Undiagnosed acute undifferentiated fever is associated with longer hospital admissions in immunocompetent adults

Houghton, Rebecca; Cleary, David; Clark, Tristan

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Undiagnosed acute undifferentiated fever is associated with longer hospital admissions in immunocompetent adults

Dr Rebecca Houghton[1,2,4], Dr Nathan Brendish[1,2,3], Dr Ahalya Malachira[1,2,3], Dr Patrick Lillie[5,6], Dr David Cleary[2] Dr Tristan Clark[1,2,3]

1. Department of Infection, University Hospital Southampton NHS Foundation Trust, UK, 2. Faculty of Medicine and Institute for Life Sciences, University of Southampton, UK 3. NIHR Southampton Biomedical Research Centre, 4. Hampshire Hospitals NHS Foundation Trust, 5. University of Hull, UK, 6. Infection Research Group, Hull University Teaching Hospitals, UK

AUFI : An acute illness with fever of ≥38°C lasting less than 21 days which lacks localisable clinical features with no clear cause identified following initial review and investigation (1,2,3)

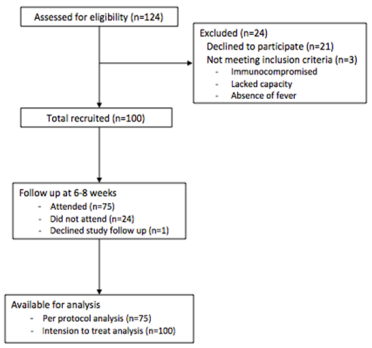
1. Introduction and purpose:

Acute undifferentiated fever (AUFI) has not been well characterised in the UK. AUFI is frequently attributed to infection, however, a high proportion of individuals remain undiagnosed (1,2,3,4) and antimicrobial use is high. There is little data on clinical outcome and admission length and few studies include follow up of patients following discharge. Most AUFI studies have been performed in countries with endemic malaria and vector borne infections which are not comparable with a UK cohort. We aimed to characterise the clinical features, aetiology, antimicrobial use and outcomes of adults hospitalised with AUFI at a UK hospital.

2. Methods:

One hundred adults were recruited within 72 hours of admission, those with significant immunocompromise were excluded. Clinical data was recorded and a predetermined set of diagnostic tests were performed in addition to standard of care. Participants were followed up at 4 to 6 weeks. Investigations, treatment, outcomes and diagnoses were recorded and analysed. This study was approved by the Research Committee (15/YH/0429) and prospectively registered with ISRCTN (ISRCTN11747901). This data was collected as part of a study which aimed to characterise the clinical features of AUFI and compare the diagnostic utility of unbiased metagenomic next generation sequencing (mNGS) to standard of care diagnostics. The clinical characteristics of the AUFI cohort are presented here.

Figure 1 trial profile



3. Results:

Between November 2015 and July 2017, 124 adults were approached by the study team (see figure 1). Over half were male and the median age was 35 years. The majority (68%) were of 'white British' ethnic origin, followed by 'European' (9%) and 'Indian' (8%). Most 77% (77/100) had at least one comorbidity (median = 1; IQR 1.0-2.0; range 1-11). These were most commonly, gastrointestinal 25% (25/100), neurological 21% (21/100) and respiratory 18% (18/100), 8% (8/100) reported to be current smokers and 8% (8/10) were diabetic (see table 1).

Travel: Half 49.0% (49/100) had travelled within the prior three months. The median interval between travel (leaving destination) and illness was nine days (IQR 1.0-28.3; range -3.0-61.0). Most popular destinations included; Europe (46.9%; 23/49), South Central Asia (24.5%; 2/49) and Sub-Saharan Africa (20.4%; 10/49).

Diagnosis: A diagnosis was confirmed in 48% (48/100) of participants. Infections predominated; viral 27% (27/100), bacterial 18% (18/100) with few non-infectious diagnosis made 3% (3/100) (see table 2). An average of 14 microbiological and radiologically investigations were performed per participant but only a small proportion of these were diagnostic (5%; 70/1401). Empirical antimicrobial use was common (81%; 81/100) (see figure 2).

Outcome: Of those who attended follow up 67% (50/75) had ongoing symptoms and ongoing symptoms were more common in undiagnosed 60% (31/52) than diagnosed participants 40% (19/48) (difference 0.44 (CI 02.-4.9), p=0.07). However, the most significant study finding was that undiagnosed patients had statistically significantly longer hospital admissions than diagnosed patients (median 2.9 IQR [1.6-4.9] days versus 1.7 [0.8-1.6] days; difference of 1.2 days (95%CI 0.04 to 1.66); p=0.036).

4. Conclusions:

Further multi-site studies should be performed to better understand AUFI in the UK and explore the impact of undiagnosed AUFI on on-going symptoms and duration of admission and the impact on the individual and healthcare resources. Focus on broad-ranging accurate infection diagnostics is crucial to accurately identify the causes of AUFI.

Figure 2 Total antibiotic consumption by agent (days) n=100

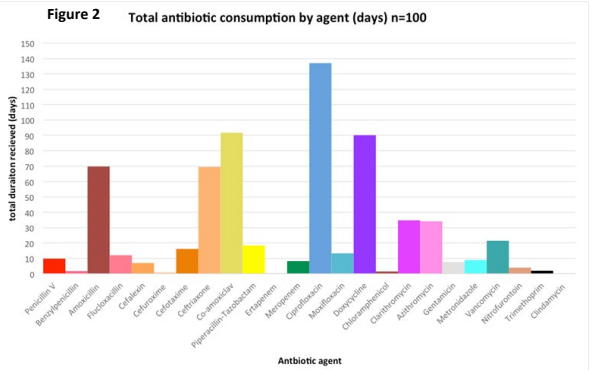


Table 1 Demographics	Diagnosed n= 48	Undiagnosed n= 52	OR (95% CI)	p value
Female	21 (44.0)	23 (44.0)	0.98 (0.43-2.2)	1.00
White British	34 (71.0)	34 (65.0)	1.29 (0.56-3.1)	0.67
Travel in prior 3 months	24 (52.0)	26(52.0)	1.00 (0.45-2.24)	1.00
Age (years)	33.0 [24.0-50.0]	36.0 [25.0-48.0]	3.00 (-5.00-8.00)	0.63
No. of comorbidities	2 [1.0-3.0]	1 [0.0-2.0]	-1.00 (-1.00-0.00)	0.08
Duration of fever (days)	3 [1.0-6.0]	4 [3.0-6.0]	1.00 (0.00-2.00)	0.07
Length of stay (days)	1.7 [0.8-1.6]	2.9 [1.6-4.9]	Diff. 1.2 (CI 0.1-1.7)	0.036
All data presented as n/n (%) and median [IQR] unless otherwise stated				

Table 2 All confirmed Infections	45/48 (94)
Viral infection	**27/48 (56)**
Influenza A (Respiratory PCR)	9/27 (33)
Dengue virus (Serology and PCR)	5/27 (19)
Enterovirus (PCR CSF and Respiratory PCR)	5/27 (19)
Epstein Barr virus (serology +/- PCR)	3/27 (11)
Hepatitis E virus (serology and PCR)	1/27 (4)
Parainfluenza virus 3 (Respiratory PCR)	1/27 (4)
Norovirus (Stool)	1/27 (4)
Chikungunya virus (EDTA + serology)	1/27 (4)
Influenza B (Respiratory PCR)	1/27 (4)
Bacterial infection	**18/48 (38)**
E. coli (n= 1 bacteraemia, n=3 urine culture)	4/18 (22)
Streptococcus pyogenes (ASO + clinical hx)	2/18 (11)
Campylobacter species (stool culture)	2/18 (11)
Mycoplasma pneumonia (serology and PCR)	2/18 (11)
Plesiomonas shigelloides (stool culture)	1/18 (6)
Salmonella enteritidis (stool culture)	1/18 (6)
Clostridiodes difficile (stool PCR)	1/18 (6)
Neisseria meningitidis serogroup B (PCR)	1/18 (6)
Shigella sonnei (stool culture)	1/18 (6)
Pseudomonas aeruginosa (blood cultures)	1/18 (6)
Rectal abscess (CT and MRI scan)	1/18 (6)
UTI (microscopy)	1/18 (6)
Non-infective diagnosis	**3/48 (6)**
Angioimmunoblastic T cell lymphoma (biopsy)	1/3 (33)
Silicosis secondary to breast implant rupture (tissue biopsy)	1/3 (33)
Seronegative autoimmune hepatitis (tissue biopsy)	1/3 (33)
All data presented as n/n (%)	

References:

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