**Title:**

The Clinical Utility of FDG-PET for Investigation of Fever in Immunocompromised Children.

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**ABSTRACT**

Purpose: Fever in immunocompromised children presents significant challenges. We aimed to determine the clinical impact of FDG-PET in combination with computerised tomography (CT) in children with malignancy or following hematopoietic stem cell transplant with prolonged or recurrent fever.

Methods: Immunocompromised children who underwent FDG-PET/CT for investigation of prolonged or recurrent fever were identified from hospital databases. The clinical impact of the FDG-PET/CT was considered 'high' if it contributed to any of: diagnosis of a new site infection/inflammation, change to antimicrobials or chemotherapy or additional investigations or specialist consult contributing to final diagnosis.

Results: 14 patients underwent an FDG-PET/CT for prolonged or recurrent fever. Median age was 11 years and 46% had diagnosis of acute lymphoblastic leukaemia. The median absolute neutrophil count on day of FDG-PET/CT was 0.47 cells/uL. The clinical impact of FDG-PET/CT was 'high' in 11 (79%) patients, contributing to rationalization of antimicrobials in three, and cessation of antimicrobials in five. Compared to conventional imaging, FDG PET/CT identified seven additional sites of clinically significant infection/inflammation, in seven patients. Of the 10 patients that had a cause of fever identified, FDG-PET/CT contributed to the final diagnosis in six (60%).

Conclusion: This study has identified potential utility for FDG-PET/CT in immunocompromised children with prolonged or recurrent fever. Further prospective studies are needed to compare FDG-PET/CT versus conventional imaging, identify the optimal timing of FDG-PET/CT, and the role of subsequent scans to monitor response to therapy.

## INTRODUCTION

Prolonged or recurrent fever in children with cancer presents significant diagnostic and management challenges. The absence of the typical manifestations of infection, coupled with low positive and negative predictive values of conventional imaging modalities such as computerized tomography (CT), magnetic resonance imaging (MRI), X-ray, and ultrasound (US) make localisation of infection in this population difficult.[1]

Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) in combination with CT, is increasingly recognized as beneficial in the identification and management of infection in the adult cancer population.[2] In a prospective study of 20 patients with prolonged febrile neutropenia (FN), FDG-PET/CT identified 8 additional sites of infection and significantly altered management in 75%, compared to conventional evaluation.[2] Other studies in the immunocompromised adult population confirm the beneficial contribution of FDG-PET/CT towards management, including a positive effect on antimicrobial usage, with cessation or rationalization of broad-spectrum empiric agents.[3,4]

Comparatively, literature regarding the use of FDG-PET and infection in immunocompromised children is limited. A retrospective study investigating FDG-PET/CT in 31 children with pyrexia of unknown origin (PUO) included 12 with immune suppression, in whom FDG-PET/CT correctly identified the source of fever in seven (88%).[5] Another retrospective study of 69 children with PUO, albeit non-

immunocompromised, found FDG-PET helpful in reaching final diagnosis in 45% of patients.[6]

We describe the clinical impact of FDG-PET/CT in immunocompromised children with prolonged or recurrent fever in our centre.

## MATERIALS AND METHODS

### Patients

Children treated with immunosuppressive therapy for malignancy, aplastic anemia or hematopoietic stem cell transplant (HSCT) who had FDG-PET/CT for investigation of prolonged or recurrent fever, were retrospectively reviewed (January 2010 to January 2016). Patients were identified from databases at Royal Children's Hospital (RCH) and Peter MacCallum Cancer Centre (PMCC). The RCH is a tertiary referral center for paediatric malignancy and the only HSCT center in Victoria, Australia. All patients requiring a FDG-PET/CT were referred to the PMCC.

Patients were included if they had a FDG-PET/CT for investigation of fever (prolonged or recurrent), within 21 days of conventional imaging (CT, X-ray, MRI, US). Patients were excluded if they had FDG-PET/CT for cancer diagnosis or staging. Patient's clinical details, pathology results, and imaging were recorded by retrospectively reviewing hospital databases. The CT component of the combined FDG-PET/CT was a non-contrast low-dose CT, performed for the purposes of attenuation correction and anatomical correlation, and was not of diagnostic quality.

Fever was defined as a temperature ≥ 38 degrees Celsius. Prolonged fever was defined as fever for ≥ 72 hours, and recurrent fever was defined as a new fever after 48 hours of being afebrile within the same period of neutropenia. Invasive fungal infections (IFI) were classified as proven, probable and possible according to EORTC criteria.[7] Bacteraemia was defined as a recognized pathogen cultured from one or more blood cultures, or common commensals cultured from two or more blood cultures drawn on separate occasions.

**Assessment of Clinical Impact**

The clinical impact of the FDG-PET/CT on patient management was assessed using previously described methodology.[2-4] The impact of the FDG-PET/CT was deemed 'high' if any of the following criteria were met:

a. Led to additional investigations or procedures (including referral to other specialist teams) resulting in diagnosis;
b. Detected inflammation suggestive of infection not identified by conventional imaging or microbiological investigations;
c. Resulted in appropriate rationalization or change of antimicrobial management

The impact was classified as 'low' if it only confirmed results previously identified on conventional imaging, did not result in any alteration of patient management, or if it failed to demonstrate infection identified by conventional imaging.[2]

**Ethics review**

This study was approved by the institutional human research ethics committee (DA009-2015-18).

## RESULTS

### Patient characteristics

193 patients underwent an FDG-PET/CT. 176 were excluded as they received their FDG-PET/CT for assessment of their malignancy. Of the remaining 17 patients, two were excluded as the FDG-PET/CT was done to stage an established infection. One further patient was excluded as the FDG-PET/CT was performed more than 21 days after conventional radiological evaluation (58 days).

14 patients underwent FDG-PET/CT in addition to conventional imaging, for evaluation of prolonged or recurrent fever (Table 1). No patient required a general anaesthetic. The median age was 11 years (range 1-17 years). The median absolute neutrophil count (ANC) was 0.47 cells/uL (range 0-6.2 cells/uL), with seven patients having an ANC of less than 0.1 cells/uL.

The FDG/PET-CT was abnormal in eight patients (57%), identifying 12 sites of infection or inflammation (Patients 10, 11, 13, 14 had two discrete sites of increased FDG uptake identified) (Table 2). Five patients (36%) had a positive FDG-PET/CT result despite profound neutropenia (ANC <0.1cells/uL).

### FDG-PET/CT evaluation

Compared to conventional evaluation, FDG-PET/CT identified an additional seven sites of clinically significant infection or inflammation in seven patients (Patients 5, 6, 8, 10, 11, 13 and 14) including multiple pulmonary nodules suggestive of IFI in three

patients. Of the ten patients that had a cause of fever identified, FDG-PET/CT contributed to the final diagnosis in six (60%). (Table 2)

In one episode FDG-PET/CT failed to demonstrate infection (possible pulmonary IFI) that was identified by conventional evaluation (Patient 9). Notably, the patient had received 15 days of voriconzole prior to the FDG-PET/CT. The patient ceased voriconazole, but represented in the next phase of neutropenia with progression of the pulmonary nodules previously identified on CT. He was recommenced on antifungal therapy with good response and resolution of nodules.

**Clinical impact of FDG-PET/CT**

The clinical impact of the FDG-PET/CT was considered 'high' in the management of 11 of the 14 (79%) patients (Table 2). The FDG-PET/CT prompted referral of 5 patients for specialist consults which resulted in a diagnosis or change to management. Nine patients (64%) had alterations to antimicrobials subsequent to FDG-PET/CT: one had rationalization of broad-spectrum antibiotics to a more targeted regime, five (36%) had their antibiotics ceased, two had rationalization of their broad-spectrum antifungal (liposomal amphotericin) to voriconazole for treatment of possible or probable invasive pulmonary aspergillosis and one had voriconazole commenced for possible pulmonary aspergillosis.

**DISCUSSION**

Our descriptive study suggests FDG-PET/CT may be useful in the evaluation of paediatric immunosuppressed patients with prolonged or recurrent fever. This is in keeping with adult studies demonstrating that FDG-PET/CT has increased ability to

identify occult infection or inflammation.[2-4] In addition, the capacity for FDG-PET/CT to diagnose infection or inflammation does not appear to be impaired by neutropenia, as FDG-PET/CT was still positive in many of the patients with profound neutropenia.

The use of FDG-PET/CT in immunocompromised patients with fever has the potential to compliment antimicrobial stewardship (AMS) efforts. As a result of the FDG-PET/CT, antimicrobials were appropriately altered in 64% of our patients. It is conceivable, that in the absence of FDG-PET/CT, some patients would have unnecessarily continued broad-spectrum antimicrobials until ANC recovery. An Australian study found that FDG-PET/CT, performed within 4 days of conventional imaging, was associated with shorter duration of empiric liposomal amphotericin-B for prolonged FN (median 4 versus 10 days) and a shorter length of stay, with associated cost savings of between AUD 7440 and 14 455 per patient, as compared to conventional imaging.[8]

Importantly, the FDG-PET/CT failed to identify a significant infection in one patient. As with other investigations, a negative FDG-PET must be interpreted with other clinical information. Duration of antimicrobial treatment prior to imaging should also be taken into account and, in the situation of discordant results, follow up FDG-PET/CT may be considered prior to the next clinical risk period.

The limitations of this study include the small number of patients, retrospective nature, and enrolment from a single institution. The time between both fever onset and conventional imaging and FDG-PET/CT was prolonged in many patients. This

may have contributed to the failure of FDG-PET/CT to identify the pulmonary nodules previously detected on CT chest in one patient. Results of other studies also suggest the clinical impact of FDG-PET is more pronounced the earlier it is performed in patients' clinical course.[2,4] In the five patients who had antimicrobials ceased after negative FDG-PET/CT results, the retrospective nature of this study limits our ability to determine if repeated conventional imaging (rather than FDG-PET/CT) would have afforded the same clinical impact. However, as FDG-PET/CT provides a whole-body overview as opposed to conventional imaging which is often targeted to a specific site (e.g. lungs or abdomen), it is likely that the negative FDG-PET/CT was more reassuring to the clinician. In addition, although few patients had confirmatory tissue diagnosis, there were sufficient additional investigatory results to aid overall diagnosis in the majority of episodes. This is is reflective of usual paediatric practice where biopsies and tissue diagnoses are not always possible.

The radiation dose from FDG-PET/CT needs to be considered. Whilst the average whole-body effective dose of an FDG-PET is not insignificant, a retrospective review of 78 children who had 248 FDG-PET/CT found the largest component of exposure came from the CT, ranging from 2.7 to 54.2 milliSieverts.[9] Since this review, there has been a significant reduction in radiation dose from CT, due to the introduction of new technology and increased awareness of radiation exposure effects.[10] Therefore, whilst doses of the magnitude reported in this review are now rare, there is increasing interest in further dose reduction possible with FDG-PET combined with MRI, as well as the benefits of improved soft tissue characterization of this imaging modality. Recently, rapid lung MRI has been shown to have high sensitivity and specificity

compared to CT for detection of pulmonary nodules in children with leukemia and FN.[11]

Our study demonstrates that FDG-PET/CT may be a valuable tool for the investigation and management of immunosuppressed children with prolonged or recurrent fever. Further prospective studies are needed to identify the optimal timing of FDG-PET, the role of subsequent scans to monitor response to therapy and the potential for MRI to replace CT.

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