022, were considered. All original articles were screened for relevance and included if related to our study question. There were no meta-analyses available on this topic. Five small, prospective, observational, single-centre studies have been published on the topic of diagnostic performance and change in management compared with conventional CT. Sample size ranged from 20 to 79 cases and used various inclusion criteria (including haematological malignancy and treatment type, and duration of neutropenic fever) and differing diagnostic gold standards. One study reported a 93% sensitivity of [^{18}F]FDG-PET-CT for cause of neutropenic fever, with several additional sources of fever identified by [^{18}F]FDG-PET-CT, compared with the designated CT gold standard. Other studies reported that [^{18}F]FDG-PET-CT had a sensitivity of 60–95% when determining the cause of fever identified at the completion of investigation, typically including CT and microbiological sampling. Assessment of change in management in these non-randomised trials ranged from 35–75%. All estimates of change in management are at high risk of bias because of their small sample size and non-randomised trial design. We found no published randomised controlled trials of [^{18}F]FDG-PET-CT compared with conventional CT for determining the cause of persistent or recurrent neutropenic fever, and, therefore, none that assessed the outcome of change in management and subsequent secondary clinical outcomes.

Added value of this study

Our trial was designed to address the aforementioned gap in knowledge, while minimising biases in a defined high-risk population comprised largely of patients undergoing allogeneic haematopoietic stem-cell transplantation or remission induction chemotherapy for acute leukaemia. This study provides the first high quality evidence that [^{18}F]FDG-PET-CT leads to more de-escalation and cessation of broad-spectrum antimicrobials in the context of persistent or recurrent neutropenic fever. This reduction in antimicrobial exposure was not associated with inferior clinical outcomes. There were also potential secondary downstream benefits, including length of hospital stay, because post-scan length of stay was shorter after [^{18}F]FDG-PET-CT, although post-randomisation length of stay did not differ.

Implications of the available evidence

Incorporation of [^{18}F]FDG-PET-CT into the diagnostic algorithm for patients with high-risk persistent or recurrent neutropenic fever will likely to lead to reduction in exposure to empirical broad spectrum antimicrobial therapy in already heavily exposed patients. This new approach could also lead to reduction in days of hospitalisation, with potential reduction in health-care-associated complications, although this will require further investigation. Reduced broad-spectrum antimicrobial exposure is highly desirable as a means of reducing antimicrobial resistance and adverse effects on the host microbiome.

risk of resistance, and adverse effects on the host microbiome.[10]

^{18}F-fluorodeoxyglucose ([^{18}F]FDG)-PET-CT is a promising investigation with improved sensitivity and specificity for identifying the causes of neutropenic fever compared with conventional approaches in small retrospective and non-randomised prospective studies.[5,11–14] Potential benefits included the ability to detect infection in dense tissues, such as the liver and spleen, and [^{18}F]FDG-PET-CT also shows promise for localising invasive fungal disease and detecting its dissemination.[15–17] We postulated that the use of [^{18}F]FDG-PET-CT could positively affect decision making in persistent and recurrent neutropenic fever by mitigating unnecessary antimicrobial escalation, with more rational use of empirical antibacterial and antifungal therapy and thus facilitate antimicrobial stewardship.[11,12] We aimed to compare the impacts on clinical management and neutropenic fever outcomes of [^{18}F]FDG-PET-CT and conventional CT in the setting of persistent and recurrent neutropenic fever.

See Online for appendix

Methods

Study design and participants

We did a multicentre, open-label, phase 3, randomised, controlled trial at two university-affiliated tertiary referral centres with an integrated haematology service based in Victoria, Australia (appendix p 2), both of which perform allogeneic HSCT and intensive chemotherapy for acute leukaemia (Royal Melbourne Hospital [RMH]), and autologous HSCT (Peter MacCallum Cancer Centre [PMCC]). The full study protocol is provided in the appendix (pp 15–57). This research project was approved by the Human Research Ethics Committee of Melbourne Health (HREC/17/MH/106).

Eligible patients were identified upon hospital admission for transplantation or chemotherapy and approached by study investigators AD, SYT, or OB-I for written informed consent. Participants were admitted to and discharged from PMCC or RMH as per standard practice. All study tests occurred during hospital admission.

Eligible patients were aged 18 years or older and about to undergo induction, consolidation, or re-induction chemotherapy for acute leukaemia (as diagnosed by a specialist haematologist based on standard investigations) with expected duration of profound neutropenia (≤0·5 cells/μl) for at least 10 days, or conditioning for an autologous or allogeneic HSCT, and had provided written informed consent. Exclusion criteria were pregnancy, allergy to iodinated contrast, or an estimated glomerular filtration rate less than 30 mL/min.

Randomisation and masking

Participants were eligible for randomisation if they had either persistent or recurrent neutropenic fever of unknown cause as determined by an infectious disease and haematology consultant. Persistent neutropenic fever was defined as neutropenic fever that occurred for more than 72 h after initial onset, despite initiation of empirical antibiotics. Recurrent neutropenic fever was defined as fever that resolved after initial onset, with 48 h of defervescence, and subsequently recurred beyond 72 h of initial onset while the patient remained neutropenic. The initial study protocol only allowed randomisation of patients with persistent neutropenic fever; however, it was observed that many patients who were ineligible for randomisation at 72 h developed recurrence of neutropenic fever (ie, recurrent neutropenic fever). Because there was clinical concern for occult infection and need for further investigation in patients with recurrent neutropenic fever, an amendment was introduced early in recruitment (approved March 23, 2018, after six participants were randomly assigned) to allow these patients to participate.

Participants were not randomly assigned if the cause of neutropenic fever was already identified (site and pathogen, eg, urinary tract infection with pathogen identified) and the treating haematology and infectious disease teams felt that imaging was not indicated.

Eligible participants with persistent or recurrent neutropenic fever were randomly assigned 1:1 to conventional CT or [^{18}F]FDG-PET plus CT imaging (appendix p 13). A computer-generated randomisation chart was prepared by the PMCC Centre for Biostatistics and Clinical Trials, and randomised imaging was allocated into sealed envelopes that were stored in a locked central repository in the departmental office. Once participants met eligibility for randomisation, sequential sealed envelopes were opened by the study investigator (AD or SYT) who assigned the participant to the intervention accordingly. The randomised scan was undertaken within 3 days of random assignment. This was an open label study as it was not possible to mask to imaging type, and results of the imaging were made available to the treating clinical team. An independent adjudicating committee assessed the clinical impact of the randomised scans and the cause of neutropenic fever (see below).

Participants who had a conventional diagnostic CT or [^{18}F]FDG-PET plus CT during neutropenic fever before randomisation were recorded as a protocol deviation and excluded from randomisation. After randomisation, if a participant had the alternate scan before the randomised scan, or did not have the randomised scan at all, this was also recorded as a protocol deviation.

After the randomised scan, participants could have the alternate scan if deemed necessary by the treating team. This was recorded as a crossover. These participants were included in the primary endpoint analysis.

Procedures

Participants were monitored as inpatients for development of neutropenic fever (defined as temperature ≥38·0°C and neutrophils ≤0·5 cells/μl) and had daily standard of care full blood counts and blood urea, electrolytes, and creatinine testing during admission. At the onset of each episode of neutropenic fever at least two sets of blood cultures (one peripheral and one per lumen of central line) were collected before antimicrobial commencement within 30 min. Other microbiology investigations included urine cultures, stool cultures, including *Clostridioides difficile* testing if participants had diarrhoea, viral respiratory multiplex PCR of nasopharyngeal swab if participants had upper respiratory tract symptoms, and sputum culture if participants had lower respiratory tract symptoms. Routine chest X-ray was also done.

Diagnostic CT scans were done on a Siemens Definition Edge or Definition Flash 128 Slice CT scanner (Siemens, Erlangen, Germany) with 0·6 mm collimation at 5·0 mm intervals reconstructed with a high spatial frequency algorithm (standard of care for neutropenic fever investigation at our centres). Participants randomly assigned to the conventional CT group had a CT scan of the chest with intravenous contrast. CT of sinuses, head, neck, abdomen, and pelvis with contrast were added at the discretion of the treating team.

[^{18}F]FDG-PET-CT scans were done on a Discovery 690 or 710 PET-CT scanner (GE Medical Systems, Milwaukee, WI) at the PMCC PET centre, including patients otherwise receiving care at RMH. Patients fasted for a minimum of 4 h and generally more than 6 h. [^{18}F]FDG administration was delayed until blood glucose was corrected to less than 10 mmol/L, then a bodyweight-corrected dose of [^{18}F]FDG was administered through a peripheral cannula according to protocol.[18] A non-contrast CT scan, including low-dose breath-hold CT, was acquired in helical mode at 140 kVp and 80 mAs and reconstructed at a slice thickness of 3·27 mm. The [^{18}F]FDG-PET scan encompassed the same axial extent as the CT scan, from the skull base to the proximal thighs. Image acquisition commenced at 60-75 min after tracer administration. Images were reconstructed by use of iterative reconstruction with the order-subset estimation maximisation algorithm.

For both groups, clinical information relating to any potential foci of fever was provided to the radiologist and results were reported as per standard protocols. As per

standard clinical practice, the radiologist or nuclear medicine physician's report and scan images were uploaded to the electronic medical record and then accessed by the treating haematology and infectious disease teams. A management plan was formed accordingly.

Participants routinely received valaciclovir or aciclovir prophylaxis and those patients receiving fludarabine plus cytarabine chemotherapy received cotrimoxazole. Patients with allogeneic HSCT or acute leukaemia generally received posaconazole as antifungal prophylaxis, with intermittent liposomal amphotericin B (100 mg three times per week) in the setting of azole drug-drug interactions or intolerance. Patients with autologous HSCT received fluconazole prophylaxis. Fluoroquinolone and letermovir prophylaxis were not routinely used. Patients were managed in high efficiency particulate air filtered, positive pressure single rooms.

A nurse-initiated clinical pathway for sepsis was standard of care.[19] At the onset of neutropenic fever, participants received either intravenous piperacillin-tazobactam (4·5 g four times a day); intravenous cefepime (2 g three times a day, for low-risk penicillin allergy) with or without oral or intravenous metronidazole (500 mg twice a day); intravenous ciprofloxacin (400 mg twice a day, for high-risk penicillin allergy or previously colonised or infected with piperacillin-resistant gram-negative organism) with intravenous vancomycin (1·5 g twice a day) and with or without intravenous or oral metronidazole (500 mg twice a day); or intravenous meropenem (1 g three times a day). Intravenous gentamicin (5–7 mg/kg ideal body weight once per day) and intravenous vancomycin (1·5 g twice a day, or 1 g twice a day if estimated glomerular filtration rate 60–90 mL/min) were added in severe sepsis, and vancomycin was also added for suspected skin and soft tissue infection or central line infection.[20] Addition of empirical antifungal therapy was at clinician discretion, and was generally liposomal amphotericin B (3–5 mg/kg per day) in the setting of posaconazole prophylaxis, or voriconazole (4 mg/kg twice per day after a loading dose) in the setting of fluconazole prophylaxis. Clinicians could broaden empirical therapy at their discretion. The expected behaviour was to narrow neutropenic fever therapy back to baseline, or to end therapy completely in the absence of demonstrated focus of infection on scans and cultures.

Further investigation for neutropenic fever was at the clinician's discretion and could include other imaging techniques, such as MRI and echocardiography. Patients with changes on CT or [^{18}F]FDG-PET-CT imaging suggestive of atypical pulmonary infection were referred for consideration of bronchoscopy. Culture-based, PCR, and antigen detection tests, including for *Aspergillus*, were done according to routine procedure.

Six independent adjudication committees (IAC) were formed, each of which comprised one independent infectious disease expert and one haematology expert. The IACs assessed the secondary outcomes of whether the randomly assigned scan led to a new diagnosis, identified a new site of infection, or excluded pulmonary invasive fungal disease as defined by the European Organisation for Research and Treatment of Cancer Mycoses Study Group criteria.[22] The IACs also defined the final cause(s) of neutropenic fever based on clinical, microbiologic, and radiologic findings, including the randomly assigned scan (appendix pp 5–7). Causes of neutropenic fever could be multiple and include infectious and non-infectious causes. If the two reviewers disagreed, a third reviewer was asked to assess, and majority ruled. Imaging specialists were not involved in the assignment of impact.

Each episode of infection was classified as either microbiologically defined infection, clinically defined infection or a fever of unknown focus according to published definitions.[23] An microbiologically defined infection was designated when both a site and causative pathogen(s) of infection were identified. A clinically defined infection was designated when a likely clinical site of infection was identified but no causative pathogen was isolated (eg, pulmonary parenchymal changes on imaging suggestive of pneumonia or pneumonitis but no pathogen detected on testing). Fever of unknown focus was designated where neither a site nor causative pathogen for fever was identified. Bacteraemia was defined as per the CDC National Healthcare Safety Network criteria, including those classified as related to mucosal barrier injury.[24] The highest score on systemic inflammatory response syndrome criteria within 3 days of scan was collected.[25]

Acute kidney injury was defined as an increase in serum creatinine by at least 0·3 mg/dL (26·5 micromol/L) or serum creatinine at least 1·5 × baseline within 1 week of trial scan.

Outcomes

The primary outcome was a composite endpoint of either commencement of an antimicrobial (antibacterial, antiviral, or antifungal) with targeted treatment intent (start antimicrobial), cessation of all agents in an antimicrobial class (stop antimicrobials), or change in antimicrobial spectrum (subclassified as broadened or narrowed spectrum[21]), which we refer to as antimicrobial rationalisation in this report, within 96 h of the performance of a study-specific scan.

The principal investigator team of infectious disease specialists (AD, KT, and MS) adjudicated the primary endpoint as any antimicrobial started or stopped within 96 h after a scan using strict criteria according to antimicrobial class and spectrum (appendix pp 3–4). Beyond the investigator panel consensus assessment, this endpoint was not centrally reviewed.

Secondary outcomes were led to starting an antimicrobial (all treatment-intent antimicrobials of a particular type

[antibacterial, antiviral, antifungal] commenced on the basis of scan result), led to stopping an antimicrobial (all treatment-intent antimicrobials of a particular type ceased on the basis of scan result), led to changing spectrum of antimicrobial (spectrum of antimicrobial therapy broadened or narrowed), led to a new diagnosis (scan diagnosed a cause of neutropenic fever [infective or non-infective] directly or following further investigation), identified new site of infection (scan identified a new infection or an area of dissemination), excluded pulmonary invasive fungal disease (scan showed clear lung fields or pulmonary parenchymal changes not related to invasive fungal disease), led to removal of central line (removed within 96 h of randomly assigned scan), led to targeted sampling of an abnormality (biopsy, aspirate, or scope of a focal site of abnormality), led to targeted drainage of collection (referral to radiology or surgery for drainage), admission to intensive care unit (ICU), length of stay, mortality, type and duration of antimicrobial therapy (appendix pp 3–4). Secondary outcome data were collected from randomly assigned scan performance up to hospital discharge, unless a new chemotherapy regimen (eg, reinduction) was introduced at which time data were censored, aside from mortality, which was followed up for 6 months from date of random assignment. Length of stay after scan was reported for two reasons: overall length of stay is heavily affected by other factors before the onset of persistent or recurrent neutropenic fever, and length of stay after scan is most indicative of the effect of the type of scan on subsequent treatment. Secondary changes in management outcomes were strictly defined as interventions that occurred or were requested within 96 h after randomly assigned scan. Post-hoc exploratory analyses were done for subgroups (chemotherapy *vs* transplantation, negative *vs* non-negative scans) for the primary outcome.

Statistical analysis

We hypothesised that [^{18}F]FDG-PET-CT would lead to more frequent antimicrobial rationalisation than standard CT. A pilot prospective study (n=20) done at PMCC in patients with high-risk neutropenic fever found conventional CT led to a change in management of 50%, and [^{18}F]FDG-PET-CT led to a change in management of 75% compared to prior to scan.[11] Using these estimates, an individual parallel-group, two-arm randomised controlled trial would require a sample size of 66 per group, with 80% power and 5% two-sided significance level. Allowing for a 10% dropout, we estimated a sample size of 73 participants per group. Categorical variables were summarised by frequency and percentage and analysed by use of χ^2 test or Fisher's exact test. Continuous variables were summarised with mean and SD or median and IQR and analysed by use of a *t*-test or Wilcoxon rank-sum. Continuous variables were assessed for skew by use of a Shapiro-Wilk test. Odds ratios were estimated with a logistical regression. Goodness-of-fit was assessed with a

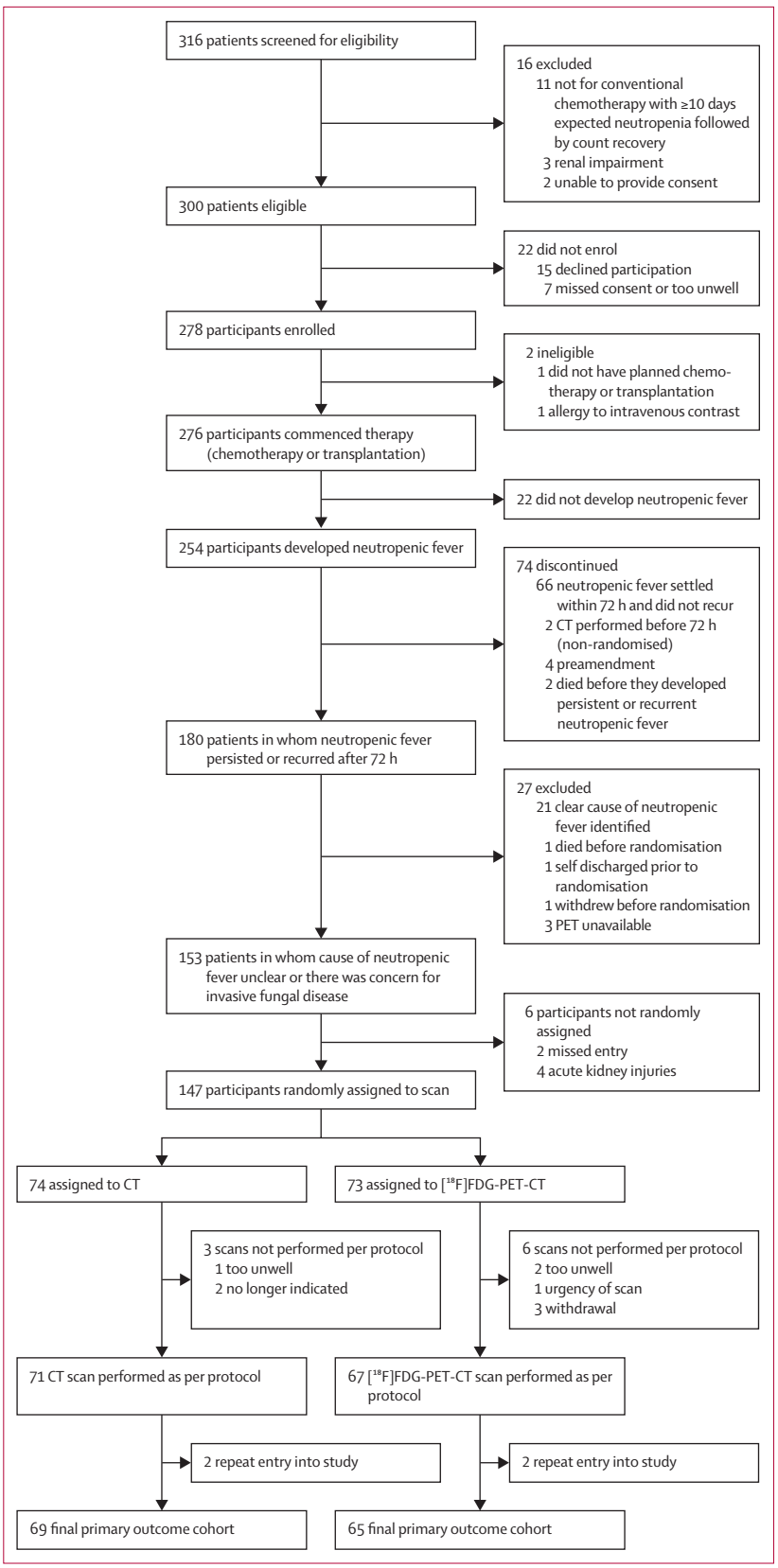

Figure: **Trial profile**

	FDG-PET-CT group (n=65)*	Standard CT group (n=69)*
Age, years	55 (19–73)	55 (18–77)
Sex†		
Male	38 (58%)	50 (72%)
Female	27 (42%)	19 (28%)
Race or ethnic group		
White	53 (82%)	58 (84%)
Asian	10 (15%)	7 (10%)
Native Hawaiian or other Pacific Islander	0	1 (1%)
Hispanic or Latinx	1 (2%)	3 (4%)
Not specified	1 (2%)	0
Indication for admission		
Allogeneic haematopoietic stem cell transplantation	30 (46%)	39 (57%)
Matched unrelated donor‡	16 (25%)	18 (26%)
Sibling‡	10 (15%)	18 (26%)
Haploidentical‡	4 (6%)	3 (4%)
Myeloablative§	13 (43%)	20 (51%)
Autologous haematopoietic stem cell transplantation	1 (2%)	1 (1%)
Chemotherapy for acute leukaemia	34 (52%)	29 (42%)
Induction	24 (37%)	21 (30%)
Consolidation	4 (6%)	5 (7%)
Reinduction	6 (9%)	3 (4%)
Primary underlying disease		
Acute myeloid leukaemia	38 (58%)	33 (48%)
Acute lymphoblastic leukaemia	3 (5%)	13 (19%)
Myelodysplastic syndrome	3 (5%)	10 (14%)
Other	21 (32%)	13 (19%)
Antimicrobial prophylaxis		
Antifungal		
Posaconazole	58 (89%)	60 (87%)
Fluconazole	5 (8%)	6 (9%)
Voriconazole	1 (2%)	0
Liposomal amphotericin B	1 (2%)	3 (4%)
Valaciclovir or acyclovir	65 (100%)	69 (100%)
Cotrimoxazole	15 (23%)	13 (19%)
Age adjusted Charlson Comorbidity Index	3 (2–7)	3 (2–7)
Days of neutropenic fever before scan	8 (3–21)	7 (3–26)
Days of neutropenia	19 (8–66)	18 (7–74)
Days of neutropenia at time of scan	12 (4–28)	10 (4–150)
Days of neutropenia after scan	8 (1–39)	9 (3–25)
Days from start of chemotherapy or conditioning to random assignment	17 (6–29)	17 (3–37)
Time from randomised assignment to scan, hours	28·50 (0·75–101·00)	23·00 (0·75–124·00)

(Table 1 continues in next column)

(Continued from previous column)

Nature of fever		
Persistent fever	25 (39%)	26 (38%)
Recurrent fever	12 (19%)	17 (25%)
Recurrent and persistent fever	28 (43%)	26 (38%)
Maximum number of systemic inflammatory response syndrome criteria within 3 days of scan	4 (2–4)	4 (2–4)
Crossover within 4 days after randomised scan¶	5 (8%)	3 (4%)

Data are n (%) or median (range). *Two patients from Peter MacCallum Cancer Centre were included in the modified primary per protocol cohort, one in the FDG-PET-CT group and one in the CT group. †Genotypic sex. ‡The most common conditioning regimen was fludarabine, melphalan, plus thymoglobulin in patients with a matched unrelated donor graft, fludarabine plus melphalan in sibling donor grafts, and fludarabine, cyclophosphamide, plus total body irradiation in haploidentical donor grafts. §Details of conditioning regimens are provided in the appendix (p 8). ¶Crossover occurred when a participant had the randomised scan and then proceeded to have the alternative scan within the same neutropenic period.

Table 1: **Patient demographics**

Hosmer & Lemeshow test. Time to event outcomes were analysed by use of a semi-parametric Cox proportional hazards regression. Hazard proportionality was assessed with a post-estimation proportional hazards test. The primary and secondary outcome analyses were done by use of a modified per protocol cohort, consisting of only first entry (ie, first randomisation) into the study per participant, because numbers of re-entry on a subsequent treatment cycle were small (four entries) and thought likely to introduce bias without adding meaningfully to results. The modified per protocol cohort included participants who had a crossover scan. Sensitivity analyses were done on the primary endpoint with exclusion of patients who had a crossover scan within 96 h of randomised scan, and included those who re-entered the study. An intention-to-treat analysis was done for admission to ICU and 6-month mortality as a sensitivity analysis.

A single interim analysis was done as per the study protocol and was limited to the primary endpoint only. All statistical analyses were done using Stata version 16 (StataCorp, College Station, Texas, USA).

This trial is registered with ClinicalTrials.gov, NCT03429387.

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 8, 2018, and July 23, 2020, 316 participants were assessed for eligibility. 169 patients were

excluded; 18 failed pre-screening, 15 declined to participate, seven missed consent or were unwell, 22 did not develop neutropenic fever, 74 did not have recurrent or persistent neutropenic fever, 21 had a clear cause of neutropenic fever, one died before randomisation, one self-discharged, one withdrew, three had no available PET, two missed entry (fever resolved and count recovered before randomisation), and four had acute kidney injury. 147 participants met the definition of persistent or recurrent neutropenic fever and were randomly assigned to receive either [18F]FDG-PET-CT (n=73) or CT (n=74; figure). The follow-up period was completed by Jan 23, 2021, with the trial meeting its target sample size, and participants were followed up for a median of 6 months (IQR 6–6). Nine patients deviated from protocol or withdrew following random assignment (six in the [18F]FDG-PET-CT group and three in the CT group). Three patients withdrew in the [18F]FDG-PET-CT group after randomisation because of anticipatory claustrophobia (one patient) and feeling too unwell to tolerate scan (two patients). One patient was randomly assigned to [18F]FDG-PET-CT while admitted to ICU, and a CT scan was done to avoid the longer acquisition time required for [18F]FDG-PET-CT imaging. Patients who re-entered the study with persistent or recurrent neutropenic fever on a subsequent treatment cycle were excluded from primary outcome analysis (two patients in each group). 134 participants were included in the primary modified per protocol analysis—65 in the [18F]FDG-PET-CT group (38 [58%] male; 53 [82%] White) and 69 in the CT group (50 [72%] male; 58 [84%] White; table 1). CT scan type, crossover scan performance, and indication by group are described in the appendix (p 14). Six patients in [18F]FDG-PET-CT group and 11 patients in the CT group went on to have further [18F]FDG-PET-CT or CT imaging to investigate ongoing fever of unknown focus. Durations of neutropenia before and after randomised scan were similar between groups (table 1).

	FDG-PET-CT group (n=65)	Standard CT group (n=69)	Odds ratio (95% CI)	p value
Primary outcome				
Primary outcome (rationalisation of antimicrobials)	53 (82%)	45 (65%)	2·36 (1·06–5·24)	0·033*
Changed antimicrobial spectrum	43 (66%)	33 (48%)	2·13 (1·06–4·28)	0·032*
Broadened spectrum	15 (23%)	16 (23%)	0·99 (0·44–2·22)	0·99*
Narrowed spectrum	28 (43%)	17 (25%)	2·31 (1·11–4·83)	0·024*
Started antimicrobial	2 (3%)	6 (9%)	0·33 (0·06–1·71)	0·17*
Stopped antimicrobial	9 (14%)	7 (10%)	1·42 (0·50–4·07)	0·51*
Secondary outcomes				
Lead to central venous catheter removal	2 (3%)	3 (4%)	0·70 (0·11–4·32)	1·00†
Lead to targeted sampling or investigation	4(6%)	9(13%)	0·48 (0·13–1·50)	0·18*
Lead to targeted microbiologic sampling resulting in diagnosis	3 (5%)	3 (4%)	1·06 (0·21–5·50)	1·00†
Lead to targeted drainage or surgery	0	0	NA	NA
Length of stay after scan, days	9 (6–14)	13 (8–18)	NA	0·016‡
Length of stay after randomisation, days	11 (7–17)	14 (9–19)	NA	0·10‡
Length of stay from start of chemotherapy or conditioning, days	28 (25–35)	30 (26–35)	NA	0·37‡
Intensive care unit admission after scan	6 (9%)	9 (13%)	0·68 (0·22–2·02)	0·48*
6-month mortality	8 (11%)	10 (14%)	0·64 (0·29–2·13)	0·64§
Perceived utility of randomised scan				
Lead to a new diagnosis or new site of infection	25 (40%)	21 (30%)	1·54 (0·75–3·18)	0·24*
Excluded pulmonary invasive fungal disease	49 (82%)	50 (77%)	1·33 (0·56–3·20)	0·51*

Data are n (%) or median (IQR), unless otherwise specified. NA=not applicable. *χ^2 test. †Fisher's exact test. ‡Wilcoxon Rank Sum test. §Cox proportional hazards regression.

Table 2: **Primary and secondary outcomes**

Antimicrobial rationalisation occurred in 53 (82%) of 65 participants in the [18F]FDG-PET-CT group and 45 (65%) of 69 participants in the CT group (OR=2·36, 95% CI 1·06–5·24; p=0·033; table 2). Most rationalisations were a change in spectrum of antimicrobial therapy (either broadening or narrowing), which occurred in 43 (66%) participants in the [18F]FDG-PET-CT group and 33 (48%) participants in the CT group, and a narrowing of spectrum more frequently occurred in the [18F]FDG-PET-CT group (28 [43%]) than in the CT group (17 [25%]; OR 2·31, 95% CI 1·11–4·83; p=0·024). Participants in the [18F]FDG-PET-CT group had more narrowing from broad spectrum therapies, such as meropenem, piperacillin-tazobactam, and vancomycin, than did those in the CT group (table 3; appendix pp 9–10). 18 patients de-escalated from intravenous therapy to oral or no antimicrobial therapy within 96 h of randomly assigned [18F]FDG-PET-CT, compared with 11 participants in the CT group. Sensitivity analyses excluding participants who crossed over to the alternative group of the study within 96 h of their randomly assigned scan did not significantly change the primary outcome (appendix p 11). Exploratory subgroup analyses to explore the primary outcome according to haematological therapy (chemotherapy or HSCT) and scan findings (negative or positive) are shown in the appendix (p 11). Scans negative for potential infective foci occurred in 22 (34%) of 65 participants in the [18F]FDG-PET-CT group and in 15 (22%) of 69 participants in the CT group (p values not included due to exploratory nature of the analysis). Sensitivity analysis including participants who re-entered the study did lead to a borderline non-significant p value (0·062); however, the effect size and CIs remained similar (appendix p 11).

There were no statistically significant differences in secondary change of management outcomes, such as central line removal and targeted sampling; however, numbers were small (table 2). Median length of stay after

	FDG-PET-CT group (n=65)	Standard CT group (n=69)
Backbone empiric antimicrobial therapy at time of scan		
Meropenem	33 (51%)	38 (55%)
Piperacillin-tazobactam	21 (32%)	23 (33%)
Cefepime	10 (15%)	6 (9%)
Other	1 (2%)	2 (3%)
Narrowed spectrum or cessation		
Narrowed spectrum from or ceased meropenem	14 (22%)	8 (12%)
Narrowed spectrum from or ceased piperacillin-tazobactam	7 (11%)	5 (7%)
Narrowed spectrum from or ceased cefepime	1 (2%)	0
Ceased gram positive cover*	14 (22%)	7 (10%)
Commencement or broadened spectrum		
Broadened empiric therapy† to meropenem	5 (8%)	9 (13%)
Added gram positive cover*	8 (12%)	13 (19%)

Full details of changes to antimicrobial therapy are provided in the appendix (pp 9-10). *Vancomycin, linezolid, daptomycin, or teicoplanin. †Piperacillin-tazobactam or cefepime.

Table 3: **Empiric antimicrobial therapy at time of randomised scan and key changes in antimicrobial therapy**

randomly assigned scan was significantly shorter in the [18F]FDG-PET-CT group compared with the CT group (9 days [IQR 6–14] *vs* 12·5 days [8–18]; p=0·016, table 2). Median length of stay after randomisation was 11 days (IQR 7–17) in the [18F]FDG-PET-CT group and 14 days (9–19) in the CT group (p=0·10). Numbers of patients admitted to ICU after scan did not differ significantly between the groups (six [9%] in the [18F]FDG-PET-CT group *vs* nine [13%] in the CT group; HR 0·68, 95% CI 0·23–2·02; p=0·48). 1-month and 3-month all-cause mortality were similar between groups at 1 month (one [2%] in the [18F]FDG-PET-CT group, and one [1%] in the CT group) and 3 months (three [5%] in the [18F]FDG-PET-CT group, and four [6%] in the CT group). 6-month all-cause mortality was 8 (11%) in the [18F]FDG-PET-CT versus ten (14%) in the CT group (HR 0·79, 95% CI 0·29–2·12; p=0·64). There was no significant difference in ICU admission or 6-month all-cause mortality in an intention-to-treat sensitivity analysis (appendix p 11).

There was no difference in mean inpatient-day-adjusted length of antibacterial therapy (censored at hospital discharge) in the [18F]FDG-PET-CT group (mean 671·52, SD 234·02) compared with the CT group (625·62 per 1000 inpatient bed days, SD 180·36; p=0·20). Empirical antifungal therapy was utilised in zero patients in the [18F]FDG-PET-CT group and four (6%) patients in the CT group, while directed antifungal use was used in six (9%) participants in the [18F]FDG-PET-CT group and three (4%) participants in the CT group.

Few patients had no identifiable infectious or non-infectious cause of neutropenic fever (five patients in the [18F]FDG-PET-CT group and three in the CT group; table 4). 51 (79%) participants in the [18F]FDG-PET-CT group and 59 (86%) participants in the CT group had at least one identified infectious cause. Both groups had a median of two identified causes of neutropenic fever. More microbiologically defined infections were recorded in the [18F]FDG-PET-CT group (68 [72%] of 94 infections) than in the CT group (64 [57%] of 112 infections, with conversley more clinically defined infections in the CT group (48 [43%] of 112 infections) than in the [18F]FDG-PET-CT group (26 [28%] of 94 infections; microbiologically defined infection OR 1·96, 95% CI 1·09–3·53; p=0·024). There were six cases of proven or probable invasive fungal diseases in the [18F]FDG-PET-CT group and four in the CT group, and zero cases of possible invasive fungal disease in the [18F]FDG-PET-CT group and five in the CT group. All three possible pulmonary invasive fungal diseases in the [18F]FDG-PET-CT group were upgraded to proven or probable by subsequent investigation, whereas three of eight in the CT group were upgraded. The scan led to a new diagnosis or identified a site of infection in 25 (40%) of 65 participants in the [18F]FDG-PET-CT group and 21 (30%) of 69 participants in the CT group (OR 1·54, 95% CI 0·75–3·18; p=0·24).

No adverse events were directly attributed to the randomly assigned scan. Three participants in each of the [18F]FDG-PET-CT and CT groups developed acute kidney injury within a week of trial scan. Two cases of acute kidney injury in each group were brief and reversible. The remaining patient in each group had mild chronic impairment that was deemed to be multifactorial on nephrology review.

Discussion

In this randomised, multicentre study of [18F]FDG-PET-CT compared with conventional CT in high-risk neutropenic fever, the primary endpoint of antimicrobial rationalisation occurred in more patients in the [18F]FDG-PET-CT group, and most commonly involved a narrowing of antimicrobial spectrum. These findings suggest that [18F]FDG-PET-CT is a diagnostic tool that could improve antimicrobial stewardship when integrated into an algorithm for investigating persistent and recurrent neutropenic fever.

Principles of antimicrobial stewardship include not only ceasing or narrowing unnecessarily broad therapy, but also commencing and refining targeted therapy to optimally treat infection (right drug, dose, route, and duration), therefore delivering the best outcomes to the patient and reducing inappropriate antimicrobial use.[9] These principles were the rationale for our choice of composite primary outcome.[11,26] Studies have shown frequent, and sometimes inappropriate, use of broad spectrum antimicrobials in neutropenic fever,[9] which is

	FDG-PET-CT group (n=65)	Standard CT group (n=69)
Infectious causes		
Patients with infective diagnosis	51 (79%)	59 (86%)
Identified infective causes (if any identified)	2 (1–2)	2 (1–3)
1	17 (26%)	21 (30%)
2	25 (38%)	24 (35%)
3+	9 (14%)	14 (20%)
Number of infections	94	112
Microbiologically defined infections		
Total	68/94 (72%)	64/112 (57%)
Bacterial	56/94 (60%)	51/112 (46%)
Bloodstream infection*	40/94 (43%)	40/112 (36%)
Gram positive	16/94 (17%)	16/112 (14%)
Gram negative	24/94 (26%)	24/112 (21%)
Bacterial infection site		
Bacteraemia without focus	22/94 (23%)	26/112 (23%)
Urine (cystitis)	4/94 (4%)	4/112 (4%)
Urine (pyelonephritis)	0/94	1/112 (1%)
Central line associated bloodstream infection	13/94 (14%)	12/112 (11%)
Pneumonia or focal lung	7/94 (7%)	2/112 (2%)
Colitis or enteritis	6/94 (6%)	3/112 (3%)
Oral	1/94 (1%)	1/112 (1%)
Liver	1/94 (1%)	1/112 (1%)
Cardiac	1/94 (1%)	0/112
Perianal	1/94 (1%)	0/112
Vaginal	0/94	1/112 (1%)
Viral	6/94 (6%)	9/112 (8%)
Cytomegalovirus		
DNAemia	1/94 (1%)	0/112
Disease	1/94 (1%)	0/112
Respiratory viruses		
Upper respiratory tract infection	1/94 (1%)	2/112 (2%)
Lower respiratory tract infection	2/94 (2%)	4/112 (4%)
Pericarditis	0/94	1/112 (1%)
BK cystitis	1/94 (1%)	1/112 (1%)
Epstein Barr virus—DNAemia	0/94	1/112 (1%)
Fungal (proven or probable)	6/94 (6%)	4/112 (4%)
Proven		
Saccharomyces spp	1/94 (1%)	0/112
Candida krusei	0/94	1/112 (1%)
Candida glabrata	2/94 (2%)	0/112
Rhizopus spp	0/94	1/112 (1%)
Probable		
Aspergillus spp	2/94 (2%)	2/112 (2%)
Saccharomyces spp	1/94 (1%)	0/112

(Table 4 continues in next column)

(Continued from previous column)

	FDG-PET-CT group (n=65)	Standard CT group (n=69)
Clinically defined infections		
Total	26/94 (28%)	48/112 (43%)
Central line associated bloodstream infection (tunnel infection)	2/94 (2%)	2/112 (2%)
Colitis, proctitis, or enteritis	2/94 (2%)	3/112 (3%)
Diverticulitis	3/94 (3%)	0/112
Pyelonephritis	0/94	1/112 (1%)
Parotitis	0/94	1/112 (1%)
Perianal or anal infection	4/94 (4%)	2/112 (2%)
Pilonidal sinus	1/94 (1%)	0/112
Pneumonia	10/94 (11%)	19/112 (17%)
Pneumonitis	3/94 (3%)	5/112 (4%)
Possible pulmonary invasive fungal disease	0/94	5/112 (4%)
Sinusitis (mild†)	0/94	3/112 (3%)
Skin or wound infection	1/94 (1%)	4/112 (4%)
Upper respiratory tract infection	0/94	3/112 (3%)
Non-infectious causes		
Total	51	50
Engraftment	4 (6%)	3 (4%)
Malignancy	2 (3%)	1 (1%)
Mucositis or neutropenic enterocolitis	40 (62%)	47 (68%)
Drug fever or allergy	4 (6%)	4 (6%)
Other	6 (9%)	4 (6%)
Cause unclear		
Total	5 (8%)	3 (4%)

Data are n (%), n/N (%), or median (IQR), unless otherwise specified. *Detailed information on bloodstream infection pathogens are provided in the appendix (p 12). †Clinical and imaging features not suggestive of invasive fungal sinusitis or bacterial sinusitis, but more in keeping with viral sinusitis or mild bacterial sinusitis.

Table 4: **Causes of neutropenic fever as assessed by adjudication committee**

often associated with the emergence of antimicrobial resistance[27,28] and adverse effects on the gut microbiome.[10,29] Although considerable progress has been made on early antimicrobial cessation following fever resolution,[30] this does not apply to patients with persistent or recurrent neutropenic fever. Small, observational studies have suggested that [^{18}F]FDG-PET-CT could improve antimicrobial prescribing in persistent neutropenic fever.[5,12] The strength of the our study is in the prospective, randomised design in a high-risk population, affording accurate assessment of the impact of [^{18}F]FDG-PET-CT compared with conventional CT, including on clinical outcomes. We report more de-escalation of carbapenems and glycopeptides in the [^{18}F]FDG-PET-CT group, key targets for stewardship programmes, without an increase in the rate of adverse clinical outcomes.

The reasons behind the more frequent antimicrobial rationalisation in the [18F]FDG-PET-CT group are manifold. There were more clinically defined infections in the CT group than in the [18F]FDG-PET-CT group, which reported proportionally more microbiologically defined infections. [18F]FDG-PET-CT has the advantage of metabolic activity measurement (ie, [18F]FDG avidity), in addition to the detection of anatomically abnormal lesions afforded by CT. Our results suggest that [18F]FDG-PET-CT, due to its metabolic component, is more accurate in identification of true infection, rather than merely detecting abnormalities that are not ultimately confirmed to be infective in origin. CT identified many pneumonias and pneumonitis in which no causative pathogen was identified and which might never have represented infection. [18F]FDG-PET-CT also identified more extra-pulmonary sites of microbiologically defined infection, including colitis and enteritis (with focal changes on imaging plus positive blood or stool culture) and perianal and pilonidal infection. Furthermore, [18F]FDG-PET-CT identified more intra-abdominal clinically defined infections, including diverticulitis. This finding is not unexpected, because infection might not be apparent at these sites on CT imaging due an absence of a definition in dense tissues. Furthermore, these sites are not routinely assessed by the standard-of-care CT protocol unless specifically requested.

This trial showed a reduction in length of stay after scan with [18F]FDG-PET-CT, although there was no statistically significant difference in length of stay after randomisation between groups. Although a secondary endpoint of this study, a reduction in length of stay is a significant outcome for high-risk patients. Spending more time in the community would probably improve quality of life and reduce health-care-associated complications and expenditure. This finding is probably a genuine reflection of scan impact, as the difference in median time from randomisation to scan was only 5·5 h longer in the [18F]FDG-PET-CT group, duration of neutropenia after the scan was similar between groups, and the median time from randomisation to discharge was 3 days shorter in [18F]FDG-PET-CT group than in the CT group (table 1). The shorter length of stay after scan is probably explained by the findings of [18F]FDG-PET-CT reassuring clinicians that serious infections were adequately ruled in and out, facilitating earlier rationalisation of antimicrobial therapy and cessation of ongoing investigations, as evidenced by the higher number of negative scans (appendix p 11), the higher proportion of microbiologically defined infections (table 4), the lower numbers of additional scans for fever of unknown focus (appendix p 14), and the greater number of patients who were switched from intravenous to oral or no antimicrobial therapy in the [18F]FDG-PET-CT group. As length of stay was a secondary endpoint, this study might be underpowered to detect a difference in length of stay after randomisation; nonetheless, a three day reduction in length of stay is clinically significant and warrants investigation. With the estimated average cost per day of admission for an allogeneic HSCT being AUD$2543 and acute myeloid leukaemia patient being $2275,[32] the cost of [18F]FDG-PET-CT (about $1000) would probably be offset by reduction in length of stay in the Australian setting. The cost of [18F]FDG-PET-CT might vary, and the cost-benefit ratio might also differ in other health systems. Formal cost-effectiveness analysis of [18F]FDG-PET-CT for neutropenic fever will be a focus for future research.

This study has some limitations. This study might not reflect practice globally, particularly where antimicrobial prophylaxis and treatment regimens differ. Our cohort had high proportion of mould active prophylaxis and a low number of invasive fungal infections, hence our results probably underestimate the benefits of [18F]FDG-PET-CT in detecting mould infections in populations at higher risk. Nevertheless, there were a lower number of negative scans in the [18F]FDG-PET-CT group compared with the CT group; [18F]FDG-PET-CT is still useful for clinical decision making in excluding invasive fungal diseases and avoiding empirical antifungal use. Additionally, we report benefits of [18F]FDG-PET-CT in the diagnosis of other causes of persistent or recurrent neutropenic fever, such that [18F]FDG-PET-CT does appear to be a worthwhile investigation in the setting of low invasive fungal disease prevalence. Although [18F]FDG-PET-CT routinely incorporates skull base to proximal thigh, whereas CT imaging comprises CT chest (with or without abdomen or pelvis at clinician's discretion), the aim was to assess the new imaging approach in the format in which it would be used in real-world patients against the current standard of care. For this reason, the body area covered by [18F]FDG-PET-CT was not identical in extent to that of CT scanning. Although many autologous HSCT recipients were monitored for development of persistent or recurrent neutropenic fever, only a few qualified for randomisation, suggesting that persistent or recurrent neutropenic fever is uncommon in this group and further imaging might only be required in particularly high-risk settings. The sensitivity analysis of the primary endpoint including participant re-entries did lead to the p value crossing 0·05; however, the effect size and CIs remained very similar, suggesting that the study's primary outcome estimate is still reliable, and probably clinically significant. Although reported outcomes included participants who had crossover scans, excluding all patients who received any subsequent CT or [18F]FDG-PET-CT imaging would result in a highly selected cohort not reflecting real-life practice. Furthermore, most crossover scans were for expected indications as displayed in the appendix (p 14). The primary outcome was based only on changes made within 96 h after scan, and crossovers during this time were small and unlikely to alter the primary outcome significantly, as was confirmed in our sensitivity analysis

(appendix p 11). Finally, this was an unblinded study, which probably influenced clinicians' prescribing practices and adjudicator's assessments of impact of the scan. However, as mentioned previously, assessment of the primary outcome was strictly criteria-based and hence not likely affected by the unblinded nature of scan results.

By comparison with diagnostic CT, [^{18}F]FDG-PET-CT used for investigation of persistent or recurrent neutropenic fever in high-risk haematology patients was beneficial in antimicrobial rationalisation and should be considered in management of these patients. Formal cost-effectiveness analysis is underway to build the case for improved access to [^{18}F]FDG-PET-CT in high-risk patients with persistent or recurrent neutropenic fever.

Contributors

AD, KT, TS, LW, SC, RH, DR, and MS were responsible for study concept and design. AD, KT, ST, OBI, JS, SH, BT, LW, LC, AN, DC, AK, GH, MY, JT, and MS did data collection. AD, KT, TS, MT, and MS analysed and interpreted the results. AD, KT, TS, JS, AB, SH, ST, MT, LW, BT, LC, AN, DC, AK, GH, MY, JT, SC, RH, DR, and MS contributed to draft manuscript preparation. AD and TS had access to study data and centre data manager validated study data. All authors received the results and approved the final version of this manuscript and take final responsibility for the decision to submit for publication.

Declaration of interests

SH has received a grant from Janssen, and honoraria from Celgene, Janseen, Novartis, and Kite/Gilead. OB has received honoraria from MSD and Abbvie. BT has received grants from Sanofi Pasteur, MSD, and Seqirus; received honoraria from Pfizer, MSD, and Gilead; and is on the data safety monitoring board (DSMB) of a study with CSL-Behring. SC has received educational grants from F2G and MSD Australia. JS has received honoraria from Alexian Australasia, Sobi Pharmaceuticals, Novartis, and Takeda; is on the DSMB and advisory board from Prevail Therapeutics; and has a leadership role in the Australian Bone Marrow Donor Registry. MY has received grants from the National Health and Medical Research Council (NHMRC) of Australia, MSD Australia, and the Medical Research Futures Fund and consulting fees, honoraria, and Advisory Board involvement for MSD Australia. TS has received speaker fees from Novartis and is on scientific committees for Biogen and Hartmann DE. SYT and AD have received a grant from Gilead. RH is the honorary director of Neuroendocrine Cancer Australia and PreMIT Pty and is the founder and equity holder of PreMIT Pty. MS has been awarded two NHMRC grants as well as grants from Gilead, Merck, and F2G and honoraria from Pfizer, Merck, and Gilead and is on the DSMB and advisory board of Pfizer, F2G, and Roche with all payments to an institution. All other authors declare no competing interests.

Data sharing

Deidentified patient data and data dictionary may be provided upon reasonable request via email to the corresponding author.

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