REVIEW

ACUTE UNDIFFERENTIATED FEVER IN ASIA: A REVIEW OF THE LITERATURE

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Abstract. Acute undifferentiated fever (AUF) is a temporary febrile illness accompanied by non-specific symptoms. Previous studies in Asia have primarily focused on delineating specific agent(s) causing AUF. None were designed to assess the frequency of undiagnosed cases. This study aimed to review the case definition, laboratory investigations, etiologies and proportion of undiagnosed episodes of AUF. We reviewed nine studies, each employing different case definitions and diagnostic tools. Malaria, dengue, leptospirosis and rickettsial illnesses were frequently identified as the etiologies of AUF and the frequencies of undiagnosed cases ranged from 8% to 80%. An international consensus definition is required to compare the occurrence of AUF in different geographical sites, particularly if this condition were to be used as an indicator for the emergence or re-emergence of infectious agents. Use of general diagnostic tools for infectious diseases might reduce the proportion of undiagnosed AUF cases.

Keywords: fever, epidemiology, Asia

INTRODUCTION

Acute undifferentiated fever (AUF) is frequently seen in clinical practice but the etiology is not always found. The condition may be distinguished from fever of unknown origin (FUO) by fever duration, progression of illness and underlying causes (Phuong *et al*, 2006; Efstathiou *et al*, 2010; Abrahamsen *et al*, 2013). In FUO, fever must be present for at least three weeks (Petersdof and Beeson, 1961; Durack and Street, 1991). Patients with AUF have a more limited duration of fever and many of the episodes resolve spontaneously and are presumed to be due to self-limiting infections (Thangarasu *et al*, 2011). Acute fever requires careful evaluation because it could be the first sign of a potentially serious infection.

Determining the cause of AUF can be a challenge for health workers, particularly in developing countries. The limited diagnostic tools, variety of potential causes of fever and non-specific clinical features make diagnosis a challenge. A knowledge of the local causes of AUF and available tests is required in the approach to an AUF patient.

Previous reports (Watt and Jongsakul, 2003; Nga *et al*, 2006; Phongmany *et al*, 2006; Chandy *et al*, 2009; Gasem *et al*, 2009; Low *et al*, 2011; Phuong *et al*, 2010;

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Premaratna *et al*, 2010; Thai *et al*, 2010) have evaluated the causes of AUF in Asia but limited data exists regarding the epidemiology of undiagnosed cases where other pathogens may be the cause. Those studies focused on particular pathogens rather than the various causes of AUF and the proportion of AUF cases that remain undiagnosed. We reviewed the literature to determine the case definition, investigations and etiologies of AUF, and to determine the proportion of AUF cases that remained undiagnosed in Asia.

MATERIALS AND METHODS

We searched PubMed using the following terms: Fever/etiology (Majr) OR Fever/microbiology (Majr) AND Asia (Mesh) AND Adult (Mesh) AND 1990/01/01 (PDAT): 2012/12/31 (PDAT) AND Journal Article (ptyp) AND English (lang). We also searched Medline, Scopus and Web of Science. Reports were obtained from the references of the articles used for analysis.

Inclusion criteria for published studies were subjects who were assessed for an acute febrile illness without a focus of infection found on initial history and examination who were investigated for more than three different causes of fever. Articles were reviewed if they were original research and were not published in the form of a review article or case report. The review was limited to English language articles from Asian countries published during 1990-2012. We used articles published only since 1990 because nucleic acid amplification testing began to be used as a routine diagnostic tool after 1990.

Exclusion criteria were studies that focused on FUO, connective tissue disorders, malignancies, autoimmune diseases, travelers returning from Asia and studies of children, immunocompromised or neutropenic subjects.

The articles identified were reviewed systematically (Fig 1). Data obtained included study design and location, period of sample collection, age of patients included, inclusion criteria for that study, microbiology methods and diagnosis. Quantitative data recorded included the number of participants, age range and frequency of diagnoses.

RESULTS

The searches were carried out on 20 September 2012 (PubMed and Medline) and 24 September 2012 (Scopus and Web of Science). Two hundred one studies were retrieved initially. After removing duplicate studies, 137 studies remained, of which 113 were removed after reading their titles and/or abstracts. The entire texts of the 24 remaining studies were reviewed, of which 9 passed all exclusion criteria and met all inclusion criteria. Table 1 summarizes the 7 prospective studies (Leelarasamee *et al*, 2004; Murdoch *et al*, 2004; Ellis *et al*, 2006; Suttinont *et al*, 2006; Chrispal *et al*, 2010; McGready *et al*, 2010; Kasper *et al*, 2012) and 2 retrospective studies (Blacksell *et al*, 2007; Joshi *et al*, 2008). The studies were from 4 countries: Thailand, Nepal, India and Cambodia.

Different case definitions were used for the different studies for AUF; including length of fever with no obvious source of inflammation or focal finding. The majority of studies evaluated patients with a duration of fever of less than 14 days (Leelarasamee *et al*, 2004; Suttinont *et al*, 2006; Joshi *et al*, 2008; Kasper *et al*, 2012); one study evaluated patients with fever of up to 21 days duration (Chrispal *et al*, 2010). The remaining articles did not specify the maximum duration of fever.

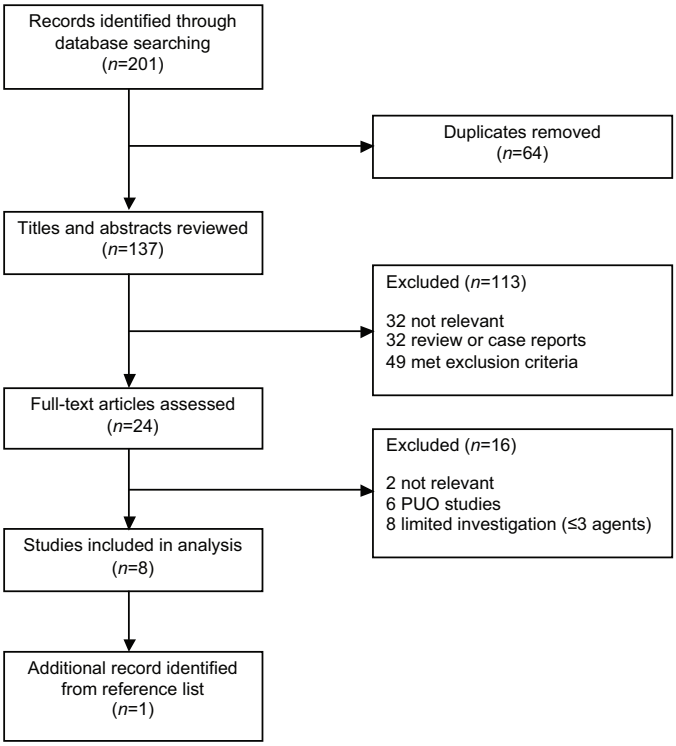

Fig 1–Flow diagram of the process and results of article selection.

There was little variation in the definition of fever. Several studies specified a fever cut-off level of ≥38ºC (Murdoch *et al*, 2004; Ellis *et al*, 2006; Blacksell *et al*, 2007; Kasper *et al*, 2012); one study (McGready *et al*, 2010) used a fever cut-off of 37.5ºC and another study (Leelarasamee *et al*, 2004) used a cut-off level of 38.3ºC. Some studies (Suttinont *et al*, 2006; Joshi *et al*, 2008; Chrispal *et al*, 2010) did not specify the fever cut-off level.

To identify the etiologies of AUF, the studies employed non-specific and specific investigations. Non-specific investigations refer to blood analysis and other laboratory testing to describe the underlying cause of the disease without determining a specific microorganism, such as a complete blood count, serum biochemistry, urinalysis and chest X-ray.

Specific investigations refer to laboratory testing investigating specific pathogens, such as malaria films, serological tests, polymerase chain reaction (PCR) assays and bacterial cultures. These methods identified specific infections, such as malaria, dengue fever, leptospirosis and rickettsioses as possible causes of AUF. *Salmonella* sp, *Escherichia coli*, and *Staphylococcus aureus* were the most common blood culture isolates (Leelarasamee *et al*, 2004; Murdoch *et al*, 2004; Suttinont *et al*, 2006; Blacksell *et al*, 2007; Kasper *et al*, 2012). A small proportion of dual or triple infections were reported, with arthropod-borne infections (malaria, rickettsial infections, dengue) and zoonotic diseases (leptospirosis) being the most common co-infections. The proportion of AUF cases that remain undiagnosed ranged from 8% to 80% (mean = 47.8%, SD = 23.3%) (Table 1).

While the criteria used to define AUF varied in terms of duration and fever thresholds, all the studies excluded cases where a specific diagnosis was made immediately after clinical evaluation and non-specific investigations. The results of complete blood counts, urinalysis tests and chest X-rays were inconclusive in AUF cases, requiring further investigation to determine the cause of fever.

In tropical countries where mosquito-borne diseases are endemic, malaria was frequently suspected as a cause of AUF and other causes of fever were ignored. Non-malarial febrile illnesses comprised

Table 1
Characteristics of acute undifferentiated fever studies in Asia, 1990-2012.

	Leelarasamee *et al*, 2004	Ellis *et al*, 2006	Suttinont *et al*, 2006	McGready *et al*, 2010	Murdoch *et al*, 2004	Blacksell *et al*, 2007	Joshi *et al*, 2008	Chrispal *et al*, 2010	Kasper *et al*, 2012
Country	Thailand	Thailand	Thailand	Thailand	Nepal	Nepal	India	India	Cambodia
Location	Ten community-based hospitals	One general hospital	Five general hospitals	Nine antenatal clinics	One general hospital	One teaching hospital	One teaching hospital	A tertiary-care referral hospital	Five clinics
Study period	1991-1993	1999-2002	2001-2002	2004-2006	2001	2001-2003	2006	2005-2007	2006-2009
Study design	Prospective	Prospective	Prospective	Prospective	Prospective	Retrospective serology	Review of medical records	Prospective	Prospective
Subjects	1,137	613	845	203	876	103	1,197	398	9,997
Age	> 2 years	Adult	Adult	Adult	≥ 14 years	Adult	> 12 years	≥ 16 years	≥ 16 years
Temperature	> 38.3°C	≥ 38°C	—	> 37.5°C	≥ 38°C	> 38°C	—	—	> 38.0°C
Fever duration	3-14 days	≥ 48 hours	<15 days	—-	≥ 24 hours	—-	<14 days	5-21 days	<10 days
Malaria excluded?	Yes	No	Yes	No	No	No	No	No	No
Specific tests									
Leptospira	S	S	SC	SC	SP	S	S[a]	S	S
Scrub typhus	S	S[a]	S	SPC	S	S	—	S	SP[a]
Murine typhus	S	S[a]	S	SPC	S	S	—	—	SP[a]
Spotted fever	—	S[a]	S	—-	—-	—-	—	S	SP[a]
Pneumonia	—	—	—	—-	SC	—-	—	—	—-
Typhoid	S	P[a]	—	C	—-	—-	—	SC	—-
Melioidosis	S	S[a]	—	—-	—-	—-	—	—	—-
Q fever	—	S[a]	S	—-	—-	—-	—	—	—-
Dengue	S	SP	S	S	S	S	S[a]	S	SP
Chikungunya	S	—	—	—-	—-	—-	—	—	SP[a]
JE	S	SP	S	—-	—-	—-	—	—	—-
HIV	—	S[a]	—	—-	S	—-	—	—	—-
Hantavirus	—	—	—	—-	—-	—-	—	S	SP
Hepatitis A	—	—	—	—-	—-	—-	—	—	S[a]
Hepatitis B	—	—	—	—-	—-	—-	S[a]	—	S[a]
Hepatitis E	—	—	—	—-	—-	—-	S[a]	—	SP
Influenza	S	—	S	—-	—-	—-	—	—	P
Diagnosed cases[b]	471 (39)	294 (48)	577 (68)	171 (81)	323 (37)	48 (47)	238 (20)	367 (92)	6,198 (38)

Table 1 (Continued).

	Leelarasamee *et al*, 2004	Ellis *et al*, 2006	Suttinont *et al*, 2006	McGready *et al*, 2010	Murdoch *et al*, 2004	Blacksell *et al*, 2007	Joshi *et al*, 2008	Chrispal *et al*, 2010	Kasper *et al*, 2012
Most common diagnoses	Scrub typhus, influenza, dengue	Malaria, leptospirosis, spotted fever	Leptospirosis, scrub typhus, dengue	Malaria, UTI, murine typhus	Bacteremia, murine typhus, pneumonia	Bacteremia, murine typhus scrub typhus	Malaria, dengue, bacteremia	Scrub typhus, malaria, enteric fever	Leptospirosis, influenza, dengue
Most common co-infections	NS	Malaria, leptospira, rickettsia	Leptospira, rickettsia, influenza	Malaria, rickettsia, dengue	Rickettsia, pneumonia, leptospira	Rickettsia, dengue, leptospira	NS	NS	Influenza, dengue, malaria
Undiagnosed cases[b]	666 (61)	319 (52)	268 (32)	171 (19)	553 (63)	55 (53)	959 (80)	32 (8)	3,799 (62)

HIV, human immunodeficiency virus; JE, Japanese enchepalitis; NS, not specified; UTI, urinary tract infection; S, serology; P, polymerase chain reaction; C, culture.
[a]Test was performed in a small subset of patients (< 20% of subjects) so the true disease prevalence was likely to be underestimated; [b]Number (%).

a greater proportion of AUF cases than malaria did (Murdoch *et al*, 2004; Joshi *et al*, 2008; Faruque *et al*, 2012; Naing and Kassim, 2012). The two prospective studies (Leelarasamee *et al*, 2004; Suttinont *et al*, 2006) highlighted the importance of malaria screening during the initial evaluation of acute febrile patients resulting in exclusion of malaria from the differential diagnosis. In one study (McGready *et al*, 2010), approximately one quarter (51/211) of febrile episodes were caused by malaria. If malaria patients were excluded from that study, the proportion of undiagnosed cases would increase from 19% (40/211) to 25% (40/160).

DISCUSSION

Due to the rapid clinical recovery of the majority of AUF patients in the studies reviewed, it is likely the main etiology of AUF was infections. Other causes of fever, such as malignancies and autoimmune diseases, only contributed to a small proportion of AUF patients. One study (Chrispal *et al*, 2010) excluded hematological malignancies, autoimmune diseases and immunocompromised patients.

Serology was the main diagnostic method used in the reviewed studies, but of studies checking titers, convalescent titers were not always performed. Only three of nine studies (Suttinont *et al*, 2006; Blacksell *et al*, 2007; McGready *et al*, 2010) obtained convalescent titers in all participants. In the other studies, convalescent titers were obtained in fewer than 25% of participants (Murdoch *et al*, 2004; Ellis *et al*, 2006; Kasper *et al*, 2012). The proportion of patients who had convalescent titers was not specified in two studies (Leelarasamee *et al*, 2004; Chrispal *et al*, 2010). In one study (Joshi *et al*, 2008), only acute titers were obtained. Diagnosis us-

ing acute titers only can be problematic. False negative results may occur when antibody titers are below detectable levels during the first few days of illness. Acute titers can also yield false positive results due to cross reactivity (De Paula and Fonseca, 2004).

Direct testing for pathogens by culture, PCR or antigen detection can be obtained from acute samples. For example, PCR to detect dengue fever during the initial infection is more sensitive than antibody detection (Kasper *et al*, 2012). Direct testing led to diagnosis in 22% of subjects in the studies evaluated.

AUF remained undiagnosed in 8% to 80% of the cases reported in the studies reviewed. Studies with a low reported number of undiagnosed cases most likely made their diagnoses using IgM levels on acute specimens only. This procedure may give false positive results, underestimating the proportion of undiagnosed cases. Diagnoses may be incorrect due to laboratory results being interpreted using preset criteria without considering the clinical presentation or without performing convalescent titers.

A possible explanation for the large proportion of undiagnosed cases in the majority of articles reviewed is the limited scope of the investigation. These studies attempted to identify the cause of AUF using specific investigations designed to detect anticipated causes of AUF. The lack of convalescent samples and the limited number of participants tested hindered the diagnosis, leading to underestimation of disease prevalence.

In spite of methodological difficulties, there was a large number of AUF that went undiagnosed. The etiologies identified and proportions of undiagnosed cases were similar to those observed prior to the introduction of PCR as a routine diagnostic test (Anderson *et al*, 1976; Brown *et al*, 1984). The use of a microarray to investigate a wide range of infectious agents is likely to be useful but this technique cannot detect the presence of novel agents (Palacios *et al*, 2007). Rapid advances in molecular biology research and the availability of high throughput sequencers are a promising tool to reduce the number of undiagnosed AUF cases in the future. These advances may enable the identification of occult infections and previously unknown pathogens (Palacios *et al*, 2008; Beck *et al*, 2009). This new method does not rely on a knowledge of the pathogens being sought but provides bulk sequencing of any nucleic acid present in the sample. This technology to diagnose AUF should be further explored.

In conclusion, despite AUF being common, studies regarding its epidemiology are limited. In Asia, serology is the most common diagnostic tool and the most prevalent etiologies of AUF are malaria, dengue, leptospirosis, and rickettsial infections. The lack of a widely agreed upon definition of AUF makes comparison of patients with AUF between regions and countries difficult. Further studies need to be conducted using a standard definition of AUF by evaluating patients using a high throughput sequencing platform for detecting infectious diseases.

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