New approaches to management of fever and neutropenia in high-risk patients

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Purpose of review
Patients receiving treatment for acute leukaemia and haematopoietic cell transplantation (HCT) have prolonged neutropenia and are at high risk of neutropenic fever, with bacterial and particularly invasive fungal infections as feared complications, possessing potentially serious consequences including intensive care admission and mortality. Concerns for these serious complications often lead to long durations of broad-spectrum antimicrobial therapy and escalation to even broader therapy if fever persists. Further, the default approach is to continue neutropenic fever therapy until count recovery, leaving many patients who have long defervesced on prolonged antibiotics.

Recent findings
This article details recent progress in this field with particular emphasis on early discontinuation studies in resolved neutropenic fever and improved imaging techniques for the investigation of those with persistent neutropenic fever. Recent randomized controlled trials have shown that early cessation of empiric neutropenic fever therapy is well tolerated in acute leukaemia and autologous HCT patients who are clinically stable and afebrile for 72 h. Delineation of the best approach to cessation (timing and/or use of fluoroquinolone prophylaxis) and whether this approach is well tolerated in the higher risk allogeneic HCT setting is still required. Recent RCT data demonstrate utility of FDG-PET/CT to guide management and rationalize antimicrobial therapy in high-risk patient groups with persistent neutropenic fever.

Summary
Acute leukaemic and autologous HCT patients with resolved neutropenic fever prior to count recovery can have empiric therapy safely discontinued or de-escalated. There is an emerging role of FDG-PET/CT to support decision-making about antibiotic and antifungal use in high-risk persistent/recurrent neutropenic fever patients.

Keywords
antimicrobials, bone marrow transplantation, febrile neutropenia, haematology, neutropenic fever, PET

INTRODUCTION

Neutropenic fever is a clinical syndrome describing the development of fever during the period of a significantly reduced blood absolute neutrophil count (ANC) ('neutropenia'). Severe neutropenia is generally considered as less than 0.5×10^9 cells/l [1,2]. The deeper and longer the neutropenia, the higher the risk of incident fever and infection, and in particular invasive fungal disease (IFD), with risk exponentially escalating beyond 7 days duration [3]. This leads to the identification of a 'high-risk neutropenia' group, defined as ANC of less than 0.5×10^9 cells/l, extending over 7 days [1], which occurs during induction and consolidation chemotherapy for acute leukaemia and following conditioning for autologous and particularly allogeneic haematopoietic cell transplants (alloHCT). It is in these high-risk patients that there is concern for development of serious infection and aggressive investigation of aetiology of neutropenic fever is most often utilized. This article will explore recent developments to improve management and outcomes for patients with high-risk neutropenic fever,

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KEY POINTS

- Acute leukaemic and autologous haematopoietic cell transplant (HCT) patients with no microbiologically defined infection identified and resolved neutropenic fever prior to count recovery can have empiric therapy safely discontinued or de-escalated to prophylaxis.
- More study is required to assess the safety of early discontinuation or de-escalation in allogeneic HCT recipients with resolved neutropenic fever.
- Ceasing empiric antimicrobial therapy in the setting of ongoing neutropenic fever of unclear cause does not appear well tolerated, with concerns for increased mortality in this subgroup on a recent randomized control trial.
- FDG-PET/CT was superior to conventional CT in rationalizing antimicrobial therapy in persistent and recurrent neutropenic fever in a recent randomized controlled trial.
- FDG-PET/CT should be considered for investigation of haematology patients with persistent or recurrent neutropenic fever of unclear cause.

including protocolized early de-escalation of antimicrobials and improving imaging modalities in persistent neutropenic fever.

EPIDEMIOLOGY, PATTERNS AND CAUSE OF NEUTROPENIC FEVER

Data on neutropenic fever epidemiology are generally limited to single-centre studies with varying antimicrobial prophylaxis use. With this in mind, in alloHCT reported neutropenic fever rates are between 62 and 98% [4–7]. In acute leukaemic patients on antibiotic prophylaxis during induction, neutropenic fever rates range from 63 to 97% [8–10,11▪]. In the absence of antibiotic prophylaxis, reported rates are 93–100% [12,13].

Neutropenic fever can occur as a single episode (termed a febrile neutropenia episode, FNE), or as multiple FNEs during the neutropenic period. The definition of a 'persistent fever' can vary and has been defined as anywhere from 3 to 6 days of ongoing fever [1,14]. Rates of persistent fever are poorly described in the literature but may range from 15 to 49% [15,16]. A 'recurrent' fever has been defined as when the patient has recovered from their first FNE, and develops further FNE(s) during the same neutropenic period [17]. The limited published data in recurrent fever is typically in the setting of ongoing therapy, demonstrating a form of 'breakthrough' fever, with reported rates between 15 and 27% [16,18].

Standardized definitions of neutropenic fever causes include: microbiologically defined infection (MDI), where a causative pathogen and site have been identified; a clinically defined infection (CDI), where there is a likely site of infection (e.g. pneumonia), however a causative pathogen has not been identified and fever of unclear origin (FUO), where there is neither a causative site nor pathogen identified [19]. In those on fluoroquinolone prophylaxis (FQP), reported rates of MDI are between 27 and 41% [15,20–24], CDI 11–40% [15,20–23] and FUO of 15–56% [4,7,8,15,20–23,25–27]. In cohorts not on FQP, MDI is identified in 13–47% [28–33], CDI in 10–70% [28–34], with an FUO of 21–62% [10,12,13,28–36]. In summary, more often than not patients with neutropenic fever do not have an MDI identified and FUO represents a sizeable proportion of FNEs, highlighting the need for better diagnostics to guide management.

OUTCOMES AND CONSEQUENCES OF HIGH-RISK NEUTROPENIC FEVER

High-risk neutropenic fever is associated with serious adverse events such as severe sepsis, requiring ICU admission and IFD, with mortality rates of 50–70% in IFD [37,38]. IFD rates are highest during AML induction chemotherapy [proven/probable: 8–17% without and 0–10% on mould-active prophylaxis (MAP)] [39–43], followed by AML consolidation and alloHCT (7–23% without and 2–3% on MAP) [44–48]. ICU admission rates during intensive leukaemia chemotherapy range from 7 to 29% [11▪,36,49–51] and are between 11 and 34% during the postconditioning hospital admission in alloHCT [52–58]. In acute leukaemia, mortality in the setting of neutropenic fever has been reported to be between 4 and 14% [11▪,12,27,49,59].

HIGH-RISK NEUTROPENIC FEVER CHALLENGES

Neutropenic patients can have fever for many reasons, including their underlying haematologic condition, chemotherapy-induced or other medication-induced fever, infection, allergy and mucositis [17]. Differentiation between the causes of neutropenic fever can be difficult, as there may be an absence of localizing symptoms and signs of infection. Furthermore, there may be multiple simultaneous causes causing such fever, hence identification of one cause does not reliably rule out other serious causes. Given consequences of untreated infection can be significant, it can be difficult for clinicians to be reassured that infection has been sufficiently ruled out, particularly in the setting of ongoing fever, or fever that

appears to have resolved following commencement of empiric antimicrobial therapy. It is, therefore, crucial that the suite of diagnostics utilized is of high sensitivity and specificity. Unfortunately, current diagnostic tests available do not deliver this high-quality test performance.

ANTIMICROBIAL MANAGEMENT OF NEUTROPENIC FEVER

Without an infective focus, therapy for neutropenic fever is often broad spectrum and frequently escalated to ever broader cover as neutropenic fever persists [60]. Therapy is often prolonged, with the reported median duration of 19–23 days during AML chemotherapy [10,11▪,61,62]. Such prolonged broad-spectrum therapy impacts the gut microbiome, with dysbiosis being linked with poorer malignancy outcomes [63▪▪,64,65]. This emerging association places additional emphasis on the importance of rational antimicrobial use [i.e. antimicrobial stewardship programs (AMS)] in the cancer setting. The implementation of effective AMS programs in haematology is challenging; however, given the high acuity and complexity of these patients, high prevalence of MDR organisms, and the highly specialized nature of haematology practice [66–69]. Recently there has been progress made both in the setting of resolved fever (early discontinuation) and in persistent/recurrent fever (enhanced imaging techniques), which will be explored in the following sections.

EARLY DISCONTINUATION OF EMPIRIC NEUTROPENIC FEVER THERAPY

Traditionally, clinicians would continue empiric neutropenic fever antimicrobial therapy until count recovery. This was based on the results of two small randomized trials in the 1970s, suggesting higher rates of mortality, BSI and clinical failure in those who discontinued therapy prior to neutrophil recovery [70,71]. However, with the growing concern of AMR and the fact that given supportive measures and other aspects of haematologic malignancy care have changed significantly since the 1970s, groups have attempted to re-examine the safety of early antimicrobial cessation in neutropenic fever, also known as early discontinuation. Early discontinuation studies can be divided into those where there is complete cessation of all broad-spectrum antimicrobials and those where there is de-escalation back to FQP following fever resolution (Table 1). Further, there are a small number of studies where there is early discontinuation/de-escalation in the context of ongoing fever.

Early discontinuation of therapy to no prophylaxis when afebrile

A recent multicentre RCT performed in Spain has particularly bolstered the practice of early discontinuation to no therapy on fever resolution (The How Long study [72]). This study found that participants with FUO who were afebrile and clinically stable for 72 h following commencement of empiric therapy were able to safely stop antimicrobial therapy, with no difference in mortality, subsequent BSI or recurrent fever between intervention and control arms. Antimicrobial-free days were also significantly higher in the intervention arm (median 13.6 versus 16.1 days). It is worth noting, however, that there were a low number of alloHCT recipients included. Also, the risk for deterioration on cessation was likely low, given the average duration of fever was less than 24 h in the intervention group, which is out of keeping with what has been typically seen in alloHCT and acute leukaemia chemotherapy-related neutropenic fever [15,73].

Other published early discontinuation studies are observational, generally single-centre, and also with few (if any) alloHCT participants [10,26,29,74] (see Table 1). Further, some studies utilized control groups where the clinician had elected not to follow early discontinuation guidelines, suggesting an inherent bias towards more vulnerable/ill patients remaining in the control group [10]. A recent pre-implementation and postimplementation study with a higher rate of alloHCT involvement (28%) found clinical failure similar between arms; however, with a higher rate of BSI in the postimplementation group [75▪▪]. This higher rate of BSI is not surprising, and reassuringly, mortality was similar, and the overall antibiotic exposure remained lower post early discontinuation protocol implementation. A recent retrospective preimplementation and postimplementation study in a single centre in France where antimicrobials were ceased after 72 h if FUO and afebrile for 48 h, with 7 days therapy if MDI/CDI and afebrile for 4 days, in mostly acute leukaemia and alloHCT patients showed an association between intervention and reduced odds of death or ICU admission [odds ratio (OR 0.29] as well as significant reductions in carbapenem and glycopeptide use [76▪]. It seems evident that this early discontinuation approach is well tolerated and potentially delivers better clinical outcomes than prolonged therapy until count recovery.

Early de-escalation of therapy to fluoroquinolone prophylaxis when afebrile

There have been no randomized trials of patients with early de-escalation to FQP when afebrile. Most

Table 1. Studies examining discontinuation or de-escalation of neutropenic fever therapy in the last 20 years

Name/year/ location	Study characteristics	Population	Timing of cessation	Mortality	Clinical failure	ICU	BSI	Days of Abx therapy	Comments
Switch from therapy to FQP if afebrile									
Kroll *et al.*, 2016, USA [61]	Retrospective single-centre study, preintervention and postintervention $N=26$ continue phase, 26 discontinue phase	Haem malig (85% AML)	At least 14 days ABx, afebrile 3 days	0/26	38.5% recurrent fever in continue phase, 19.3% in discontinue	0/26	0/26	No significant difference	Not well matched cohorts
Snyder *et al.*, 2017, USA [77]	Retrospective, single-centre ($n=46$ pts de-esc, 74 pts contin)	AlloHCT (haplos and cords excluded)	At least 5 days ABx, afebrile 48h → switch to FQP	No difference	recurrent fever within 72h 15% de-esc, 19% contin group	No difference	No difference	Less Gram-positive ABx in de-esc, trend to less gram neg	–
Petteys *et al.*, 2020, USA [62]	Retrospective single-centre ($n=107$ pts, 22.4% de-escalation)	AlloHCT and autoHCT with FUO	Any switch from broad-spectrum ABx to FQP prior to count recovery	None in either group	No difference	None in either group	None in either group	No difference in DOT	Poorly matched groups – most in de-esc were haplo with early fevers, most in continue group were autos with later fevers
Rearigh *et al.*, 2020, USA [78]	Retrospective single-centre study ($n=297$ pts, 83 de-esc)	alloHCT and autoHCT	Afebrile for 48 h → switch to FQP if more than 24 h prior to count recovery	No difference	Recurrent fever (w/n 30 days of initial NF)- 15% de-esc versus 8.4% control	No difference	No difference	LOT shorter in de-esc (3.86 versus 4.62 days)	Short median duration of neutropenia post de-esc- 1.7 days
Niessen *et al.*, 2020, Netherlands [79]	Retrospective single-centre, preintervention and postintervention ($n=201$ pts, 362 FNEs)	AML/MDS receiving ChemoTx or HCT	Discontin of carbapenem and vancomycin; Promoting switch to FQP	None	Not reported	No difference	No difference	Reductions in carbapenem and vancomycin use	
Switch from therapy to no prophylaxis if afebrile									
Cherif *et al.*, 2004, Sweden [29]	Prospective multicentre, open-label, Observational to discontin intervention $N=60$ FNEs (29 cont, 31 ceased)	Haem malig, high-risk ↓PMN MM, lymphoma, acute leukaemia, HSCT (20–22% HCT)	Afebrile 48h	Nil in discontin	18% in discontin and 18% in continued	Not reported	Not reported	Not reported	Median duration neutropenia was 6.2 days post inclusion
Le Clech *et al.*, 2018, France (phase 1) [26]	Prospective single-centre observational ($n=45$)	Haem malig (MM, DLBCL, auto, AML, alloHCT)	Afebrile 48 h if FUO	1/45 (2.2%)	Relapse of fever in 42.7% (phase 1) versus 40.5% (phase 2 – see below)	1/45 (2.2%)	Not reported	Median duration therapy 7 days (phase I)	Phase 2 was discontin in ongoing fever (see below)
Aguilar-Guisado *et al.*, 2017, Spain [72]	Prospective multicentre randomized study ($n=79$ controls, 78 discontin)	Haem malig (MM, lymphoma, auto and alloHCT) with high risk ↓PMN Small alloHCT numbers ($n=14$)	Afebrile 3 days, recovered (CDI or FUO)	No difference	Recurrent fever 14% discontin, 18% control	Not reported	No difference	Discontin arm – more antibiotic-free days (13.6 versus 16.1 days)	Most pts had very brief fever (<24 h)

Table 1 (*Continued*)

Name/year/location	Study characteristics	Population	Timing of cessation	Mortality	Clinical failure	ICU	BSI	Days of Abx therapy	Comments
van de Wyngaeart *et al.*, 2019, France [82▪▪]	Prospective single-centre observational study ($n=62$ FNEs, 49 discontin, 13 controls)	AML induction/consolidation Excluded relapsed/refractory patients	After at least 7 days of therapy, 5 days of apyrexia (FUO and primary bacteraemia)	No deaths in discontin arm	20% in discontin had fever recurrence	No ICU in discontin arm	2/49 (4%) discontin arm	AMT longer in control group (19 versus 10 days)	Controls were selected based on noncompliance with protocol (high risk of bias)
La Martire *et al.*, 2018, France [74]	Prospective single-centre observational interrupted time series ($N=100$ FNEs, 66pts, $N=30$ discontin)	Haem malig Included 30% of pts who were not ↓PMN but high risk of infection * Excluded severe sepsis at onset	Included de-esc as well as discontin At least 5 days ABx, afebrile 48 h	No diff	None in de-esc or discontin groups	No diff	No diff	Reduction in carbapenem use No overall change in ABx consumption (cost savings observed)	Gut decontam is standard practice
Micol *et al.*, 2014, France [83]	Prospective single-centre observational study ($n=7$)	AML NF patients with FUO	At least 7 days Abx, afebrile for 5 days Excluded ESBL/CRE colonisation, ICU adm'n, HCT	0/7	3/7 rapid recurrence of fever, 1 septic shock	1/7	2/7	Median duration of spared Abx – 3 days	Median of 15 days of ABx prior to ceasing
Verlinden *et al.*, 2021, Belgium [75▪▪]	Preintervention and postintervention study ($N=512$ preintervention, 446 postintervention)	Acute leukaemia, alloHCT or autoHCT	Cease antibiotics after 72 h, afebrile at least 48 h	0.7% discontin 2.7% contin	34.7% discontin, 41.6% contin	Infection related 4.9% discontin 4.1% contin	46.9% discontin, 30.5% contin	Median 12 days discontin versus 14 days contin	
Contejean *et al.*, 2022, France [76▪]	Retrospective preintervention and postintrevention study ($N=164$ pre and 148 post)	Acute leukaemia, autoHCT (exclusions – severe illness, steroids, complex infections)	Cease ABx after 72 h, afebrile at least 48 h If CDI/MDI, contin Abx until day 7 and 4 days a pyrexia	OR ICU/death of 0.29 postintervention	Not reported	OR ICU/death of 0.29 postintervention	Not reported	Reduced carba and glyocopeptide use by 85 and 72%	
Switch from therapy to no therapy even if still febrile									
Le Clech *et al.*, 2018, France (phase 2) [26]	Prospective single-centre interventional cohort study ($n=37$)	Haem malig (MM, DLBCL, auto, AML, alloHCT)	After 5 days, irrespective of fever	Same as afebrile group (phase 1)	Same as afebrile group (phase 1)	Same as afebrile group (phase 1)	Not reported	Shorter duration of Abx – 5 versus 7 days in afebrile group	Phase 2 patients were lower risk – median ↓PMN 12 versus 20 days (high risk of bias)
Switch from therapy to FQP even if still febrile									
Slobbe *et al.*, 2009, Netherlands [73]	Prospective single-centre observational study ($N=177$ FNEs of FUO: 155 discontin, 22 contin)	Haem malig with high risk ↓PMN 31% autoHCT 3% alloHCT 66% high-dose ChemoTx But also included MM and NHL	After 3 days, even if febrile	30 day all cause – 3.6%. 2/6 pts had infection cause	57 pts had further 1 FNE, 32 had 2+ FNEs	Not reported	Not reported	Mean duration of imipenem was 4.7 days	
Schauwvlieghe *et al.* 2021, Belgium/Netherlands [11▪]	Retrospective cohort study, ($n=575$)	AML/MDS induction ChemoTx	After 3 days, even if febrile	Discontin – 8.5% Contin – 4.4% Adjusted OR- 1.46 (not significant)	Discontin- 51% restart ABx	Discontin- 9.2% Contin- 7%	Discontin- 32.5% Contin- 27%	Discontin- 9 days median, versus 19 days	

Table 1 (*Continued*)

Name/year/location	Study characteristics	Population	Timing of cessation	Mortality	Clinical failure	ICU	BSI	Days of Abx therapy	Comments
de Jonge *et al.*, 2022, Netherlands [82▪▪]	Multicentre, open-label randomized controlled trial ($n = 281$)	HM on intensive ChemoTx with expected ↓PMN >7 days autoHCT (63%) alloHCT (9%)	Carbapenem therapy- After 3 days, even if febrile, cease (short) Control 9–14 days (extended)	Short – 3.5% Extended – 0.7% (in subgroup of ongoing fever, short 4.9% versus 0%)	Short – 35.4%, extended 16.1% restart ABx	Short – 4.9% Extended 2.9%	Short 13%, extended 13%	Overall Abx Short – 6 days median versus 8 days extended	Small alloHCT numbers Higher mortality in short arm if ongoing fever on cessation

ABx, antibiotics; adm'n, admission; alloHCT, allogeneic haematopoietic cell transplant; AML, acute myeloid leukaemia; autoHCT, autologous haematopoietic cell transplant; CDI, clinically defined infection; chemoTx, chemotherapy; CRE, carbapenem-resistant enterobacteriaceae; decontam, decontamination; de-esc, de-escalation; disconfin, discontinuation; DOT, days of therapy; ESBL, extended spectrum beta-lactamase; FNEs, febrile neutropenic episodes; FQP, fluoroquinolone prophylaxis; FUO, fever of unknown origin; haplos, haploidentical donor transplant; HCT, haematopoietic cell transplant; LOT, length of therapy; Malig, malignancy; MDI, microbiologically defined infection; MDS, myelodysplastic syndrome; MM, multiple myeloma; NF, neutropenic fever; NHL, non-Hodgkin lymphoma; PMN, polymorphonuclear cells; w/n, within.

published studies are retrospective or prospective observational, and the de-escalation and continuation arms are often not well matched (Table 1). Within the limitations of these studies, most found similar outcomes including rates of ICU admission and mortality in the de-escalation arm to the continuing antibiotic arm [61,62,77–81]. Some reduction in carbapenems and vancomycin use has also been shown [77,79].

Early discontinuation of therapy to no prophylaxis in the context of ongoing fever

A small number of studies have been performed where antimicrobials were completely ceased in the context of ongoing fever. Phase 2 of one study involved cessation of broad-spectrum therapy after 5 days, irrespective of fever [26]. Compared with phase 1 (where patients had defervesced prior to cessation), the rates of clinical failure, subsequent BSI and ICU admission were similar, and duration of therapy shorter in phase 2 (median 5 versus 7 days). Importantly, however, the phase 2 patients had a median neutropenia duration of 12 days as compared with 20 days in phase 1, hence risk of poor outcomes was likely to be considerably lower in the phase 2 group. Therefore, the results of this study should be interpreted with caution.

Early de-escalation of therapy to fluoroquinolone prophylaxis in the context of ongoing fever

In centres where FQP is prescribed, recent studies have been conducted to assess benefits of early de-escalation to FQP regardless of fever status. One small single-centre observational study in intensive leukaemia chemotherapy and autoHCT de-escalated antimicrobials after 3 days. Thirty-day all-cause mortality was low; however, rates of recurrent fever were high and ICU and BSI rates not reported [73]. A more recent retrospective cohort study comparing different approaches in two European hospitals (one with de-escalation to FQP and the other continuation until neutrophil recovery), when adjusted for confounders, found a hazard ratio of 1.5 for death and ICU admission within 30 days for the de-escalation hospital, although the difference between groups was not significant [11▪]. A significantly reduced number of antimicrobial days in the de-escalation arm was observed (median 9 versus 19 days). Recently, a multicentre RCT in mostly autologous HCT and induction chemotherapy for haematologic malignancies with expected neutropenic duration more than 7 days, randomized to short-course carbapenem therapy (3 days) versus

extended therapy (9–14 days) in FUO regardless of fever status [82▪▪]. The composite primary outcome of treatment failure, shock, respiratory failure, ICU admission or death from day 4 to count recovery was noninferior on intention to treat but not noninferior on a per protocol analysis. Whilst ICU rates were similar between arms, death within 30 days of count recovery was significantly higher in the short-course arm if there was ongoing fever at 72 h. These studies bring into question the safety of antimicrobial de-escalation to FQP in the setting of ongoing fever and suggest that this approach is best restricted to those who have defervesced.

In summary, it appears that in the setting of acute leukaemia chemotherapy and autologous HCT with neutropenic fever with a period of defervescence, clinical stability and no CDI or MDI identified, antimicrobials may be safely ceased and lead to reduced antimicrobial utilisation [72]. The alloHCT group and those with particularly longer duration of neutropenic fever prior to defervescence (e.g. ≥3 days) would benefit from further study. The safety of ceasing antimicrobials in the setting of ongoing fever is unclear, and current literature suggests that the interim measure of de-escalation to FQP may be associated with a higher risk of ICU and death.

DIAGNOSTICS IN PERSISTENT AND RECURRENT NEUTROPENIC FEVER AND/OR INVASIVE FUNGAL DISEASE

Computed tomography

High-resolution pulmonary computed tomography (HRCT) has long been the standard-of-care for persistent neutropenic fever with the aim of detecting pulmonary IFD. Typical HRCT features include nodules with or without a halo sign and/or central cavitation [83,84]. HRCT findings, however, can be nonspecific and given scarring may occur following treatment of invasive pulmonary aspergillosis (IPA), complete resolution of pulmonary findings may not be seen despite adequate therapy [85]. A study in those with more than 2 days of neutropenic fever found a specificity of 57% for pneumonia of any infectious cause [86]. A study of patients with 5 days of persistent neutropenic fever found all 22 patients had abnormalities on HRCT [87]; however, on bronchoscopic alveolar lavage (BAL), only 12 of 22 had an infectious cause identified (Table 2). Sensitivity of HRCT in those with neutropenic fever may be high at the expense of likely poorer specificity, with potential implications for over-investigation and over-treatment.

Computed tomography of other body regions as part of neutropenic fever investigation

Despite CT abdomen and pelvis (CTAP) often being performed in addition to pulmonary CT as part of persistent neutropenic fever investigation in practice, data relating to its yield and impact on clinical management are sparse (Table 2). One single-centre study found 45% of AML patients with neutropenic fever had abnormalities on CTAP, predominantly suggestive of bowel inflammation/infection, with a change in management in 24%, typically bowel rest and/or addition of anaerobic antimicrobial therapy [88]. A study performed in alloHCT recipients found 35% of patients had CTAP abnormalities that were mostly nonspecific and rarely led to a change in management [89].

Empiric CT sinus investigation in persistent neutropenic fever is also controversial. Limited data exist, with only three retrospective single-centre studies examining this issue in the adult population (Table 3). When performed routinely in patients with persistent neutropenic fever, CT sinuses are infrequently positive and may have issues with poor specificity [97]. However, in those with high index of suspicion, it is of great importance to urgently perform imaging, so urgent management of invasive fungal sinusitis can be instituted [89,98].

Impact of computed tomography scan on clinical management of neutropenic fever

Despite CT being part of many neutropenic fever management guidelines, few studies have prospectively compared the impact of CT to alternative diagnostics on clinical management of patients with neutropenic fever. A prospective single-arm study where both CXR and HRCT were performed, reported a 28% change in management because of CT; however, how this was assessed is unclear [99]. A single-arm study of HRCT followed by BAL found changes were made on 12 of 22 (55%) patients following results of both investigations [87]. A retrospective noncomparative study in high-risk neutropenic fever estimated that CT chest leads to a change in management in 54% [98]. Finally, a retrospective study of HRCT in alloHCT found that most changes to management were made in those with a negative scan (addition of steroids), whereas addition of antifungal therapy only occurred in a small percentage (16%) [89]. The latter study does highlight that the benefits of scanning in neutropenic fever may not only be in the positive scan but also in a negative one.

Very few studies of CT in neutropenic fever report clinical outcomes. Mortality has been

Table 2. Computed tomography for investigation of persistent neutropenic fever in last 30 years

First author/ year/coconut	Population	NF details	CT type	Comparator	Prophylaxis	Findings of scan	Impact of scan
CT chest							
Ho 2011, USA [98]	Retrospective single-centre, 1998–2005 AML ($n=70$) ALL ($n=18$)	All patients with NF ≥4 days and abN CT chest	Unclear	None	Unclear – 58% antifungal drugs at time of CT	79% nodular opacities 24.1% nodules + halo 48% pleural effusion 37% GGOs 31% consolidation	54% change in AFT 56% had diagnostic procedures (BAL lung biopsy, sinus biopsies)
Patsios 2010, Canada [99]	Prospective single-centre, 2003–2004 AML ($n=40$)	'Neutropenic'' and 'requiring imaging to exclude pulm infection or complications' Average PMN 0.8, 80% febrile	Low-dose CT	CXR same day	Unclear	77.5% of CXRs were abN Poor concordance between reviewers reporting CXR 95% of CTs were abN, with good concordance	27.5% alteration in management 10/11 added AFT 1/11 – early discharge based on normal CT
Gerritsen 2017 Netherlands [90]	Prospective single-centre, 2013–2014 HM receiving chemoTx or allo or autoHCT ($n=67$)	On first day of NF (but HRCT also requested, if persistent NF at day 4)	Low dose CT, (new gen 64–256 slices)	Consensus Dx of NF by expert panel, incorporating CXR and HRCT, not low-dose CT	FQP Fluconazole Twice weekly GM monitoring	Consensus Dx of pulm infection in 16.4% 19.4% LDCTs indicative of pneumonia, 5 'false pos' 3 'false neg' LDCT more sensitive than CXR (73 versus 36%), not more specific (91 versus 93%) 2 possible and 3 probable IFD - 4/5 IFD had changes on CT, 0/5 on CXR	Not reported
Cornetto 2016 France [89]	Retrospective single-centre, 2009–2010 Post alloHCT ($N=68$)	Those who underwent at least one HRCT w/n first 30 days post alloHCT Fever main indication (78%)	HRCT	Nil	Unclear 65% on an AFT prior to scan	76% had pulm abN on HRCT, but many nonspecific (65% atelectasis, 40% pleural effusion, 35% septal thickening) GGOs in 33%	54% had changes to therapy 62% of changes-adding steroids 16% of pts- antifungal added or altered
Kim 2014, Korea [91]	Prospective single-centre, 2008–2011 HM (AML 54.6%, HCT 15.5%) ($n=207$)	NF for 2–3 days, regardless of known or suspected sources	Ultra low dose CT (mean radiation dose 0.6mSv)	Consensus based on clinical + lab findings incl BAL, 2 weeks of CXRs. BAL in all patients regardless of imaging changes	Unclear	67% had pneumonia 27% IFD (?prov/prob/ possible) 63% sensitivity for 'infectious pneumonia', of any pathogen on BAL Compared to ULDCT- CXR found only 38.5% of abN	Not reported
Kang 2013, India [92]	Prospective single–centre, years not specified ($n=104$) Any patient with NF (haem, onc or other)- 76 HM	NF w/n 48 h of inset	HRCT	Unclear	Unclear	86% patients with normal CXR had an abN HRCT 89.4% of HRCTs abN, 74% highly suggestive of pulm infection 11 pts highly suspicious of IFD. BAL 8/11 aspergillus, 1/11 candidaemia Fungal sens and spec- 95% sens, 97% spec, 86% PPV and 99% NPV	Not reported

Table 2 (*Continued*)

First author/ year/coconut	Population	NF details	CT type	Comparator	Prophylaxis	Findings of scan	Impact of scan
Heussel 1999, Germany [86]	Prospective single-centre Years not specified ($n=112$, 188 scans) Mostly HM 24% HCT (5% allo, 19% auto)	NF of 48 h despite ABx and normal CXR	HRCT	Eventual changes on CXR and/or 'microbiologic evidence'	Unclear	60% scans showed pneumonia HRCT: sens 87%, spec 57%, NPV 88% 49/112 had BAL 42/112 had identified lung microorganism 61/112 micro positive	Not reported
Heussel 1997, Germany [93]	Prospective single-centre, 1994–1995 ($n=87$, 146 scans) during ChemoTx for HM (small number for breast cancer)	NF >48 h days despite ABx + normal or nonspecific CXR	HRCT Followed by BAL	CXR	Unclear	In 20/20 with nonspecific CXRs, HRCT demonstrated pneumonia. 11/20 had microorganisms found 38% true neg 70/147 normal CXR + abN HRCT- microorganisms detected in 30/70 cases, predated eventual CXR changes	7/11 with abN CXR + HRCT had changes to management 19/30 with normal CXR + abN HRCT had changes to management
Caillot 1997, France [100]	Retrospective single-centre, 1988–1996 ($n=32$ AML, 2 allo, 3 autoHCT) Only reporting on those with a positive fungal Dx	Unclear criteria for HRCT Routine CXRs twice a week Daily BCs Routine adding amph B if persistent fever Serum GM monitoring	HRCT	Pre-HRCT introduction	Unclear	23 proven IFD 14 'highly probable' IPA	10/37 died of IPA (all pre voriconazole) IPA-attributable death pre and post intro of routine CT (50% versus 17%)
Ramila 2000, Spain [87]	Prospective single-centre, Years not specified ($n=22$, 20 haem, 2 breast cancer)	NF 5 days unresponsive to ABx, normal CXR Group A (9 FNEs, 8 pts)- no resp Sx Group B- (13 FNEs, 12 pts) resp symptoms/ signs	HRCT Followed by BAL	Nil	Unclear	HRCT abN in all 22 episodes 7/22 GGOs 12/22 infectious cause identified- group A 5/9, group B 7/13 = 54% diagnostic yield	12/22 made changes based in HRCT and/or BAL 3 deaths due to pulmonary infection
CT angiography							
Sonnet, 2005, Switzerland [94]	Prospective single-centre, 2003 ($N=10$ pts, 12 scans: 9/10 HM, 4/10 ↓PMN)	'Antibiotic resistant fever' and ''clinically suspected IPA'	16-multidetector CT angiography	Nil	Unclear	14 pulm lesions >10 mm in 8/10 patients evaluated 5 lesions with angioinvasion on histopathology → 4 vascular occlusion on CT angiography Only 2/5 had halo sign	Not reported

Table 2 (*Continued*)

First author/ year/coconut	Population	NF details	CT type	Comparator	Prophylaxis	Findings of scan	Impact of scan
Ciledag 2012, Turkey [95]	Retrospective single-centre, 2009-2010 Auto or alloHCT pts ($N=37$)	NF not responding to 72 h Abx Serum GM twice weekly	Multidetector CT angiography	Nil	FQP Fluconazole Bactrim	14 probable and 11 possible IPAs 41/72 focal lesions had vascular occlusion 25/41 with vascular occlusion had a halo sign 18/25 vascular occlusion in pts with IPA	Resolution of fever in 19/25 (76%) following AFT 6 (25%) died with IPA
Stanzani 2015, Italy [96]	Prospective single-centre, 2008–2014 HM (1/3 HCT) ($N=750$ HRCT→ 100 CTPAs)	Fever >72 h despite Abx, clinical suspicion of IMD 84% ↓PMN	HRCT, then CTPA if macrodense infiltrate >10 mm. Not performed in those with cavitation	Nil	1/3 on MAP	41/750 patients had IMD (proven/probable) MAP not associated with reduced CTPA positivity Vessel occlusion greater diagnostic sensitivity for IFD than halo and hypodense signs (100% sensitive, 51% specific) 1 false pos CTPA in a patient with *S. aureus* infection	No reported
CT abdomen/pelvis							
Lim, 2016 Australia [88]	Retrospective single-centre, 2010–2015 ($N=89$) AutoSCT ($n=33$) AML ($n=56$)	CT A/P in those with persistent fever' and abdo Sx	CT A/P (83% i. v. contrast)	Nil	Fluconazole for autoHCT Posaconazole for AML	64% of scans in autoHCT showed findings 45% of scans in AML showed findings	Therapy change in 14% in auto and 24% of AML (mostly bowel rest and anaerobic cover)
Cornetto, 2016 France [89]	Retrospective single-centre, 2009–2010 alloHCT only ($N=68$, many no longer profoundly ↓PMN)	Those who underwent at least one HRCT w/n first 30 days post alloHCT - fever main indication (78%)	CT A/P (90% with i.v. contrast)		Unclear 65% on AFT prior to scan (?proph versus treatment)	34% of pts had abdominal imaging 35% of imaging was abN → mostly nonspecific: hepatomegaly, peritoneal effusion, splenomegaly Only one intra-abdo collection was noted post recent splenectomy	Not reported
CT sinuses							
Ho, 2011, USA [98]	Retrospective single-centre, 1998–2005 AML ($n=70$) ALL ($n=18$) All patients with NF and abN CT chest ($n=19$)	NF ≥4 days (18 CTs, 1 MRI), 4/19 had sinus symptoms 15/19 for protracted fever	CT sinus	Final Dx	Unclear 58% receiving AFT at time of CT (? proph versus treatment)	14/19 (73.7%) scans reported as abnormal	5/7 sinus biopsies positive for IFD (only 2/5 had symptoms)

Table 2 (*Continued*)

First author/year/coconut	Population	NF details	CT type	Comparator	Prophylaxis	Findings of scan	Impact of scan
Cornetto, 2016 France [89]	Retrospective single-centre, 2009–2010 (N = 68 alloHCT, many no longer profoundly ↓PMN)	Those who underwent at least one HRCT w/n first 30 days post alloHCT - fever main indication (78%)	CT sinus	Final Dx	Unclear 65% on AFT prior to scan [⁉proph versus treatment)	Sinus imaging in 16 pts (23%) 7 scans were abN, mainly nonspecific sinus mucosal thickening One patient diagnosed with acute sinusitis	Not reported
Choi, 2022, USA [97]	Retrospective single-centre, 2017 (n = 262 cancer/HCT NF patients)	Unclear NF duration Those who underwent CT sinus and chest during NF	CT sinus and chest	Nil	Unclear	13% of CT sinuses suggestive of infection No data on confirmation of infection	Not reported

abN, abnormal; AFT, antifungal therapy; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; amp B, amphotericin B; autoHCT, autologous haematopoietic cell transplant; BAL, bronchoalveolar lavage; chemoTx, chemotherapy; CT A/P, CT abdomen/pelvis; CT, computed tomography; CTPA, CT pulmonary angiography; CXR, chest x-ray; Dx, diagnosis; FNE, febrile neutropenic episodes; FQP, fluoroquinolone prophylaxis; GGO, ground glass opacities; GM, galactomannan; HM, haematology malignancy; HRCT, high-resolution computed tomography; IFD, invasive fungal disease; IMD, invasive mould disease; intro, introduction; IPA, invasive pulmonary aspergillosis; i.v., intravenous; MAP, mould-active prophylaxis; NF, neutropenic fever; NPV, negative-predictive value; PMN, polymorphonuclear cells; PPV, positive-predictive value; proph, prophylaxis; pulm, pulmonary; sens, sensitivity; spec, specificity; w/n, within.

reported in some studies as an outcome; however, given that most are noncomparative and observational, interpretation is hampered by an unknown underlying background mortality rate. One preintervention and postintervention study reported that invasive aspergillosis-attributable mortality reduced from 50% preroutine CT chest to 17% postroutine CT chest [100]. Impact on hospital length of stay and ICU admission have been largely unreported.

^{18}F-fluorodeoxyglucose-PET/computed tomography

^{18}F-fluorodeoxyglucose PET combined with low-dose CT (commonly known as FDG-PET/CT) is a functional imaging technique that assesses glucose metabolism of cells, traditionally used for cancer staging. Given the limitations of conventional CT imaging, and FDG-PET/CT's additional metabolic dimension and whole of body scan capability, FDG-PET/CT has been recently studied as a diagnostic modality for persistent neutropenic fever. Up until recently, only small singe-centre studies had been performed in this area; however, showing sensitivity for cause of neutropenic fever at least as good as CT, with often many other additional foci identified [101–103]. These studies reported that 55–75% of FDG-PET/CT scans lead to change in diagnostic or therapeutic management [101,103] and in particular led to cessation of antifungal therapy [104]. Particular strengths of FDG-PET/CT included identifying intra-abdominal and perineal infections and septic thrombophlebitis [102–104]. These studies are limited by small sample size and a lack of assessment of clinical outcomes as a result of any findings on FDG-PET/CT.

Recently, we performed a multicentre, randomized study comparing conventional CT with FDG-PET/CT in those with persistent and/or recurrent neutropenic fever to assess changes to management made and ultimately patient outcomes including hospital length of stay, ICU admission and mortality (The PIPPIN study) [105▪▪]. The primary outcome of antimicrobial rationalization was a composite of starting targeted antimicrobial therapy, stopping all antimicrobial therapy of a particular class, or changing spectrum of therapy (broadening or narrowing) within 96 h postrandomized scan. The study found a significantly higher odds of antimicrobial rationalization in FDG-PET/CT compared with conventional CT (OR = 2.36, 95% CI 1.06–5.24, $P = 0.033$), with the predominant outcome in this composite being narrowing therapy, with significantly higher odds of narrowing therapy post FDG-PET/CT scan (OR = 2.31, 95% CI 1.11–4.83, $P = 0.024$). Length of stay post scan was significantly

Table 3. Recent studies in ^{18}F-fluorodeoxyglucose-PET/computed tomography and invasive fungal disease

First author/year/ location	Population	Types of IFI	Performance compared with CT	Change in management	Response to therapy
Douglas, 2019, Australia [106▪]	Retrospective single-centre study 2007–2017 Solid organ and haem malignancy patients ($n=45$ patients, 48 IFDs)	Proven/probable, including: 31 *Aspergillus* spp. 3 *Candida* spp. 4 *Cryptococcus* spp. 7 *Scedosporium/Lomentospora* spp.	Identification of clinically occult infection 48 versus 38%, PET/CT to CT Detecting dissemination- 35 versus 5%	Not assessed	Discordant results in 11/18 patients- resolution on PET/CT, ongoing on CT
Leroy-Freschini, 2019, France [107]	Retrospective single-centre study 2006–2017 Immunocompromised patients ($n=51$ patients)	Proven/probable/ Possible, including 23 *Aspergillus* spp. 17 *Candida* spp. 5 *Cryptococcus* spp. 2 *Mucorales* spp.	Sensitivity for pulm IFD- PET/CT > CT in 5/21 cases Sensitivity for hepatic IFD- PET/CT > CT in 4/9 cases Sensitivity of splenic IFD- PET/CT > CT in 5/6 cases	Influenced diagnostic work up/management in 55% of patients	Problematic, assessed in retrospect. Discordant results in four cases -- liver and spleen persistent abnormalities on PET/CT Resolution of septic arthritis case
Ankrah, 2019, Netherlands [108]	Retrospective single-centre 2009–2018 All patients ($n=28$ patients)	Proven/probable/possible (36%), including 18 *Aspergillus* spp. 9 *Candida* spp.	Not assessed	Prolongation of therapy- 64% of patients Change in therapy- 29% of patients Cessation of therapy- 21% of patients	No comparison to CT Majority led to prolongation of therapy because of persistent changes on PET/CT

CT, computed tomography; IFD, invasive fungal disease; IFI, invasive fungal infection; PET/CT, PET/computed tomography; pulm, pulmonary; spp, species.

shorter in the FDG-PET/CT arm (median 3.5 days shorter). ICU admission and 6-month mortality were not different between arms. This study demonstrated that FDG-PET/CT was well tolerated when incorporated into a diagnostic strategy for persistent/recurrent fever and promoted narrowing of broad-spectrum of empiric therapy. The applicability of this approach in the real world needs to be considered on a centre-by-centre basis, based on availability of FDG-PET/CT.

^{18}F-fluorodeoxyglucose-PET/computed tomography and invasive fungal disease

FDG-PET/CT appears to be particularly beneficial in detecting sites of IFD and its dissemination (Table 3). An Australian single-centre 10-year retrospective study reported positive FDG-PET/CT findings in 45 patients with 48 proven/probable IFDs [106▪]. Compared with conventional CT, FDG-PET/CT detected more sites of dissemination (35 versus 5%) and in treated patients frequently demonstrated FDG-avidity resolution where conventional CT continued to demonstrate lesions, suggesting that FDG-PET/CT may have the ability to detect response to therapy at an earlier stage than CT (Fig. 1).

A small single-centre French study in adults and children also demonstrated high sensitivity of FDG-PET/CT for *Aspergillus* spp. (97%) with moderate specificity (80%), and diagnostic accuracy of 90% [107]. Conversely, FDG-PET/CT had moderate sensitivity for invasive candidiasis (83%) but high specificity (100%) and diagnostic accuracy of 87%. These findings could be explained by the predominant presentation of invasive aspergillosis being pulmonary, where there are several differential causes of pulmonary lesions; in contrast to invasive candidiasis, which often has only blood culture positivity without focal organ involvement; however, if there is focal involvement, it is quite specific. FDG-PET/CT also showed superior performance to CT in detecting dissemination. This study did, however, highlight that FDG-PET/CT is not sensitive for central nervous system (CNS) infection and cannot rule out CNS involvement, and dedicated CNS imaging (typically MRI) is required. Finally, change of management related to FDG-PET/CT (diagnostic workup or antifungal management) was reported in 55% of patients. This assessment, however, was performed in retrospect, sometimes many years post scan performance, so reliability of this measure is unclear.

A group from the Netherlands reported their experience with FDG-PET/CT in 18 proven/probable and 10 possible IFD cases, mostly invasive candidiasis and aspergillosis [108]. As a result of FDG-PET/CT, 29% of patients had a switch in antifungal

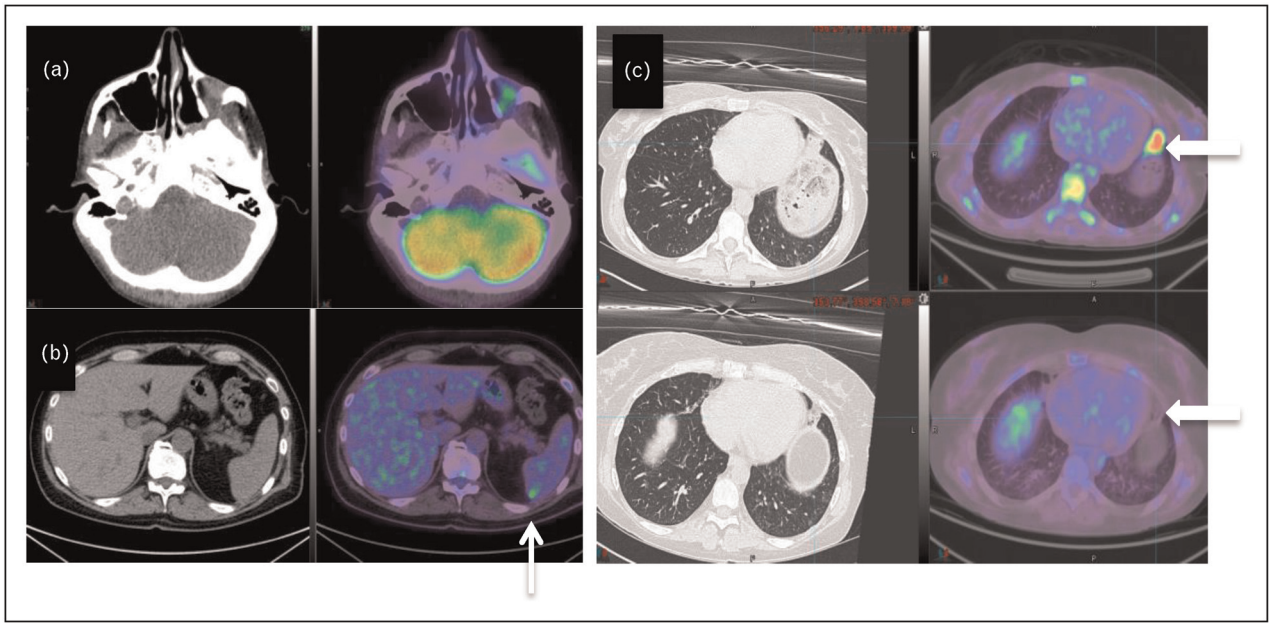

FIGURE 1. Selected ^{18}F-fluorodeoxyglucose-PET/computed tomography images illustrating appearances of invasive fungal infection. (a) Low-dose CT and fused PET/CT image of sino-orbital infection with *Aspergillus*. (b) Low-dose CT and fused PET/CT image of disseminated scedosporiosis with avid splenic lesion (thin white arrow). (c) Typical pulmonary *Aspergillus* lesion in left lower lobe (top images – low-dose CT and fused PET/CT), with postantifungal treatment images (bottom – low-dose CT and fused PET/CT) demonstrating discordant PET/CT and CT response (thick white arrows). Reproduced with permission from Douglas *et al.* [106▪]. CT, computed comography; FDG-PET, ^{18}F-fluorodeoxyglucose-PET.

therapy, 21% had therapy ceased and 43% had therapy prolonged, with durations of therapy often very prolonged. This does raise concerns about FDG-PET/CT interpretation and the lack of accuracy of some diagnoses (10 possible IFDs with unclear pathogen) as possible contributors to this prolongation. A prospective, interventional study assessing the safety and outcomes of FDG-PET/CT-guided therapy would be the logical next step.

Recently, there has been research into novel ways to specifically radiolabel fungal pathogens for detection on PET. Siderophores are iron scavenger molecules utilized by specific fungal or bacterial species. *Aspergillus fumigatus* utilizes the siderophores triacetylfusarinine C (TAFC) and fusarinine C [109▪▪], and researchers have radiolabelled TAFC with gallium-68 (^{68}Ga-TAFC) and demonstrated targeted uptake of this molecule in IPA mouse models [110]. A first-in-human pilot clinical trial is about to commence of adult patients with proven/probable invasive aspergillosis to assess potential clinical translation of this exciting technology. Conversely, a group in Germany have developed radiolabelled antibodies targeting *A. fumigatus*, which have also shown reliable identification of IPA on PET in mouse models [111]. These pathogen-specific PET techniques would be game changers for clinicians managing potential IFD in high-risk patients, and progress in this field is keenly awaited.

CONCLUSION

In the challenging field of high-risk neutropenic fever, progress has been made in the area of early discontinuation of antibiotic therapy in those patients who are clinically stable. Delineation of the best approach such as timing of cessation and/or use of FQP and further study in the higher risk alloHCT setting is still required. Imaging investigation of those with persistent neutropenic fever has recently progressed with promising findings with the incorporation of FDG-PET/CT into the diagnostic algorithm. There are several potential new roles and areas of study for FDG-PET/CT to support antimicrobial management in high-risk neutropenic fever patients, including cessation of antifungal therapy in IFD, and the use of labelled PET in defining infection.

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Conflicts of interest

The authors report no direct conflicts of interest in the writing of this manuscript. A.D. has received a fellowship grant from Gilead and has been granted honoraria from Gilead (paid to her institution). M.S. has been awarded two NHMRC grants as well as grants from Gilead, Merck and F2G, as well as honoraria from Pfizer, Merck and Gilead, and is on the DSMB/advisory board of Pfizer, F2G and Roche with all payments to an institution. K.T. reports no competing interests.

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