

Undiagnosed undifferentiated fever in Far North Queensland, Australia: a retrospective study



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SUMMARY

Objectives: This study aimed to describe the causes of acute undifferentiated fever (AUF) and to develop a robust definition of undiagnosed undifferentiated fever (UUDF).

Methods: This was a retrospective study of AUF over 3 years (2008–2011) in an Australian tertiary hospital. Request for laboratory investigation of one or more infectious agents was used as the search tool.

Results: A total of 340 patients with AUF, aged 15–65 years, were identified over the study period. A final diagnosis was made in 147 (43.2%) patients, dengue fever being the most frequent. The aetiology of fever was not determined in 193 (56.8%) patients. Elevations of C-reactive protein (CRP) and hepatic aminotransferase levels were common in these patients; two patients died. The characteristics of UUDF were fever for ≤ 21 days and failure to reach a diagnosis after clinical evaluation and specific laboratory investigations.

Conclusion: The high burden of UUDF argues for a better diagnostic approach to fever that is capable of identifying a broad range of infectious agents.

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1. Introduction

Fever is a common complaint in healthcare settings with various possible aetiologies including infection, connective tissue disorders, malignancies, and a number of miscellaneous conditions. The cause of fever may not be immediately obvious because of non-specific clinical manifestations and a lack of specificity in initial laboratory findings. The condition is referred to as undifferentiated fever and there is a broad differential diagnosis, usually influenced by the geographical location. Further laboratory investigations are usually undertaken to determine the cause of fever. Sometimes, despite investigation, undifferentiated fevers remain undiagnosed, and whilst some undiagnosed undifferentiated fevers (UUDFs) resolve spontaneously, others may be associated with considerable morbidity and even mortality.

Prolonged fever cases without an identified cause are classified as fever (or pyrexia) of unknown origin (FUO/PUO). Petersdorf and Beeson in 1961 defined FUO as fever without a determined cause,

despite investigation, that lasts for more than 21 days.¹ Three decades later, the definition was modified by Durack and Street, who distinguished classical FUO from nosocomial, neutropenic, and HIV-associated FUO. They also suggested a shorter duration of investigation, i.e. three outpatient visits or 3 days of in-hospital evaluation.²

In contrast to FUO, which is clearly defined and widely studied, there is no case definition for short-term febrile illnesses with unknown aetiology. This syndrome has clinical similarities to FUO, but the shorter duration of fever and the differing aetiologies necessitates a different term. [Figure 1](#) depicts the outcomes of undifferentiated fever and the terminology used in this paper.

It has been known that infections are the most common cause of acute fever and other conditions become more frequent causes as fever duration increases.³ Nevertheless, diagnosing infectious causes of fevers is a challenge as many infections present with a similar clinical picture. Current diagnostic approaches often fail to detect the aetiology of fever, with physicians attempting to minimize laboratory investigations by only requesting tests for the most likely aetiologies. Broad spectrum diagnostic tools could improve the diagnostic yield.

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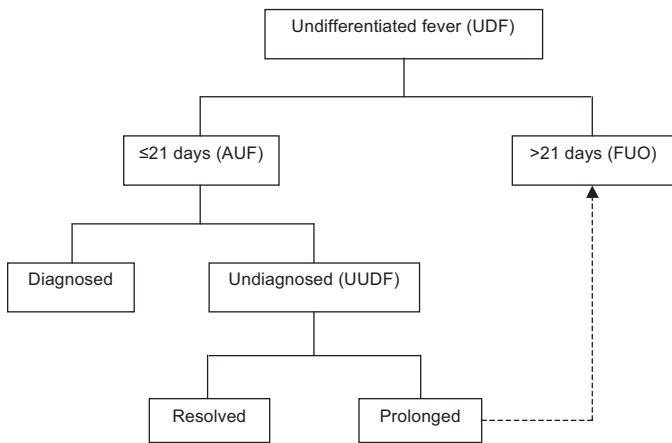


Figure 1. Outcomes of undifferentiated fever (UDF). AUF, acute undifferentiated fever; UUDF, undiagnosed undifferentiated fever; FUO, fever of unknown origin.

Situated in a tropical zone, and a major tourist destination in Australia, the Cairns region is endemic for a range of tropical infections and is susceptible to the introduction of infections from other countries. Some of the known prevalent diseases in this area are leptospirosis, scrub typhus, spotted fever, melioidosis, and infections caused by mosquito-borne viruses.⁴ *Aedes aegypti* is present in North Queensland urban areas and dengue outbreaks are frequently reported.^{4,5}

We hypothesized that UUDFs comprise a considerable proportion of acute undifferentiated fevers (AUFs) in Far North Queensland and sought to determine the frequency of specific diagnoses. The secondary aim was to develop a working definition of UUDF, based on clinical and laboratory profiles, that could be used in comparable settings.

2. Methods

The study was conducted at Cairns Hospital (CH), located in a regional city on the east coast of Australia with 170 586 inhabitants.⁶ As the referral hospital for Far North Queensland, CH has a comprehensive diagnostic capacity for investigating the aetiology of undifferentiated fever. The hospital serves a broader population of about 400 000 residents in the surrounding districts and the broader catchment areas of Cape York and Torres Strait. A number of smaller hospitals serve the region, so not all patients meeting the definition of AUF in the region are seen at CH.

This study included a retrospective review of the medical charts of patients aged 15–65 years who presented to CH from July 1, 2008 to June 30, 2011. We defined AUF as a raised body temperature to $\geq 38^{\circ}\text{C}$, or a history of fever (with chills or shivering) for durations up to 21 days, without an immediately obvious cause on the basis of clinical findings and rapidly available pathology and radiological investigations, and not associated with nosocomial infection, neutropenia, or immunosuppressing conditions.

We identified potential AUF cases by searching AUSLAB (a laboratory management software system in Queensland) for test requests to diagnose one or more specific pathogens. Following the identification of potential subjects, we reviewed the medical charts to determine patients who met the criteria for AUF.

The following information was retrieved from the medical records: demographic data (age, gender, date of birth, residential address), clinical and hospitalization data (details of any referral, symptoms, fever duration prior to hospital presentation, highest recorded body temperature, duration of hospitalization, admission to intensive care), laboratory findings (white blood cell (WBC)

count, neutrophil count, lymphocyte count, platelet count, C-reactive protein (CRP) level, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood culture results, cerebrospinal fluid analysis, serology, and any other specific investigations), radiology findings, diagnoses made, and follow-up records.

Diagnoses were categorized into two groups: (1) provisional clinical diagnosis, which was recorded from the discharge record or from the working diagnosis at the emergency room if the discharge diagnosis was not available; and (2) the final diagnosis, which was made after the results of investigations and follow-up visits were available.

Final diagnoses were adjudicated by an infectious diseases specialist (WJHM). We defined a laboratory-confirmed case as meeting one or more of the following criteria: the isolation of a pathogen from a clinical specimen, the detection of pathogen nucleic acid in a clinical specimen during the acute phase of the illness, the detection of a four-fold rise in serum IgG antibodies by indirect immunofluorescence assay, or neutralization and/or seroconversion on ELISA on testing of paired sera. If a paired serum analysis was not performed, a single raised IgM test together with consistent clinical, laboratory, and radiology investigations became the basis of a final diagnosis.

Data were incorporated into a Microsoft Excel spreadsheet and analysed using IBM SPSS version 20 software (IBM Corp., Armonk, NY, USA). Descriptive statistics and cross-tabulations were done for presenting data. The normality of data distribution was assessed by Kolmogorov–Smirnov and Shapiro–Wilk tests. Inter-group comparisons were made by the Pearson Chi-square test for categorical variables and the Mann–Whitney test for continuous variables. A *p*-value of <0.05 was considered statistically significant.

3. Results

The study flow chart is shown in Figure 2. During the period July 1, 2008 to June 30, 2011, there were 970 requests for investigation of one or more infectious agent(s) recorded by AUSLAB. Of these, we identified 340 AUFs that met our definition.

Around half of AUFs ($n = 166$, 48.8%) were tested for one to three agents, over a quarter of patients ($n = 94$, 27.8%) were tested for four to six agents, and the remainder ($n = 80$, 23.5%) were tested for six to 20 agents. Most patients with AUFs were investigated for dengue ($n = 267$, 78.5%), and many for leptospirosis ($n = 137$, 40.3%) and malaria ($n = 84$, 24.7%). A final diagnosis was possible in 147 (43.2%) patients. Eighteen patients were admitted to intensive care and there were three deaths in our series. One death was due to *Staphylococcus aureus* septicaemia, whilst the cause of the other two deaths was not identified.

We retrieved rainfall data from the Bureau of Meteorology (BOM) database⁷ and found that the occurrence of AUFs and dengue predominated during the wet season (data not shown). Almost all (66/68, 97%) of the dengue cases occurred during an outbreak in late 2008 and early 2009. During this period, we also found a high incidence of AUFs; 83 cases had specific diagnoses and 66 cases were undiagnosed.

Table 1 shows the demographic and laboratory characteristics of patients with diagnosed and undiagnosed undifferentiated fever. Patients with UUDF were admitted for a shorter period, whilst patients with lower platelet and WBC counts but with higher liver aminotransferases were more likely to have specific diagnoses made.

The symptoms of UUDF were non-specific with a high prevalence of constitutional and gastrointestinal symptoms. The most common symptoms of UUDF were headache (135/193, 69.9%), muscle pain (105/193, 54.4%), joint pain (95/193, 49.2%), nausea (81/193, 41.9%), and vomiting (76/193, 39.4%).

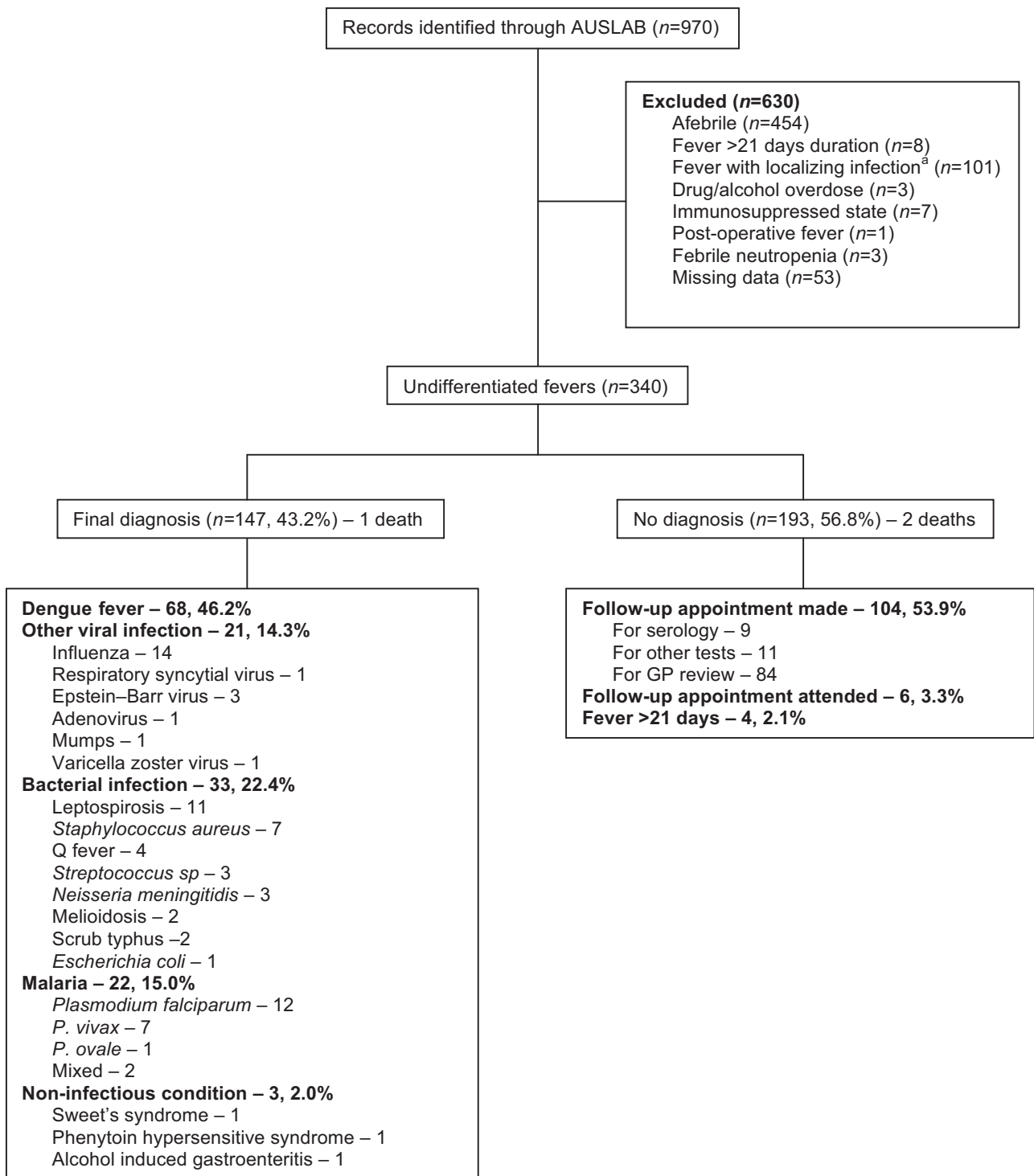


Figure 2. Study flow chart.

^aIncluding community-acquired pneumonia, skin and soft tissue infection, bone and dental infection, intra-abdominal infection, pelvic inflammatory disease, and urinary tract infection.

The majority of patients with UUDF had normal results of full blood count (130/193, 67.4%) and renal function tests (173/193, 89.6%). Notable abnormalities on laboratory testing were elevated levels of hepatic aminotransferases and CRP. Among 189 patients tested for aminotransferases, 102 (53.9%) had increased levels (ALT and/or AST). Eighty-eight out of 98 patients tested (89.8%) had an elevated CRP. Around a quarter (51/187, 27.3%) of patients with UUDF were thrombocytopenic and nearly one-third (61/191, 31.9%) of those patients had a high leukocyte count. Less than 10%

of patients tested had increased urea or creatinine levels. All patients with UUDF had normal results of urinalysis. Nineteen patients had subtle abnormalities on chest X-ray, such as evidence of hyper inflated lungs, increased lung markings, peribronchial thickening, and pleural effusion. Four patients with UUDF went on to fulfil FUO criteria when the fever duration exceeded 21 days without a definite diagnosis made during hospitalization.

A 60-year-old man died due to staphylococcal infection. This patient presented to hospital with 7 days of fever, with the highest

Table 1
Demographic and significant laboratory characteristics of patients with diagnosed and undiagnosed undifferentiated fever^a

	Diagnosed patients (n = 147)	Undiagnosed patients (n = 193)	p-Value
Age, years	36 (25–47)	32 (24–44.5)	0.122
Male sex	60.5%	60.6%	0.988
Residential address			0.500
Suburban	76.9%	74.1%	
Rural	17.7%	17.1%	
Overseas	5.4%	8.8%	
Body temperature, °C	38.9 (38.3–39.4)	38.8 (38.1–39.4)	0.371
Duration of fever before hospital presentation, days	3 (2–5)	3 (2–5)	0.068
Type of referral			0.914
Self-referred	68.7%	67.4%	
Local doctors	22.4%	24.4%	
Other hospital	8.8%	8.3%	
Length of hospital stay, days	1 (0–5)	0 (0–3)	0.001
Number of agents tested for	3 (2–7)	4 (2–6)	0.716
Dengue test done	74.1%	81.9%	0.086
Platelet count, × 10 ⁹ /l	131 (67.5–180.5)	185 (134–242)	0.000
WBC count, × 10 ⁹ /l	5.35 (3.325–8.175)	8.3 (5.6–12.3)	0.000
ALT level, U/l	80.5 (29.5–137.25)	37 (20–74.5)	0.000
AST level, U/l	70 (29–147.5)	32 (22–70)	0.000

WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^a Results are presented as the median (interquartile range), or as the percentage.

temperature being 40.1 °C, back pain, dyspnoea, and palpitations. A chest X-ray identified pleural effusion. Routine blood tests showed an elevated CRP as well as serum urea, creatinine, ALT, and AST (162 mg/l, 19.2 mmol/l, 219 µmol/l, 87 U/l, and 217 U/l, respectively). The leukocyte count was high (40.9 × 10⁹/l) with neutrophil predominance (96.2%). Specific investigations included tests for *Rickettsia sp*, *Leptospira sp*, dengue, *Legionella sp*, and *Mycoplasma pneumoniae*; the results were all negative. He was admitted to intensive care and *S. aureus* was isolated from blood culture. A computed tomography (CT) scan showed multiorgan abnormalities including brain ischemia, pleural effusions, splenic infarcts, cirrhosis, and cholelithiasis. He died on day 8 in hospital.

Two deaths of unknown cause were recorded, involving a boy with intellectual impairment and a woman from Western Province, Papua New Guinea. We could not find the autopsy reports for those patients in the hospital database or medical notes, so we assumed that an autopsy was not performed in both cases.

The first fatal case was a teenage boy with Lennox–Gastaut syndrome, a medical problem characterized by frequent seizures and mental deficiency. This patient went to a local doctor with 1 day of fever up to 41 °C. The initial diagnosis was that of an upper respiratory tract infection and conjunctivitis. At home, the patient developed a seizure and was sent to a local hospital before being transferred to CH. He had an elevated CRP as well as serum creatinine, ALT, and AST (44 mg/l, 219 µmol/l, 378 U/l, and 1220 U/l, respectively). The platelet count was very low (35 × 10⁹/l) and WBC count increased (25 × 10⁹/l) with lymphocyte predominance (54.2%). There was no abnormality detected on chest X-ray and PCR tests were negative for *Neisseria meningitidis* and *Streptococcus pneumoniae*. He died after several hours in intensive care.

The second fatality was a 21-year-old woman who was transferred from Thursday Island Hospital with 14 days of fever (the highest temperature was 38.6 °C), night sweats, anorexia, cough, dyspnoea, pleuritic chest pain, and abdominal pain. Laboratory tests showed haemolytic anaemia, increased CRP and liver aminotransferases (CRP 85 mg/l, ALT 108 U/l, AST 75 U/l), leukocytosis (25 × 10⁹/l) with neutrophil predominance (90.2%), and progressive thrombocytopenia (platelets decreased from 76 × 10⁹/l to 9 × 10⁹/l over 5 days). Blood culture was sterile and specific tests were negative for numerous pathogens including malaria, *Streptococcus sp*, *Legionella sp*, *Mycoplasma sp*, *Burkholderia pseudomallei*, HIV, and hepatitis viruses (HAV, HBV, HCV).

Mycobacterium sp was not found in sputum, pleural fluid, ascites, and a bone marrow specimen. Bone marrow biopsy ruled out myelodysplastic syndromes and there was no evidence of lymphoma or haemophagocytic disorder. Chest X-ray and CT chest showed bilateral effusions, while CT abdomen showed massive splenomegaly and a large amount of ascites. Despite having localized signs, we included this patient in our study because the cause of her fever was obscure. However, by the time she died – day 9 in hospital – she had fulfilled the criteria of FUO and should be excluded from the UUDF series.

4. Discussion

Despite being common and more prevalent than FUO, AUF is not well described. A particularly important subset of this syndrome is what we have described as UUDF. Patients with UUDFs may have common infections for which testing is not normally available (e.g. enteroviruses). In short-lived episodes, both the patient and clinician are usually satisfied that further investigation is not warranted, and an explanation that a patient has a 'viral infection' is generally acceptable, although there is a paucity of data to support this common explanation. Intensive investigative efforts are performed for more prolonged or severe episodes. The UUDFs that are associated with severe illness and intensive investigation are clearly important illnesses and the causes may have important public health implications. The occurrence of this syndrome, particularly if its incidence rises above a baseline threshold, could be an early indication of the emergence of a condition that requires recognition.

In this study, we investigated a common clinical presentation and described the causes of AUFs. The diagnosed diseases were consistent with what has previously been described in this region.^{8–11} In addition, we have now quantified and described a syndrome of undiagnosed short-term fever in Far North Queensland. The implications of this study are that clinicians are either failing to order appropriate tests, current diagnostic methods are not adequate, or that there are causes of fever that are yet to be discovered.

This study has underlined the importance of dengue, malaria, and leptospirosis in patients with AUF. The findings are consistent with similar studies conducted in tropical countries in Asia,^{12–20} West Africa,²¹ and South America.²² Other studies conducted in

European countries have found Q fever to be a significant cause of AUF.^{23,24} The finding that less than half of AUF patients had a confirmed clinical diagnosis is also consistent with some of the studies previously mentioned.^{12,14,16,20}

Our study identified a high incidence of both diagnosed and undiagnosed undifferentiated fever in late 2008, which coincided with a dengue outbreak in Cairns during that period. It is possible that some of the UUDF patients did indeed have dengue, which would indicate that there were missed diagnoses. Alternatively there may have been an increased presentation of febrile patients who would not otherwise have presented to hospital, or there may have been concurrent circulation of an unrecognized cause of fever.

This study illustrates the challenges faced by physicians in diagnosing infectious causes of fever since many infections have non-specific features. Conventional methods contribute to identifying pathogens in less than half of the patients with fever. The non-specific clinical features lead to frequent requests for well recognized pathogens. As an example, despite the frequent requests for dengue testing in this study, only 68/267 (25.5%) patients had a positive result.

The weakness of this study is that a significant amount of data was missing, including lost or incomplete medical histories, absent discharge summaries, and some patients identified on AUSLAB not matched to medical records. Furthermore, we could not include febrile cases that were not investigated for infectious agents. The retrospective design of this study meant that we could not establish a standardized testing regimen for subjects and this was likely to have resulted in fewer people with a specific diagnosis. On the other hand the study does provide insights into how this syndrome is currently managed.

Despite these weaknesses, useful information has been obtained. The majority of patients presented early and required only short periods of hospitalization, suggesting that acute infection is the main cause of AUF. Moreover, frequent requests for tests for arboviruses and leptospirosis suggest that the assessment of AUF was influenced by the local occurrence of infectious diseases. The diagnostic approach in Northern Queensland, and elsewhere, should be tailored to the local epidemiology of the known infectious aetiologies.

This study is important as it documents the feasibility of defining UUDF as (1) a fever of ≥ 38.0 °C or symptoms suggestive of fever; (2) a duration of fever of ≤ 21 days; (3) a failure to reach a diagnosis after performing clinical evaluation and laboratory investigations, including complete blood count, serum biochemistry, urinalysis, blood culture, and chest X-ray; (4) a request by the clinician for a specific test for at least one infectious agent; and (5) a failure to make a specific diagnosis. Using this definition we found a wide variation in disease severity and we propose a grading system to help identify patients for whom additional diagnostic measures are required. Patients could be scored on the basis of several criteria, as listed in Table 2. Using this scoring system, we found that the average score of diagnosed cases was higher than that of undiagnosed fevers: 5.42 (standard deviation 1.66) vs. 4.71 (standard deviation 1.68).

We noted that the occurrence of a dengue outbreak (November 2008–April 2009) influenced the diagnostic approach at CH, as evidenced by frequent requests for a dengue test. On average, during this period, doctors ordered 3.32 specific tests (standard deviation 1.83, median 2, interquartile range 2–4). There was no evidence of increased testing on the individual during the epidemic. In our opinion, this will not significantly affect the third criterion of the scoring system, i.e. thoroughness of investigation, because the number of agents tested during the dengue outbreak was similar to those applied to all cases (see ‘Number of agents tested for’ in Table 1). If anything, there were

Table 2
Scoring system to determine the significance of undifferentiated fever

Criteria	Score
Duration of fever: from time of recorded ≥ 38 °C or historically suggestive fever onset to time of fever lysis (recorded temperature not exceeding 37.5 °C for 48 h)	
1 day	0
1–3 days	1
4–21 days	2
Duration of hospital admission	
<1 day	0
1–3 days	1
>3 days	2
Thoroughness of investigation (number of investigations for specific agents that are appropriate for known regional diseases or for the patient’s clinical signs and symptoms)	
1 agent	0
2–3 agents	1
≥ 4 agents	2
Laboratory abnormalities (thrombocytopenia; leukocytes, lymphocytes and/or neutrophils outside of normal range; elevated AST and/or ALT; elevated CRP; abnormal renal function)	
No abnormal values	0
1–2 abnormalities	1
≥ 3 abnormalities	2

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

fewer tests done during the dengue epidemic, probably as clinicians were focused on this disease. This could serve to lower the score for a patient with UUDF in some circumstances.

A possible diagnostic approach to UUDF would be to use metagenomics, a method that directly identifies genetic material from environmental and clinical samples. In contrast to the traditional microbiological approach, metagenomics does not require prior knowledge of the pathogen being sought or the ability of the organism to grow in culture. A metagenomics approach has provided new perspectives in microbiology because of its ability to reveal previously unrecognized pathogens and broaden our knowledge in regards to microbial diversity.^{25–27} Recent studies with next-generation sequencing (NGS) have identified occult and novel infections by generating an unbiased characterization of organisms that exist in clinical samples.^{28–33}

In terms of cost-effectiveness, NGS reduces the cost of sequencing one million nucleotides (1 Mb) to 0.1–4% of that associated with Sanger sequencing.³⁴ For example, a single lane of the Illumina HiSeq platform can produce 35 Gb of sequencing data from up to 24 samples at the cost of approximately USD3000 in total. However, the NGS technology is only available in research centres, and is not currently available for routine diagnosis in a timely fashion. We expect that, in the near future, this technology will continue to mature and become more cost-effective.

The scoring system proposed may assist in selecting the most clinically significant samples for more intensive investigations. We propose that patients scoring 5 or more points should be considered for investigation using an NGS platform. Alternatively, the use of proteomics, multiplex PCR, or microarray hybridization might be useful to improve the diagnostic yield.

In conclusion, undifferentiated fevers are common in the population of Far North Queensland. Even thorough history taking, careful examination, and appropriate investigation in consultation with infectious disease specialists failed to reach a diagnosis in a significant proportion of cases. We found that more than half of AUFs do not have a specific diagnosis made despite the availability of extensive diagnostic facilities at a tertiary referral hospital. A robust definition for UUDF is proposed so that comparison of this disease entity can be monitored and compared between different geographical sites and over time. Evaluation of the application of next-generation sequencing in clinical practice may be a useful approach in this condition.

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Conflict of interest: None declared.

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