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

Tri Nugraha Susilawati *, William John Hannan McBride

School of Medicine and Dentistry, Faculty of Medicine, Health and Molecular Sciences, James Cook University, Queensland, Australia

A R T I C L E   I N F O

S U M M A R Y

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.

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.

* Corresponding author. Tel.: +61 7 4226 6996; fax: +61 7 4226 6831.
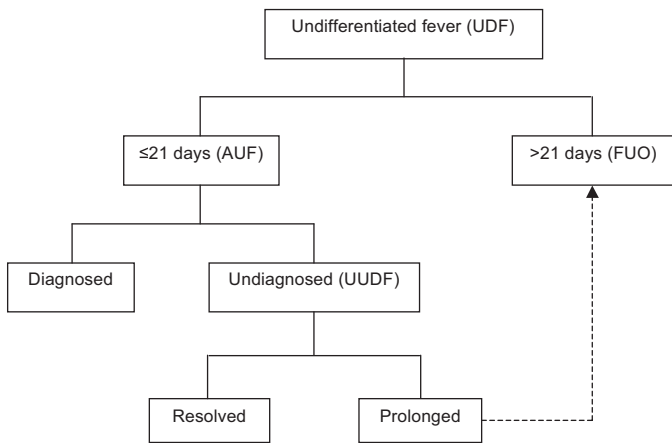E-mail address: tri.susilawati@my.jcu.edu.au (T.N. Susilawati).

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 spread sheet 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) database[7] 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%).