Title

Use of FDG-PET/CT for investigation of febrile neutropenia: evaluation in high-risk cancer patients.

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Abstract

Purpose

Febrile neutropenia (FNP) is a frequent complication of cancer care and evaluation often fails to identify a cause. [^{18}F]fluorodeoxyglucose Positron Emission Tomography Computerised Tomography (FDG-PET/CT) has the potential to identify inflammatory & infectious foci, but its potential role as an investigation for persistent FNP has not previously been explored. The aim of this study was to prospectively evaluate the clinical utility of FDG-PET/CT in patients with cancer and severe neutropenia and 5 or more days of persistent fever despite antibiotic therapy.

Methods

Adult patients with a diagnosis of an underlying malignancy and persistent FNP (temperature >= 38^{o}C and neutrophil count < 500 cells/μl for 5 days) underwent FDG-PET/CT as an adjunct to conventional evaluation and management.

Results

Twenty patients with FNP fulfilled eligibility criteria and underwent FDG-PET/CT scanning in addition to conventional evaluation. The median neutrophil count on the day of the FDG-PET/CT scan was 30 cells/μl (range 0–730). Fourteen distinct sites of infection were identified by conventional evaluation, 13 (93%) of which were also identified by FDG-PET/CT, including all deep tissue infections. Nine additional likely infection sites were identified by FDG-PET/CT, 8 of which were subsequently confirmed as "true positives" by further investigations. FDG-PET/CT was deemed to be of 'high' clinical impact in 15 of 20 (75%) patients.

Conclusion

This study supports the utility of FDG-PET/CT scanning in severely neutropenic patients with 5 or more days of fever. Further evaluation of the contribution of FDG-PET/CT in management of FNP across a range of underlying malignancies is required.

Keywords; FDG-PET/CT, Febrile neutropenia

Introduction

More than 50% of patients with fever and neutropenia (febrile neutropenia, FNP) have established or occult infection which may be life threatening [1]. Both bacterial and fungal organisms are frequently implicated as pathogens, however evaluation of the patient with FNP often fails to isolate a cause or site of infection. Initiation of broad-spectrum antibiotics at the onset of FNP and rapid diagnosis and therapy for invasive fungal infections (IFI) both reduce mortality, but are associated with drug toxicities and cost [2-5]. Persistence of fever after 3-5 days of initial antibiotic treatment often necessitates additional laboratory and imaging investigations and sometimes escalation of antimicrobial therapy including empiric antifungal agents [1,2].

Diagnosis of infections in patients with FNP, in particular IFI, is hampered by the low positive and negative predictive values of available investigations [4-6]. Culture of blood, urine and other specimens has variable yield for many infections and targeted attainment of tissue for culture (e.g. by biopsy) has risks. More recently antigen assays (e.g. B-1,3-glucan and galactomannan) and polymerase chain reaction (PCR) techniques have been developed, however sensitivity and specificity remain less than perfect [5,6]. Conventional radiography has very low sensitivity and computerised tomography (CT) scanning may have transient findings which are non-specific. An ideal diagnostic imaging tool for patients with FNP would be highly sensitive for identifying infections at all body sites and have an excellent negative predictive value, effectively excluding infection when the test was negative.

By localising to metabolically active cells, Fluorine-18-deoxyglucose (FDG) is a useful tracer for the imaging of neoplastic conditions [7]. It is recognised that FDG is also taken up by neutrophils and activated macrophages associated with inflammatory, infectious or granulomatous processes [7, 8]. When FDG-PET is performed on a hybrid device allowing contemporaneous computerised tomography (FDG-PET/CT), anatomical localisation and characterisation of focal areas of radiotracer accumulation may allow differentiation of malignancy from infection [7,8].

Preliminary studies and case series suggest that FDG-PET/CT may be a useful tool for diagnosis of infection in patients with malignancy [9-13]. FDG-PET/CT is able to identify infections in patients with multiple myeloma, including some patients with severe neutropenia, lymphopenia or $CD4^+$ lymphocytopenia [9]. FDG-PET/CT may also detect infected central venous catheters, deep septic thrombophlebitis and IFI [10-13]. In patients with IFI, FDG-PET/CT scanning appears at least as sensitive as conventional imaging techniques in identifying infections. Additionally, it may reveal previously unidentified foci of infection, and may have a role in monitoring response to antifungal therapy [12-14]. Whether FDG-PET/CT would be a useful addition to the routine investigations performed for persistent FNP is unknown.

The objective of this study was to evaluate the clinical impact of the addition of FDG-PET/CT scanning in patients with FNP, when compared to conventional investigation and management. We prospectively evaluated the incremental value of FDG-PET/CT scanning subsequent to conventional evaluation of 20 patients with persistent FNP at a cancer centre.

Materials and methods

Patients

The study was conducted at the Peter MacCallum Cancer Centre (Melbourne, Australia). This hospital is a tertiary referral centre for patients with a range of haematological and solid malignancies. As a pilot study, an arbitrarily designated cohort of 20 patients was planned for recruitment and prospective evaluation. The study was performed between May 2008 and September 2010.

The target population consisted of hospitalised adult patients undergoing investigation and treatment for chemotherapy or disease-related FNP. Eligibility criteria included persisting fever (temperature $\geq 38^0$C) and neutropenia (absolute neutrophil count < 500 cells/μl) five days after onset of FNP, regardless of whether a potential cause of fever had been identified. Patients were enrolled on day 5 of

the febrile episode, with view to undergoing FDG-PET/CT scanning within 3 days. Exclusion criteria were pregnancy, uncontrolled diabetes, concurrent administration of medication which would interfere with FDG uptake or PET image ascertainment, or if FDG-PET/CT scanning had already been scheduled as part of routine care.

Conventional evaluation

Conventional evaluation included daily complete clinical assessment of the patient and laboratory testing (blood and urine cultures, blood film, biochemistry and C-reactive protein). Additional microbiological investigations (such as sputum and wound swab cultures), serologic tests, antigen capture assays, polymerase chain reaction assays and imaging were performed upon request of the treating clinician based on perceived clinical need. Imaging modalities available included conventional X-ray, ultrasound, CT, magnetic resonance imaging and nuclear medicine scans. Invasive diagnostic procedures (including bronchoscopy and biopsy) were performed upon request of the treating clinician.

FDG-PET/CT imaging protocol

All PET/CT studies were acquired on a PET/CT scanner (Discovery STE, GE Medical Systems, Milwaukee, WI, USA). Patients were fasted for a minimum of four hours prior to scanning and generally in excess of 6 hours. Blood glucose levels were <10 mmol/L at the time of FDG administration. A dose of 285-370 MBq was administered intravenously. A non-contrast CT scan was acquired in helical mode at 140 kVp, 80 mAs and reconstructed at a slice thickness of 3.27mm. The FDG-PET scan encompassed the same axial extent as the CT scan, from the skull base to the proximal thighs, representing 4-6 bed positions depending on the size of the patient. Each bed position had an acquisition time of 5-minutes and was acquired in 2-D or 3-D mode depending on the patient's weight with 2-D imaging reserved for patients weighing >100kg. The images were reconstructed using iterative reconstruction using the order-subset estimate maximization (OSEM) algorithm.

FDG-PET/CT reporting

Each FDG-PET/CT image was interpreted by a nuclear medicine physician who was provided with results of clinical evaluation, laboratory testing and conventional imaging (current at the time of scanning). FDG-PET/CT scan results were made available to the treating physicians immediately upon reporting. It was considered unethical to withhold diagnostic information in the context of a potentially life-threatening medical condition. As the study aim was to assess the incremental rather than independent diagnostic utility of FDG-PET/CT compared to conventional techniques, there was no attempt at blinding of cases.

PET, CT and PET/CT fused images were reviewed on a dedicated workstation (Xeleris; GE Medical Systems). The FDG-PET/CT scan was interpreted qualitatively on images normalised for hepatic uptake using a linear grey scale for the PET images and a rainbow colour scale for fused images set with an upper threshold standardised uptake value (SUV) of approximately 7. On this scaling, hepatic activity, which typically has a SUV of around 3.5 is displayed in the middle of the colour range and represents approximately a transition from blue to green. On this colour scale, areas of enhanced FDG uptake are seen as yellow, orange or red. The FDG-PET/CT was reported as negative, equivocal or positive. *Negative* was defined as no FDG uptake beyond normal physiological activity, *equivocal* as focal FDG uptake considered to be greater than expected physiological activity, but with uncertainty regarding the likely aetiology of this increased uptake based on pattern, intensity or correlative CT findings, and *positive* as FDG uptake beyond normal physiological activity suggestive of infection.

Comparison of FDG-PET/CT with conventional evaluation

For each study participant, all conventional investigations were reviewed to determine the presence or absence of infection at the time of FDG-PET/CT scan. This assessment was performed independently by two infectious diseases physicians, at least one of whom was not involved with the patient's care. In the event of disagreement, adjudication was sought from a third infectious diseases physician.

The impact of the FDG-PET/CT scan result on patient management was assessed using an adaptation of previously described tools for evaluating the impact of FDG-PET/CT on infection and cancer management [9,15]. Impact was deemed '*high*' if FDG-PET/CT prompted additional investigations or

procedures including referral for consultation, detected infections not identified by conventional evaluation or it resulted in a change of antimicrobial management (prolongation of, alteration of or withholding antimicrobial therapy which would otherwise have been initiated). Clinical impact was deemed '*low*' if FDG-PET/CT only confirmed results of the conventional evaluation and no other management alterations ensued, or it failed to show infection identified by conventional evaluation.

Ethics review
The study was approved by the institutional human research ethics committee. Patients were required to provide written informed consent prior to participation.

Statistical analysis
Sensitivity of FDG-PET/CT was defined as the number of infections identified by FDG-PET/CT that had been identified by conventional evaluation prior to FDG-PET/CT imaging. A 95% confidence interval was calculated using exact method with binomial distribution.

Results

Patient characteristics are reported in Table 1. Results of conventional evaluation, FDG-PET/CT scanning and evaluation of FDG-PET/CT scan impact are summarised in Table 2. No adverse events related to FDG-PET/CT scanning were reported.

Patient characteristics
Twenty neutropenic patients (13 males, 7 females) underwent FDG-PET/CT scanning in addition to conventional evaluation after a minimum of 5 days of persistent FNP (Table 1). The median age was 61.5 years (range 28 – 70 years). The median duration of documented neutropenia prior to the onset of fever was 9 days (range 0 – 129 days). Twelve patients had FDG-PET/CT scanning on days 5-7 of their febrile episode and 8 patients had scans on day 8 or later due to logistic difficulties in accessing a scanning appointment.

Conventional evaluation
Fourteen infections were diagnosed in 11 patients by conventional evaluation and were thought likely to have been present at the time of FDG-PET/CT scanning (Table 2). Two of these infections had microbiological confirmation: mixed enterobacteriaciae blood stream infection thought to have arisen from an intra-abdominal process (Figure 1) and *Pseudomonas aeruginosa* sternal osteomyelitis, which had been confirmed 4 months previously. Four patients (patients 2, 3, 5 and 8) had venous catheter-associated bloodstream infection prior to or at the onset of their febrile neutropenic episode. All had undergone removal of the vascular catheter, directed antimicrobial therapy, conventional radiological exclusion of septic thrombophlebitis and repeat blood cultures. These infections were therefore deemed not to be present at the time of FDG-PET/CT scanning and were considered not to be responsible for the persisting febrile episode.

FDG-PET/CT scanning
Sixteen FDG-PET/CT scans were positive, 1 was equivocal and 3 were negative. Twenty two likely sites of infection were apparent (Table 2). Patient 9 had an equivocal scan which revealed uptake beyond normal in the cardiac atria of uncertain aetiology or significance, and no further investigation was performed.

Comparison of conventional evaluation and FDG-PET/CT scanning
Compared to conventional evaluation, FDG-PET/CT had a sensitivity of 92.9% (95% CI, 66.1 – 99.8%) for identifying infections, finding all except 1 infection diagnosed by conventional evaluation. FDG-PET/CT located 9 additional likely foci of infection that were not diagnosed by conventional evaluation. These likely infections were: pneumonitis (2), enterocolitis (2), pre-vertebral abscess (1), muscle abscess (1), perianal infection (1), pancreatitis (1) and tonsillitis with regional lymphadenitis

(1). With the exception of pancreatitis, these infections were all confirmed by subsequent conventional evaluation including microbiological sampling, imaging and bronchoscopy.

Impact of FDG-PET/CT scanning on patient management

FDG-PET/CT scanning was considered 'high' impact in the management of 15/20 (75%) patients (Table 2). FDG-PET/CT identified 8 (subsequently confirmed) infections that were not previously diagnosed by conventional evaluation. The FDG-PET/CT scan prompted 3 patients to be referred for surgical review and resulted in altered antimicrobial management in 9 patients.

Discussion

This study supports the utility of FDG-PET/CT scanning in severely neutropenic patients with persistent fever who are at high risk of infection. Importantly, FDG-PET/CT scanning identified all deep tissue and organ infections identified by conventional evaluation and located an additional 8 infections which conventional evaluation failed to identify.

The FDG-PET/CT scan had 'high' impact on patient management in 75% of the studied cohort. FDG-PET/CT identified additional likely infections in 9 patients, 8 of which were subsequently confirmed by further investigation. The FDG-PET/CT scan prompted alteration of antimicrobial management in 9 patients, including 1 patient who underwent prolonged therapy for liver abscess and 1 patient commenced antifungal therapy. Notably, 5 patients (patients 2, 9, 12, 14 and 17) had empiric antifungal therapy withheld at day 5 of their FNP episode, this decision being supported by a FDG-PET/CT which suggested the absence of IFI. These patients all recovered and did not manifest evidence of IFI following the scan. In the five patients whose FDG-PET/CT had 'low' impact upon management, 2 patients had no cause of the FNP identified by either FDG-PET/CT or conventional evaluation, 2 patients had enterocolitis identified by both techniques and 1 patient had an infection diagnosed by conventional evaluation but a normal FDG-PET/CT.

Patient 7 had an infection diagnosed by conventional evaluation that was not identified by FDG-PET/CT scanning (i.e. a false negative scan result). This patient was a 61 year old man undergoing fludarabine and cytarabine induction chemotherapy for acute myeloid leukemia. Six days after the onset of FNP, he developed throat and neck pain. Palpation of the neck revealed a tender left-sided lymph node and otolaryngoscopy revealed supraglottitis without mucosal ulceration. CT of the neck revealed a single, small left-sided lymph node (1.3cm) but no abnormality of the glottis. Swabs of the pharynx and supraglottis failed to identify a causative viral or bacterial pathogen. The FDG-PET/CT was performed on day 8 of FNP, within 48 hours of the onset of clinical findings. It is possible that the location and nature of this infection (i.e. involvement of superficial mucosa) and relatively small burden of infection were beyond the sensitivity of FDG-PET/CT.

Limitations of the study include the small number of patients, enrolment from a single institution and that allogeneic bone marrow transplant recipients were not included. FDG-PET/CT is more readily available at our centre than at many other centres treating cancer patients and our centre's reporting nuclear medicine physicians have considerable expertise in use of FDG-PET/CT for infection. The delay experienced by some patients in awaiting a scan (beyond day 5-7 of the febrile episode) may have reduced the sensitivity of FDG-PET/CT for detection of infection. The presence of neutropenia appears not to compromise the sensitivity of this technique and has an advantage over conventional nuclear medicine infection scanning, where the requirement for radio-labelling of white blood cells may not be met in the setting of low circulating numbers of leukocytes [16]. Radio-labelled anti-granulocyte monoclonal antibodies, or their fragments, have been employed to image infectious diseases [17]. When compared to FDG-PET/CT, images obtained with anti-granulocyte monoclonal antibodies are generally of lower resolution, which is often the case with monoclonal antibody type studies. Moreover, anti-granulocyte monoclonal antibodies are not able to reliably differentiate inflammation from infection, and are therefore not necessarily more specific than FDG-PET/CT [17].

To our knowledge there is no reported use of radio-labelled anti-granulocyte monoclonal antibodies in the assessment of febrile neutropenia.

Our study adds further support to the usefulness of FDG-PET/CT scanning in severely neutropenic patients [9,13]. In contrast to the study by Mahfouz et al, where the majority of patients were scanned as a staging tool for their malignancy and a small proportion of patients were severely immunocompromised (neutropenic, lymphopenic or $CD4^+$ lymphocytopenic), our patients with severe persistent neutropenia were all scanned to identify new or already documented infections. While most patients in both studies had one or more infections identified (including previously unidentified and silent infections), the FDG-PET/CT more frequently impacted on patient management in the current study (75% vs 48% of patients).

FDG-PET/CT has previously been used for monitoring response to therapy and to help establish when discontinuation of therapy is appropriate, in the setting of bacterial and fungal infections [8,12,13,15]. In the instance that FDG-PET/CT identifies infection in a patient with persistent FNP, follow up scanning has theoretical merit in monitoring response to treatment, and excluding other new clinically unsuspected sites of infection, although this was not evaluated as a part of the current study. In light of the findings from this pilot study, the current role of FDG-PET/CT is perhaps as an adjunct in persistently febrile patients (for more than 5 days) to identify or exclude occult infection missed in their conventional diagnostic workup. A negative FDG-PET/CT test may support a clinical decision to withhold empirical antifungal therapy in this situation. Use of FDG-PET/CT as an upfront test (i.e. in the first 1-3 days of FNP) to direct further imaging or sampling tests may be worth evaluating.

In conclusion, FDG-PET/CT is a useful investigation modality in patients with severe neutropenia and fever present for 5 days, and is capable of detecting deep tissue and organ infections identified by conventional evaluation. Additional sites of infection may be identified and significant management alterations result following the use of FDG-PET/CT scanning in this population. A negative FDG-PET/CT scan may provide greater confidence in a decision to withhold empiric antifungal therapy. Larger multi-centre evaluation of the contribution of this technique to the management of FNP in patients with a broad range of underlying malignancies, the optimal timing of FDG-PET/CT scanning for diagnostic yield, and the cost-benefit of this investigation are required.

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The authors declare they have no conflict of interest.

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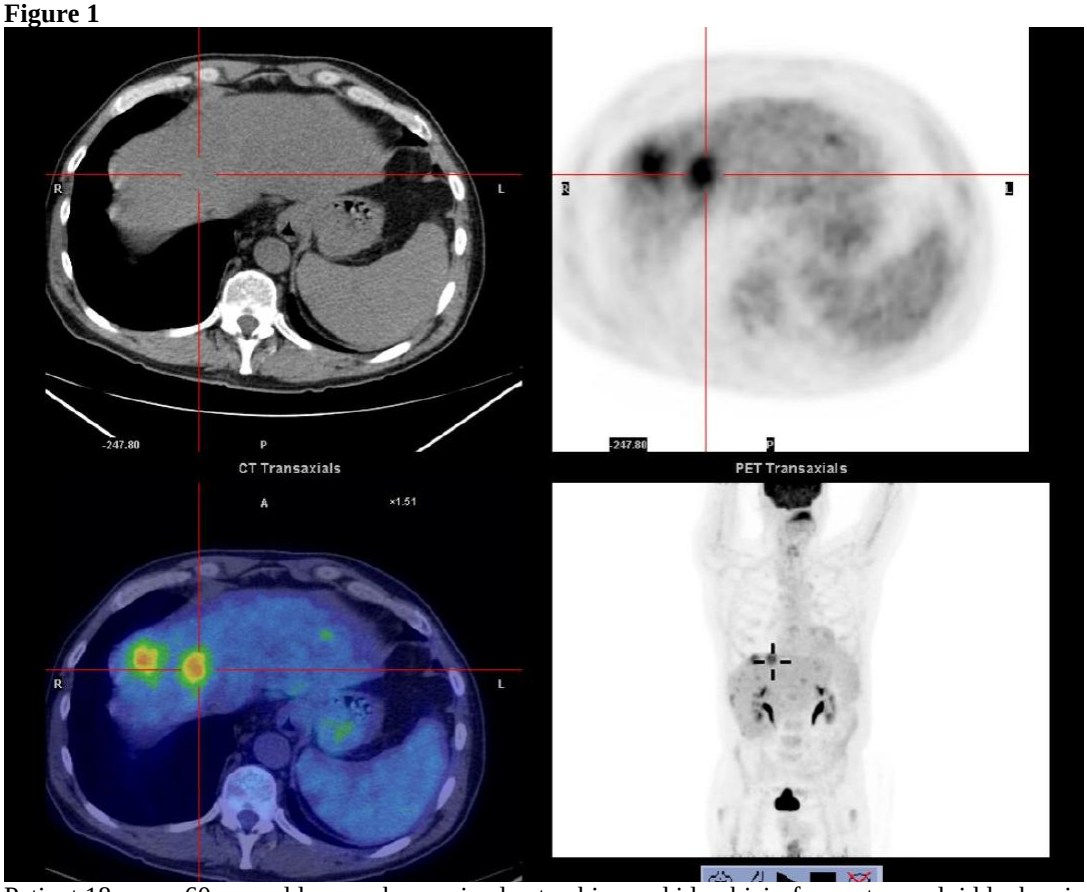
Figure 1



Patient 18 was a 60 year old man who received cytarabine and idarubicin for acute myeloid leukemia. On day 16 of neutropenia he developed fever, and blood cultures yielded *Escherischia coli* and *Klebsiella pneumoniae*. Conventional imaging including Computerised Tomography and ultrasound failed to demonstrate abnormality. FDG-PET/CT performed on day 14 after the onset of his FNP episode when his neutrophil count remained at 30 cells/µl demonstrated probable liver abscess.

Table 1 Characteristics of patients with febrile neutropenia (FNP)

Patient	Age	Sex	Underlying disease and therapy	Duration of neutropenia before fever	Days of FNP before FDG-PET/CT scan	ANC (cells/µl) day of FDG-PET/CT
1	28	M	Tonsillar and pyriform fossa SCC; cis-platin	0	9	130
2	62	M	MDS and secondary AML; idarubicin & cytarabine	21	7	10
3	51	M	Follicular lymphoma; autologous stem cell transplant	1	5	0
4	54	M	Relapsed AML; cytarabine & idarubicin	2	6	10
5	62	M	Follicular lymphoma; autologous stem cell transplant	4	5	80
6	62	M	Relapsed AML; cytarabine & idarubicin	0	7	80
7	61	M	AML; fludarabine & cytarabine	0	8	70
8	52	M	Multiple myeloma; autologous stem cell transplant	15	9	730
9	41	M	Relapsed AML; fludarabine, cytarabine, etoposide, & gemtuzumab	9	8	30
10	45	M	T-cell ALL; autologous stem cell transplant	14	7	30
11	35	F	AML; cytarabine & idarubicin	14	6	10
12	63	M	AML; cytarabine & idarubicin	4	8	30
13	58	F	AML; cytarabine & idarubicin	11	6	160
14	69	F	AML; cytarabine & idarubicin	7	7	480
15	70	F	AML; fludarabine & cytarabine	12	6	0
16	68	F	AML; cytarabine & idarubicin	9	6	30
17	64	M	AML; fludarabine, cytarabine & gemtuzumab	38	11	60
18	60	F	AML; cytarabine & idarubicin	16	14	30
19	65	F	Follicular lymphoma; no recent therapy	129	7	20
20	63	M	AML; fludarabine & cytarabine	0	14	30

SCC, squamous cell carcinoma; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; FNP, febrile neutropenia

Table 2 Results of investigations and evaluation of impact of FDG-PET/CT

Patient	Conventional evaluation	FDG-PET/CT scan	Impact (high/low) and change to patient management
1	Negative	1. Cervical pre-vertebral abscess	**High**; MRI scan and surgical consultation
2	1.Tonsillar bed ulcer	1. Tonsillar bed infection & lymphadenitis	**High**; Antifungal therapy withheld despite further fevers
3	Negative	Negative	**Low**
4	1. Perianal infection 2. Epididymo-orchitis	1. Perianal infection 2. Epididymo-orchitis	**High**; Further CT imaging of perianal pathology, surgical consultation
5	Negative	Negative	**Low**
6	Negative	1. Pneumonitis	**High**; Further HRCT chest and microbiological sampling, addition of targeted antimicrobial therapy
7	1. Supraglottitis & cervical lymphadenitis	Negative	**Low**
8	Negative	1. Pneumonitis	**High**; Clinical deterioration ensued, further HRCT chest confirmed diffuse pneumonitis
9	Negative	Equivocal; Uptake in cardiac atria	**High**; Empiric antifungal therapy withheld, alteration of antimicrobial therapy
10	Negative	1. Obturator internus abscess	**High**; Additional focus of infection identified
11	1. Enterocolitis	1. Enterocolitis	**Low**
12	Negative	1. Sigmoid & jejunal enterocolitis	**High**; Directed antimicrobial therapy, empiric antifungal therapy withheld
13	1. Sigmoid colitis	1. Sigmoid colitis	**Low**
14	Negative	1. Perianal infection	**High**; Directed antimicrobial therapy, empiric antifungal therapy withheld
15	1. Pneumonitis	1. Pneumonitis, 2. Pancreatitis	**High**; Further investigation for pancreatitis
16	1. Pneumonia	1. Pneumonia 2. Tonsillitis & cervical lymphadenitis	**High**; Additional focus of infection identified
17	1. Perianal infection	1. Proctitis	**High**; Directed antimicrobial therapy, empiric antifungal therapy withheld
18	1. Mixed enterobacteriaciae bacteraemia (normal CT abdomen and pelvis)	1. Liver abscess	**High**; Prolonged antibiotic therapy, surgical consultation and consideration for drainage
19	1. Sternal osteomyelitis 2. Pneumonia 3. Sigmoid diverticulitis	1. Sternal osteomyelitis, 2. Pneumonia 3. Sigmoid diverticulitis	**High**; Bronchoscopy and addition of empiric antifungal therapy
20	1.Pneumonitis	1. Pneumonitis, 2. Sigmoid/descending colitis	**High**; Additional focus of infection, further lung imaging and directed antimicrobial therapy

MRI, magnetic resonance imaging; CT, computerised tomography; HRCT, high resolution computerised tomography

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