British HIV Association guidelines on the management of opportunistic infection in people living with HIV:
The clinical investigation and management of pyrexia of unknown origin 2023

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1 Introduction

Now that the majority of people living with HIV take combination antiretroviral therapy (ART), the spectrum of causes of pyrexia of unknown origin (PUO) has changed compared with the pre-ART era. In these guidelines, we focus on causes and evaluation of PUO among people living with HIV with CD4 counts <350 cells/mm^3. Causes of PUO in people living with HIV with higher CD4 counts are likely to be similar to those in HIV-negative individuals. Therefore, for those with higher CD4 counts we recommend following guidance for management of PUO in the general population [1-3], with the caveat that some infections, for example invasive pneumococcal disease [4] and tuberculosis (TB) [5], are more common among people living with HIV than those without HIV even on ART and with higher CD4 counts.

Infective, inflammatory, neoplastic and miscellaneous causes need to be considered in all cases. HIV alone is rarely a cause of PUO, and other possible causes should always be investigated.

Guidance on supporting patients living with HIV with opportunistic infections, including PUO, can be found on the British HIV Association (BHIVA) website (https://www.bhiva.org/file/6225e44b53c49/OI-guidelines-supporting-patients.pdf).

A full review of these guidelines is due by 2028, with interim updates only if recommendations need updating in line with new data.

2 Methods

The scope, purpose and guideline topics were agreed by the writing group. The search (population, intervention, comparator and outcome [PICO]) questions were set and an independent systematic literature review carried out. The Medline, Embase and Cochrane Library databases were searched and the literature reviewed to address each question. The PICO questions and search strategies are outlined in Appendix 1.

Further details of the methodology can be found on the BHIVA website (https://www.bhiva.org/file/5d514ec9b503d/OI-guidelines-methods-general.pdf), including the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess and grade the evidence.

Good practice points (GPPs) are recommendations, based on the clinical judgment and experience of the writing group, with which few clinicians are expected to disagree and for which evidence is unlikely to emerge as they are generally considered to be good practice.

3 Summary of recommendations

From Section 8 Essential clinical evaluation and investigations

- **For any individual with PUO, a lifelong travel history should be taken and documented (GPP).**
- **For any individual with fever, essential baseline investigations should be carried out and results known before PUO is diagnosed and before moving to second-line investigations (GPP).**
- **For any individual with PUO, a full sexual health screen should be completed, including blood tests for viral hepatitis and syphilis (GPP).**

From Section 9.1 ^{18}F-fluorodeoxyglucose (^{18}FDG) PET-CT

- **We suggest that ^{18}FDG PET-CT is considered early in the diagnostic work-up if the history, examination and baseline investigations have not revealed a potential cause of the PUO or site for biopsy (Grade 2D).**
- **For individuals with low CD4 counts (<350 cells/mm^3), we suggest that the utility of ^{18}FDG PET-CT is limited to identifying a site for tissue biopsy where one has not been located using other means (Grade 2C).**
- **We suggest that, in people living with HIV with low CD4 counts (<350 cells/mm^3), the degree of avidity on ^{18}FDG PET-CT is not useful in distinguishing between infectious and non-infectious pathology (Grade 2C).**

From Section 9.2 Bone marrow culture, microscopy and histology

- **We suggest that bone marrow examination may be most useful where fever coexists with cytopenias (Grade 2C).**
- **Bone marrow samples should be cultured for bacteria including mycobacteria and fungi as well as examined microscopically (GPP).**

From Section 9.3 Comparison of fine needle aspiration (FNA), Tru-Cut® biopsy and whole lymph node excision

- **We suggest that, in general, a larger tissue sample from a core biopsy may have better diagnostic yield in culture for mycobacteria than a smaller sample from FNA (Grade 2C).**

From Section 9.4 Mycobacterial blood culture

- **As mycobacterial blood culture is minimally invasive, we suggest that it is part of the initial investigation of PUO in people living with HIV who have low CD4 counts (<200 cells/mm^3) or are hospitalised (GPP).**

From Section 9.5 Liver biopsy

- **We suggest that liver biopsy may be considered, and that diagnostic yield may be greatest, where there is hepatomegaly and raised alkaline phosphatase and when other less invasive investigations have not confirmed a diagnosis (Grade 2D).**
- **We suggest that where mycobacterial disease is a possible diagnosis, a thorough search for sites suitable for less-invasive investigation, including lymph node biopsy, induced sputum/bronchoalveolar lavage or early morning urine, may reduce the need for invasive procedures (Grade 2C).**

From Section 10 Should empirical antimicrobial therapy be prescribed to individuals with HIV and PUO?

- **We suggest that before starting empirical antimicrobial therapy, consideration is given to a second opinion from another relevant specialist (for example a rheumatologist) (GPP).**

From Section 12 IRIS

- **IRIS is a diagnosis of exclusion and other causes for the clinical deterioration should be considered (GPP).**

4 Summary of audit measures

- Percentage of individuals with HIV and CD4 counts <350 cells/mm^3 presenting with PUO for whom a lifetime travel history (including place of birth and countries of residence) is recorded.

- Percentage of individuals with HIV (irrespective of CD4 count) presenting with PUO for whom a full sexual health screen, including blood for viral hepatitis and syphilis, is offered.

- Percentage of individuals with HIV and CD4 counts <200 cells/mm^3 presenting with PUO for whom mycobacterial blood cultures are included as part of initial investigations.

- Where tissue sampling is undertaken, including bone marrow, percentage of samples sent for bacterial including mycobacterial culture as well as histology.

5 Definitions

Over time, the definition of PUO has changed, to keep pace with the increased speed and accuracy of diagnostic tools and the reduced use of hospitalisation to investigate fever (Box 1). The original definition, published in 1961 before the discovery of HIV, required an illness of at least 3 weeks' duration, fever of 101°F (38.3°C) on several occasions and a week of inpatient investigation without reaching a diagnosis [6]. The definition was updated by Durack and Street in 1991, to include four categories of PUO: classical, nosocomial, neutropenic and HIV-associated [7]. HIV-associated PUO requires >4 weeks' duration of illness (or >3 days in hospital), with 3 days of investigation (including at least 48 hours' incubation of blood cultures and to allow time for other first-line tests, such as serology, to yield results) (Box 1). An update was published in 2003 by Knockaert *et al.* to account for changes in diagnostic methods, including the advent of rapid molecular diagnostics, with the previous requirement for 3 days' investigation replaced by 'appropriate, intelligent, standard inpatient or outpatient work-up' [8] (Box 1).

Box 1 Definitions of PUO

Original definition: 1961 [6]

A temperature >38.3°C on several occasions, accompanied by more than 3 weeks of illness, and failure to reach a diagnosis after 1 week of inpatient investigation.

Updated definition: 1991 [7]

A temperature >38.3°C on several occasions over more than 4 weeks for outpatients, or more than 3 days in hospital, where diagnosis remains uncertain after initial diagnostic work-up, including at least 2 days' incubation of cultures.

Further updated definition: 2003 [8]

The requirement for 3 days' investigation after which no diagnosis has been made replaced by 'appropriate, intelligent, standard inpatient or outpatient work-up'.

6 Frequency and causes of PUO among people living with HIV in the ART era

The search strategy as outlined in Appendix 1 generated seven studies relevant to the frequency of PUO in people living with HIV with CD4 counts <200 cells/mm^3 (Appendix 2). All were observational studies and included individuals admitted to hospital prior to the advent of effective ART. Across these studies, all providing low or very low quality of evidence, the observed frequency of PUO ranged from 1.1 to 26.3 per 100 patients/year. The frequency of PUO reduced markedly following the introduction of ART in the late 1990s, a phenomenon undoubtedly driven by rising CD4 counts and virological control among people living with HIV [9,10].

One nested case–control study conducted in Spain, spanning the pre-ART and post-ART eras, showed that not only has the incidence of PUO in Spain decreased since the introduction of ART but also the spectrum of diagnoses has changed discernibly [10]. As ART was introduced, TB became less common and visceral leishmaniasis, known to be endemic in some regions of Spain, more common. The commonest cause of PUO among individuals not on combination ART was *Mycobacterium avium* complex infection. The cause of PUO in people living with HIV obtained from 14 studies is shown in Appendix 3 (Figure and Table). In summary, infection was the major cause in all studies, inflammatory causes were rare, and the diagnosis remained unknown, despite extensive investigation, in up to 41% of individuals. In the general population the range of causes of PUO is associated with geographical location [11], and this is also evident in people living with HIV [10,12].

Immune reconstitution inflammatory syndrome (IRIS) is also a reported cause of fever in people living with HIV who have started ART and should be considered in the relevant clinical setting (see Section 12).

Common and uncommon causes of PUO that have been reported in people living with HIV are shown in Box 2. The list of causes is not exhaustive, but may help in considering wider causes in the appropriate clinical setting.

Box 2 Common and uncommon reported causes of PUO in people living with HIV

	Common causes[a]	**Uncommon causes**
Infection-related		
Bacterial	Bacterial infection [64]	Bacillary angiomatosis (bartonellosis, including visceral disease, where there is epidemiological risk) [65]
	Non-tuberculous mycobacteria [12,51,64, 66-69]	Prostatic abscesses [70]
	Tuberculosis [9,10,51,66-68,71-75]	Pyomyositis [76]
		Rhodococcus equi infection [77]
		Salmonellosis [78]
		Sinusitis [51]
		Splenic microabscesses of various aetiologies [77]
		Syphilis [79]
Viral	Cytomegalovirus disease [12,51]	Untreated HIV [51]
Fungal	Cryptococcosis with meningitis [74]	Cryptococcosis without meningitis [80,81]
	Pneumocystosis (including extrapulmonary disease) [12,69,73,74]	Travel-related mycoses (including paracoccidiodes, coccidiodes, talaromycosis and histoplasmosis) [82-84]
Parasitic	Visceral leishmaniasis (where there is epidemiological risk) [9,10,64,66,68,71,72]	Babesiosis [85]
		Disseminated toxoplasmosis (with or without brain lesions) [86]
		Visceral leishmaniasis (may be more common, depending on geography) [10,51,87]
Non-infectious		
Neoplastic/ lymphoproliferative	Lymphoma [10]	Castleman's disease [88]
		Kaposi's sarcoma [68]
Inflammatory/ miscellaneous		Autoimmune disease, including vasculitis [64,68]
		Haemophagocytic lymphohistiocytosis [89]
		Drug-related fever [90,91]
		Factitious fever [51,64]
		Subacute thyroiditis [92]
		Interleukin-1β antagonistic activity deficit [93]
		Thromboembolic disease [94]

[a]This includes conditions that comprise more than 10% of infectious aetiologies identified in reported series; the frequency of many will depend on CD4 count and viral load or ART status.

7 Do the causes of PUO differ by age and subgroups?

In the general population the spectrum of causes of PUO has changed over time. In addition to geographical location, the range of causes of PUO differs by age of the population studied and risk profile, for example among returning travellers, migrants or people with neutropenia [7,10].

7.1 Age

Among people living with HIV, no associations have been reported between different causes of PUO and age or specific subgroups. The literature on causes of PUO among people living with HIV is largely from the 1980s and 1990s and the age profile of the population of people living with HIV has changed since then with the introduction of effective ART, new and late diagnoses in older people and longer life expectancy [13]. This is likely to affect presenting causes of PUO, particularly among those on ART with higher CD4 counts, for whom causes of PUO are likely to be similar to those experienced by people without HIV.

Among people without HIV and, probably, people with HIV and higher CD4 counts, malignancies may be more common among older individuals and vasculitides and other non-infectious inflammatory causes may be more common among those who are younger [1].

7.2 Migrants and travellers

Causes of PUO will differ depending on exposure to pathogens in specific geographical areas [10] (see also the travel-related opportunistic infection chapter in the BHIVA and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011 [14]) and a lifelong travel history is essential to ensure that geographical exposures are taken into account.

There are clear associations between TB disease and birth or long-term residence in a country with a high incidence of TB [15-17]. A lifelong travel history will assist in formulating a differential diagnosis for returning travellers or migrants, who may have been exposed to infections prevalent in

geographically restricted areas (for example visceral leishmaniasis and endemic fungal infections including talaromycosis and histoplasmosis) and guide appropriate parasitological or fungal investigations.

In Public Health England's 2019 report on HIV in the UK (using 2018 data), data are presented for place of birth (UK or outside of the UK) for people accessing HIV care in the UK. For those who probably acquired HIV through heterosexual sex, 31% were born in the UK and the remaining 69% were born outside the UK; for newly diagnosed gay or bisexual men, 71% were born in the UK or elsewhere in Europe [13].

7.3 People who inject drugs

Late diagnosis is more common among people who inject drugs than in other groups [13] as is delayed treatment start and difficulties with engagement in care and treatment adherence. The spectrum of causes of PUO in this group may be more likely to include bacterial infections (particularly *Staphylococcus aureus* and group A streptococcus) [18], such as infective endocarditis and bone infections. Among new diagnoses of HIV in the UK in 2018, 2% were in people who inject drugs [13].

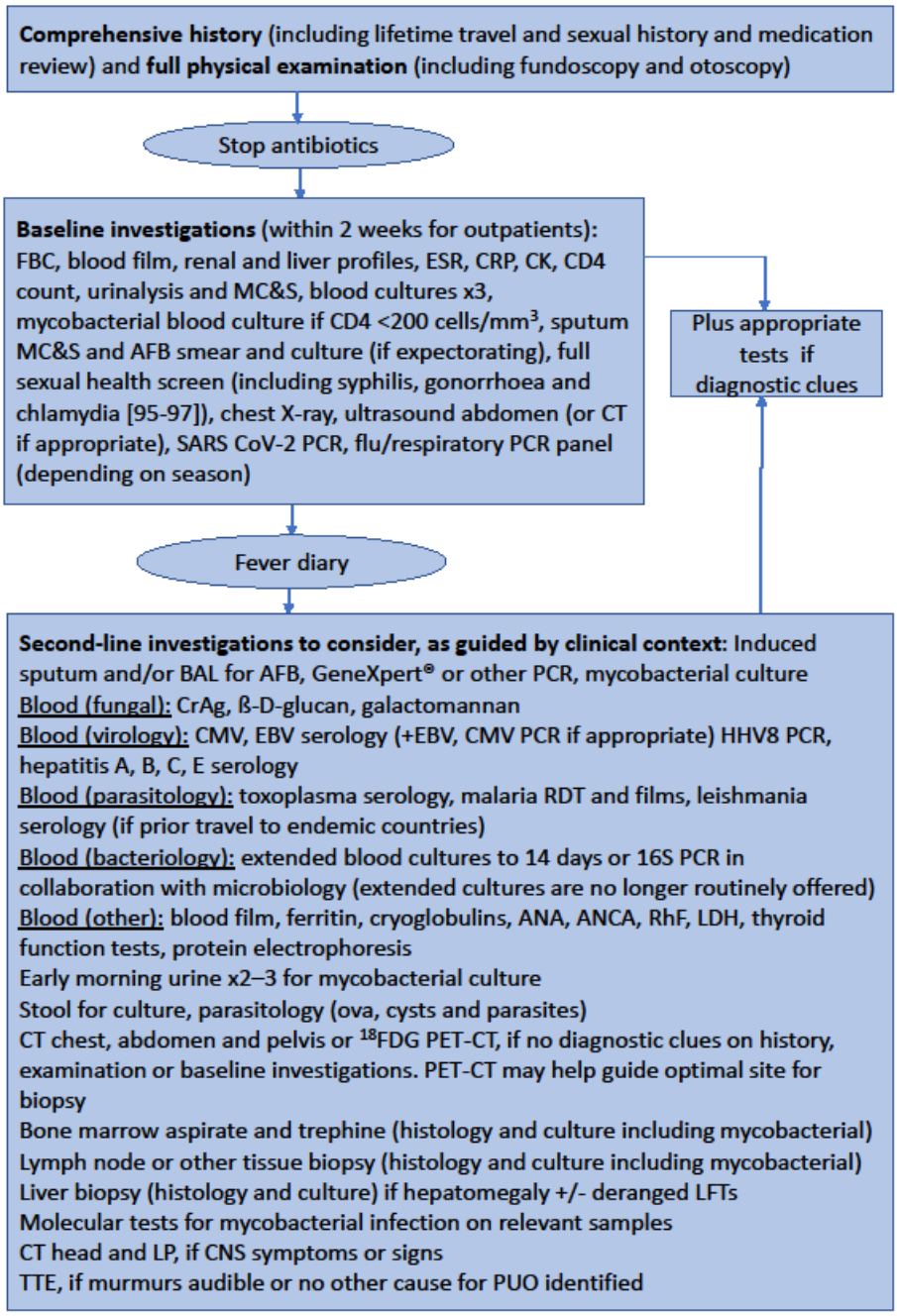
8 Essential clinical evaluation and investigations

Recommendations

- **For any individual with PUO, a lifelong travel history should be taken and documented (GPP).**
- **For any individual with fever, essential baseline investigations should be carried out and results known before PUO is diagnosed and before moving to second-line investigations (GPP).**
- **For any individual with PUO, a full sexual health screen should be completed, including blood tests for viral hepatitis and syphilis (GPP).**

In individuals with PUO, a comprehensive history and a full examination, often repeated on more than one occasion, are essential. The history should include medical history and comorbidities; surgical history, in particular the presence of indwelling foreign material; family history; lifetime travel history, including place of birth and countries of residence; sexual history; drug use; animal contacts; occupation; hobbies; and medication history. In addition to a full cardiovascular, respiratory, abdominal and neurological examination, a detailed physical examination should include dilated fundoscopy and otoscopy, examination of temporal arteries, sinuses, ear, nose and throat, lymph nodes, liver and spleen, search for bone and joint tenderness and skin and mucous membrane lesions, and prostate examination. Fever should always be verified with a temperature chart and, where there is concern about factitious fever, hospitalisation may rarely be needed to record the temperature. Of note, antibiotics and anti-inflammatory agents should be stopped where possible before assessing temperature and initiating investigations. Essential baseline investigations should be carried out before diagnosing PUO and before moving to second-line investigations (Figure 1). We suggest that baseline investigations could largely be completed and results available within 2 weeks for outpatients, with samples still in mycobacterial culture at that time and imaging depending on availability. Timelines (other than culture) should be shorter for inpatients. Signs, symptoms or other abnormalities, for example lymphadenopathy or jaundice, are potential diagnostic clues and should guide further investigation [2,3].

Figure 1 Flowchart of investigation for HIV-associated PUO



AFB, acid-fast bacilli; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; BAL, bronchoalveolar lavage; CK, creatine kinase; CMV, cytomegalovirus; CNS, central nervous system; CrAg, cryptococcal antigen; CRP, C-reactive protein; CT, computed tomography; EBV, Epstein–Barr virus, ESR, erythrocyte sedimentation rate; FBC, full blood count; HHV8, human herpes virus 8; LDH, lactate dehydrogenase; LFT, liver function test; LP, lumbar puncture; MC&S, microscopy, culture and sensitivity; PCR, polymerase chain reaction; RDT, rapid diagnostic test; RhF, rheumatoid factor; TTE, trans-thoracic echocardiogram.

9 What diagnostic tests are useful for investigation of PUO in people living with HIV?

The literature review included a search for data on positron emission tomography-computed tomography (PET-CT) and liver, bone marrow and lymph node biopsy. Other investigations, for example specific serological tests, may be warranted depending on the individual history and clinical presentation and should be considered within a multidisciplinary team including infectious diseases, microbiology, virology, parasitology, rheumatology, haematology and other specialties as relevant. The imported fever service from the UK Health Security Agency (UKHSA) is a useful resource for further expert advice on managing fever in returning travellers and migrants [19].

9.1 ^{18}F-fluorodeoxyglucose (^{18}FDG) PET-CT

Recommendations

- **We suggest that ^{18}FDG PET-CT is considered early in the diagnostic work-up if the history, examination and baseline investigations have not revealed a potential cause of the PUO or site for biopsy (Grade 2D).**
- **For individuals with low CD4 counts (<350 cells/mm^3), we suggest that the utility of ^{18}FDG PET-CT is limited to identifying a site for tissue biopsy where one has not been located using other means (Grade 2C).**
- **We suggest that, in people living with HIV with low CD4 counts (<350 cells/mm^3), the degree of avidity on ^{18}FDG PET-CT is not useful in distinguishing between infectious and non-infectious pathology (Grade 2C).**

^{18}FDG PET-CT hybrid imaging is widely used in the diagnosis and staging of malignancy, particularly lymphoma, and assessing response to treatment [20,21]. Increasingly it is used to image infectious and inflammatory conditions in both immunocompetent and immunosuppressed individuals [22,23]. ^{18}FDG PET-CT is frequently used early in the diagnostic work-up of PUO in people without HIV. By contrast, there are limited data on use of this modality in the investigation of an individual living with HIV with PUO [23-28]. Six studies were identified that recorded inclusion of individuals living with HIV, with a total of 202 individuals included. Apart from one study (a systematic review, meta-analysis and Delphi review), the overall quality of data was moderate/low to very low. The studies were inconsistent in their approach to inclusion of ^{18}FDG PET-CT in the diagnostic algorithm for investigation of PUO. ^{18}FDG PET-CT imaging did not appear to provide discrimination between specific diagnoses but was useful in identifying lymph nodes with increased avidity that could be targeted for biopsy. Additionally, a lack of focal ^{18}FDG avidity aided in ruling out significant pathology, and a high HIV viral load did not appear to impair interpretation of ^{18}FDG PET-CT images.

9.2 Bone marrow culture, microscopy and histology

Recommendations

- **We suggest that bone marrow examination may be most useful where fever coexists with cytopenias (Grade 2C).**
- **Bone marrow should be cultured for bacteria including mycobacteria and fungi as well as examined microscopically (GPP).**

Bone marrow examination (which should include both bone marrow aspirate and trephine biopsy) is useful in the diagnostic work-up of PUO in the general population. However, the yield from culture is minimal, compared with the yield from histopathological analysis (in particular for diagnosis of haematological malignancy or haemophagocytic lymphohistiocytosis) [29]. No guidelines exist for clinicians to use when deciding on the timing of bone marrow examination in relation to performing other investigations in a patient with PUO [30].

Ten studies were identified that examined the utility of bone marrow examination in individuals living with HIV (with a total of 673 people included). All were single-centre studies and eight were retrospective [31-40]. The data quality ranged from very low to moderate. The overall yield from bone marrow examination ranged from 0% to 63%, and in several studies reporting a good yield from bone marrow examination the diagnosis was also made based on other investigations but was made earlier based on bone marrow examination (histology/cytology or microscopy). Comparison between studies is limited by a lack of uniform approach to timing of bone marrow examination in relation to other investigations.

9.3 Comparison of fine needle aspiration (FNA), Tru-Cut® biopsy and whole lymph node excision

Recommendation

- **We suggest that, in general, a larger tissue sample from a core biopsy may have better diagnostic yield in culture for mycobacteria than a smaller sample from FNA (Grade 2C).**

There is no good evidence to support a preference for use of FNA, Tru-Cut® biopsy or whole lymph node excision in the investigation of PUO in people living with HIV. Small studies investigating lymph node biopsy for diagnosis of TB have shown good sensitivity of FNA compared with excision biopsy for cytological evidence of TB [41,42]. One study [41] showed equal sensitivity for culture, but as an observational study there may have been bias in terms of liquid or purulent FNA samples being selectively sent for culture. Meghji and Giddings support a strategy of proceeding to open culture if AFB smear is positive, as positive culture is likely [43]. However, it is important to note that a culture-based diagnosis is paramount, where possible, for mycobacterial infections, in order to be able to confirm organism identification and drug susceptibility, because a histological diagnosis is not definitive. The 2019 update of the National Institute for Health and Care Excellence guideline on TB

does not provide advice on whether to use excision biopsy or FNA [44]. In general, a greater biomass is more likely to yield positive culture and an excision biopsy will allow histological examination. Again, in studies of lymph node biopsy to diagnose TB, there is no evidence that excision biopsy leads to greater risk of sinus formation or ulceration [41].

9.4 Mycobacterial blood culture

Recommendation

- **As mycobacterial blood culture is minimally invasive, we suggest that it is part of the initial investigation of PUO in people living with HIV who have low CD4 counts (<200 cells/mm^3) or are hospitalised (GPP).**

One study reported on the yield of mycobacterial blood cultures plus liver biopsy results in 12 individuals with HIV and PUO in the pre-ART era [45]. In this comparison of the yield of blood culture, bone marrow culture and liver biopsy in PUO, CD4 counts were not recorded, but most individuals were lymphopenic and all had some liver function test abnormalities. Eight ultimately had mycobacterial infection, with six, five and six of these showing mycobacterial blood culture, bone marrow culture and liver biopsy culture positivity respectively. Histological examination of bone marrow and liver biopsy specimens gave earlier indication of mycobacterial disease than blood culture, although culture was required for organism identification and drug susceptibility. Absence of acid-fast bacilli or granulomas on bone marrow or liver biopsy specimens did not exclude eventual growth of mycobacteria from these specimens.

9.5 Liver biopsy

Recommendations

- **We suggest that liver biopsy may be considered, and that diagnostic yield may be greatest, where there is hepatomegaly and raised alkaline phosphatase and when other less invasive investigations have not confirmed a diagnosis (Grade 2D).**

- **We suggest that where mycobacterial disease is a possible diagnosis, a thorough search for sites suitable for less-invasive investigation, including lymph node biopsy, induced sputum/bronchoalveolar lavage or early morning urine, may reduce the need for invasive procedures (Grade 2C).**

Liver biopsy has the potential to confirm histological or microbiological diagnosis of mycobacterial and other infections as well as malignant and inflammatory conditions. The literature review yielded largely observational studies, with consistent evidence that diagnostic yield is likely to be greater in the presence of hepatomegaly, splenomegaly or raised alkaline phosphatase levels.

Of nine relevant studies on the use of liver biopsy in the investigation of PUO among people living with HIV, eight were single-centre observational studies [46-53]. The ninth was the comparison by Prego *et al*. [45], discussed above, of mycobacterial blood culture, liver biopsy and bone marrow biopsy among 12 individuals in the pre-ART era.

The eight single-centre studies evaluated a total of 356 individuals with HIV and PUO, from settings across Europe, North America, East Africa and South East Asia, and were published between 1990 and 2015. Quality of evidence for individual studies was very low, but some results were similar across studies [46-53].

Four studies showed that mycobacterial infection was more frequently identified among those with raised alkaline phosphatase levels [46-49]. In one of these studies, conducted in Spain, in which the predominant diagnoses were TB and visceral leishmaniasis, liver biopsy was found to be helpful in the presence of hepatomegaly or splenomegaly and, for those with TB, in the presence of hepatomegaly and raised alkaline phosphatase [48]. In the same study, in 4/31 cases in which liver biopsy was considered helpful in diagnosing TB, the organism was isolated from another site (blood, bone marrow or lymph node) and among 12 individuals diagnosed with leishmaniasis, nine also had amastigotes visible on bone marrow examination [48]. One study performed in France before the availability of cartridge-based nucleic acid amplification tests (for example Xpert MTB/RIF®)

demonstrated that among those for whom a liver biopsy was diagnostic, other, less invasive tests, for example blood culture, bronchoalveolar lavage, sputum and urine, were more likely also to yield diagnostic results, with a shorter time to positive culture for non-invasive samples (mean ± standard deviation [SD] 15 ± 5 days) than for liver biopsy (mean ± SD 28 ± 9 days) [50]. The authors concluded that liver biopsy did not increase the diagnostic yield compared with non-invasive sampling. However, more rapid turnaround of histology compared with culture may be helpful in guiding initial therapy. In another French study [51], 44 of 57 individuals with PUO had CD4 counts <100 cells/mm^3; in addition, among 49 in whom a cause was found, 41 had infections. Of those with mycobacterial infection, non-tuberculous mycobacteria were associated with lower CD4 counts than TB. Liver biopsy enabled identification of mycobacterial and other infections as well as lymphoma.

Diagnoses other than mycobacterial infection, made by liver biopsy, included: leishmaniasis, cryptococcal disease, schistosomiasis and lymphoma in the two above-mentioned studies from France [50,51]; cytomegalovirus disease, malignancy and bacillary angiomatosis in the above-mentioned study from Thailand [46]; and cytomegalovirus, lymphoma and schistosomiasis in a study from New York [52].

Before the ART era, liver biopsy in people living with HIV was reported to be associated with an increased risk of haemorrhage and death, in part thought to be related to concurrent thrombocytopenia and/or clotting disorders [54,55]. This should be considered when deciding whether to proceed with liver biopsy. The risk of serious complications resulting from biopsies taken for assessment of liver disease from people with hepatitis B infection is very low at between 1 in 4000 and 1 in 10,000 [56], although in 2001 it was reported that 1–3% of individuals undergoing liver biopsy needed hospitalisation, mostly for pain or hypotension [57]. Given the risk of complications, albeit low, consideration must be given to the likelihood of confirming a diagnosis from less-invasive sampling, for example blood, lymph node or urine, versus the potential benefit of confirming a histological diagnosis by liver biopsy.

10 Should empirical antimicrobial therapy be prescribed to individuals with HIV and PUO?

Recommendation

- **We suggest that before starting empirical antimicrobial therapy, consideration is given to a second opinion from another relevant specialist (for example a rheumatologist) (GPP).**

There is no published evidence to support practice in this area. In principle, the risks and benefits of empirical antimicrobial treatment should be considered, including the likelihood of benefit from treatment, the toxicity of treatment and the severity of illness, along with lifetime travel history. All relevant sampling should be completed before starting treatment if possible.

Fever in itself is not an indication for antibiotics. In clinically unstable patients, for example showing signs of sepsis, broad-spectrum antibiotics may be administered after blood cultures and other relevant bacteriological samples (depending on the clinical scenario and may include urine, cerebrospinal fluid, pus and pleural fluid) have been collected and while results of investigations are pending. If possible, antibiotics with anti-mycobacterial activity (macrolides, fluoroquinolones and carbapenems) should be avoided. Broad-spectrum antibiotics may reduce diagnostic yield and are associated with toxicity, including hospital-acquired infections such as *Clostridiodes difficile,* as well as contributing to the burden of antimicrobial resistance. Empirical treatment for mycobacterial, fungal or parasitic disease requires further consideration and discussion within a multidisciplinary team.

11 Should ART be considered in individuals with PUO who are not already on ART?

There is very limited published evidence to address this question. In general, it is good practice to investigate, diagnose and begin treatment for febrile conditions before starting ART, and starting ART while the source of fever remains undetermined is not usually recommended.

In particular:

- If mycobacterial disease is strongly suspected but extensive tests are negative, it should be excluded or empirical treatment started.
- Cryptococccal disease should be excluded using blood cryptococcal antigen testing.
- Central nervous system (CNS) infections should be excluded, if suggested by clinical symptoms and signs, before ART is started.

For specific recommendations, see current BHIVA guidelines on ART [58], TB [59] and other opportunistic infections [14] (of note, the BHIVA opportunistic infection guidelines are being updated chapter by chapter; for the latest chapters see https://www.bhiva.org/guidelines).

In some cases, it may be necessary to start ART while fever persists and a cause for the fever has not been determined after thorough investigation, because further delay to ART initiation presents a risk of further opportunistic infections.

Starting ART in the presence of potentially undiagnosed or undertreated opportunistic infections may unmask the infection and increase the risk of IRIS. However, the World Health Organization now recommends earlier ART for all except those with CNS infections, because of evidence of low mortality from IRIS and no benefit in delaying for those starting treatment for TB [60] (see also BHIVA TB guidelines [59]).

12 IRIS

Recommendation

- **IRIS is a diagnosis of exclusion and other causes for the clinical deterioration should be considered (GPP).**

In the appropriate clinical situation, IRIS should be considered as a cause of fever. Paradoxical IRIS refers to the clinical situation of paradoxical worsening of a partially treated opportunistic infection or disease after starting ART. 'Unmasking' IRIS refers to clinical deterioration after starting ART due to an undiagnosed opportunistic infection or disease that was not previously clinically apparent [61]. Definitions have been published by Haddow *et al*. [61] and Meintjes *et al*. [62] for TB-associated IRIS and by Haddow *et al*. for cryptococcal IRIS [63]. Risk factors for IRIS include recent initiation of ART with good virological or immunological response and starting ART early in the course of treatment of opportunistic disease.

13 References

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14 Acknowledgements

The writing group thanks Dr Roshina Gnanadurai, Southmead Hospital, North Bristol NHS Trust, Dr Ewan Hunter, Royal Victoria Infirmary, Newcastle-upon-Tyne, and Dr Mark Melzer, Barts Health NHS Trust, London, for their reviews and helpful comments. The writing group also thanks Mr Ben Cromarty and Prof Nicoletta Policek, both of UK Community Advisory Board (UK-CAB), for reviewing this chapter.