Etiologies of Acute Undifferentiated Febrile Illness in Thailand

Amorn Leelarasamee MD*, Chanpen Chupaprawan MD**,
Mongkol Chenchittikul MSc*** , Suthipon Udompanthurat MSc****

* Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University
** Health System Research Institute, Thailand
*** National Institute of Health, Department of Medical Sciences Ministry of Public Health, Thailand
**** Office for Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University

Background : *Acute pyrexia of unknown origin (Acute PUO) was reported to affect approximately 200,000-400,000 patients each year reported by the national Annual Epidemiological Surveillance Report. The patients usually present with fever of less than two-week duration and non-specific symptoms such as malaise, myalgia, headache and loss of appetite. Its mortality rate is less than 0.02 percent. It would be interesting to find the etiologies and propose a management plan if the etiologies are discovered.*

Objective : *This prospective epidemiologic study aimed to discover the etiologies of acute undifferentiated febrile illness in a tropical region like Thailand.*

Subjects and Method : *Ten community-based hospitals were chosen as representatives in each part of Thailand to enroll patients into the study. Patients aged over two years old who presented with fever at the participating hospitals during year 1991-1993 were eligible for the study. Entry criteria of acute undifferentiated febrile illnesses (AUFI) included oral temperature over 38.3ºC within the last 24 hours, duration of fever ranging from 3-14 days, no specific single organ involvement by history taking and physical examination, normal or non-specific results of the following investigations: complete blood count, thick film for malaria, urinalysis and chest roentgenogram. The patients were hospitalized and a preset diagnostic protocol was performed. Other diagnostic procedures deemed necessary by attending physicians were perform. Patients were followed up within one month after hospital discharge.*

Results : *1,240 patients were enrolled but only 1,137 case records and results of the serological tests were available for analysis. Etiologies could be found in 471 cases (38.7%). Primary bacteremia was detected in 36 cases (3.2%). E. coli, streptococci, salmonella, Enterobacter spp. and S. aureus were the five most common blood isolates. Serological studies revealed positive results for scrub typhus (7.5%), influenza (6.0%), dengue fever (5.7%), murine typhus (5.3%), enteric fever (1.9%), chikunkunya infection (1.1%), leptospirosis (1.1%) and melioidosis (0.9%). Thirteen cases succumbed (1.1%) in this study.*

Conclusion : *The etiologies in the majority (61.3%) of AUFI remained unknown. Rickettsial infection, influenza and dengue fever are the most common identifiable diseases in a tropical country like Thailand especially during the rainy season. A management guideline for diagnosis and treatment of the AUFI with emphasis on primary bacteremia and antimicrobial-treatable AUFI was proposed.*

Keywords : *Acute PUO, Acute febrile illness, Rickettsial infection, Scrub typhus, Influenza, Dengue fever, Leptospirosis.*

Correspondence to : Leelarasamee A, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. Phone: 0-2419-7786, Fax: 0-2411-4412, E-mail address: siall@mahidol.ac.th

In Thailand, acute pyrexia of unknown origin (acute PUO) was reported to affect approximately 200,000-400,000 patients each year[1]. These patients usually present themselves at health stations or

hospitals outside Bangkok with the major complaint of fever of less than two-week's duration and non-specific symptoms such as malaise, myalgia, headache and loss of appetite. In the year 2001, there were 269,740 reported cases and the illness has ranked the second highest frequency among the notifiable communicable diseases in recent years. Its prevalence and mortality were calculated to be 434.41 and 0.09 cases per 100,000 population respectively and the case-fatality rate was 0.02 percent[1]. This unduly large reported incidence not only casts doubts on the quality of national disease surveillance but compromises the utility of surveillance data with regard to the occurrence of febrile illnesses[2]. In fact, the diagnosis given to such patients is apparently not conformed with those criteria of well known or classical PUO[3-4]. The acute PUO in the Thai report should be changed to acute undifferentiated febrile illness (AUFI)[2] since fever in these patients occurred abruptly and disappeared almost in all cases diagnosed as such within one or two weeks. Laboratory investigation is seldom performed unless the fever does not subside within 7 days. The so called "acute PUO" reaches its peak in the rainy season and mostly affects children. The majority of the reported cases come from various health stations located in every part of Thailand where laboratory facilities for microbiological diagnosis are very limited. It would be very interesting to know as much as possible about the causes of the illnesses which are expected to be heterogeneous in terms of etiology and the result might be applicable to other countries in the tropical zone.

When epidemiological data were reviewed, various viral infections are firstly anticipated to cause the majority of the illnesses, some of which can be prevented by vaccination, vector control or health education such as dengue fever and influenza[5-7]. The causes due to these viruses need no antimicrobial therapy unless the patients also exhibit obvious signs of superimposed bacterial infection. On the contrary, other causes might also be discovered during the study for which effective therapy with an antibiotic does exist, for example, rickettsial and leptospiral infections[8-10]. Once the causes are discovered, guidelines for investigation and antimicrobial therapy when indicated, can be developed for general physicians to deal with the illness. Laboratory facilities and serological tests needed to diagnose the diseases can also be developed or made available if deemed necessary or can even be tailored to local needs. The authors designed and conducted the study to reveal the manageable causes of AUFI especially for that which can be quickly eliminated with antimicrobial therapy and also primary bacteremia since it can pose a serious threat to each patient[11].

Material and Method

A prospective epidemiologic study was employed. A total of ten community-based hospitals as representatives in each part of Thailand participated in the study. Each hospital enrolled the patients for one year from 1991 to 1993. Entry criteria were patients aged over two years who presented at the outpatient department (OPD) of participating hospitals with the criteria of AUFI. These included duration of fever ranging 3-14 days and oral temperature over 38.3°C within the last 24 hours before the enrollment. Single organ involvement or an infectious disease could not be diagnosed by history and physical examination. The following investigations showed normal values or non-conclusive diagnosis of any specific diseases: complete blood count, thick film for malaria, urinalysis and chest roentgenography. In children without respiratory symptoms, chest roengenography was not done. Once the patient fulfilled the criteria; blood culture, collection of acute and convalescent sera samples were performed while the patients were hospitalized. Other diagnostic procedures and therapy deemed necessary by attending physicians were performed and the results were recorded in case record forms.

The following laboratory investigations were done with the aim described below: blood smear to rule out acute leukemia and malaria, hematocrit, platelet count or thrombocytopenia and percentage of atypical lymphocyte to detect dengue hemorrhagic fever or dengue shock syndrome. Urinalysis to rule out urinary tract infection especially in children. Chest roentgenography to rule out asymptomatic pulmonary infiltration due to tuberculosis and other causes of fever. Blood culture to rule out primary bacteremia.

Serological tests used in the study with their interpretation criteria were outlined as follows. For leptospirosis, *leptospira bataviae* was used as an antigen in microscopic agglutination test (MAT). The cut-off titer was 1:100 or over. For melioidosis, indirect immunofluorescent method was used (IFA) and interpretation of a positive IFA for the disease was either one of the following: IgM =1:40 or over, IgG =1:80 or over or a 4 fold rising in titers. For subclinical melioidosis, IgM = 1:10 or over or IgG = 1:40 or over.

For enteric fever, a Widal agglutination test was used and O titer = 1:160 or over or H titer = 1:160 or over were considered a positive test for salmonella gr. A to D. For JE viral infection, the tests were positive when a four-fold rising of hemagglutination inhibition titer was demonstrable or IgM titer by IgM antibody capture ELISA was 40 units or over. For dengue type 2 and 4 infections, primary dengue infection was diagnosed when the titer of acute serum was less than 1:20 and convalescent titer was between 1:40-1:2560. For secondary dengue infection, titer of acute serum was greater than 1:20 or convalescent titer was greater than 1:80. If a single serum sample was available, positive titer greater than 1:2560 was considered positive. For recent chikungunya viral infection, a four-fold rising of specific antibody was labeled as positive. For the diagnosis of influenza A (H_1N_1), (H_3N_2) and B, the four-fold rising of HI antibody titer must be demonstrable. For rickettsial infections, a four-fold rise of antibody titer was diagnostic using Weil-Felix test. If immunofluorescent or immuno-peroxidase technique was used, a titer of 1:200 or higher was labeled as positive. A single titer greater than 1:400 was also positive. Acute and convalescent serum samples were collected at participating hospitals and sent to the Thai National Institute of Health, Ministry of Public Health by EMS (Courier transportation). Serum samples were sent to be processed and serological diagnostic procedure of the above-mentioned infectious diseases was performed at the National Institute of Health of Thailand to avoid variation in serological method. Interpretation of the results was done without knowledge of individual clinical settings.

Blood culture for bacteria was done at participating hospitals. Positive culture of blood and other suitable specimens was also considered as the gold standard method for diagnosis of a specific etiologic agent that caused fever in that case.

Guidelines to conduct the study and fill the case record form was produced and discussed with health personnel during the first visit at each participating hospital before the study commenced. Final clinical, local laboratory data and result of treatment were collected within four weeks after patient discharge which was long enough to collect acute and convalescent sera for the serological tests. Though a management guideline of AUFI was introduced to physicians at the initial site visit, treatment of each individual depended on the judgement of the on-site physicians.

Result

A total of 1,240 patients were enrolled but only 1,137 case record forms with results of serological tests were available for the analysis. The majority of symptoms reported were headache, chill, myalgia, nausea as shown in Table 1. The etiologies could be found in 471 cases (38.7%) by blood culture and serology. Serological study revealed the etiologies of AUFI to be scrub typhus (7.5%), influenza (6.0%), dengue fever (5.7%), murine typhus (5.3%), enteric fever (1.9%), chikunkunya infection (1.1%), leptospirosis (1.1%) and melioidosis (0.9%) as shown in Table 2. Primary bacteremia was found in 36 cases (3.2%). *E. coli*, streptococci, salmonella, *Enterobacter* spp. and *S. aureus* were most commonly isolated (Table 3.). Seasonal variation of the

Table 1. Percentage of symptoms of the participating patients (n =1,137)

Symptoms	Percent
Headache	80
Chill	71
Myalgia	70
Nausea	56
Cough	53
Vomiting	44
Calf tenderness	40
Abdominal pain	38
Polyarthralgia	37
Productive cough	34
Constipation	32
Diarrhea	14
Rash	14

Table 2. Etiologies of AUFI by blood culture and serology

Diagnoses	Number of case (%)
Bacteremia	36 (3.0)
Scrub typhus	91 (7.5)
Influenza	73 (6.0)
Dengue fever	70 (5.7)
Murine typhus	65 (5.3)
Salmonellosis	23 (1.9)
Chikungunya virus infection	14 (1.1)
Leptospirosis	14 (1.1)
Melioidosis	11 (0.9)
Japanese encephalitis viral infection	7 (0.6)
Ebstein-Barr viral infection	2 (4.8)
Dual infections	58 (4.8)
Triple infections	7 (0.6)
Total	471 (38.7)

identifiable causes of AUFI by percentage found in each month is shown in Fig. 1. It could be seen that scrub typhus, influenza and dengue fever were the three dominant illnesses found the during rainy season or just before winter. Murine typhus and melioidosis were the other two illnesses that found slightly more often from midyear to the end of the year. Leptospirosis, chikungunya virus infection, Ebstein-Barr virus infection was detected all year round as well as primary bacteremia. Thirteen cases succumbed (1.1%) in the present study mostly due to nosocomial infection or their underlying diseases during hospitalization. Their clinical data are shown in Table 4.
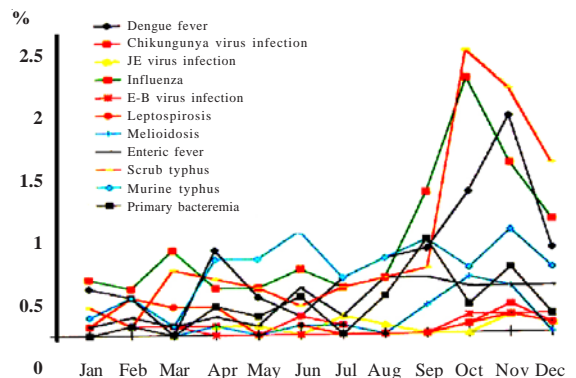

Fig. 1 Seasonal variation of the notifiable diseases by month

Table 3. Bacteria isolated from blood culture (primary bacteremia)

Micro-organism	No. (%)
Escherichia coli	13 (36.1)
Streptococcus spp.	6 (19.4)
Streptococcus pyogenes	2
Streptococcus group D	2
Streptococcus pneumoniae	1
Salmonella spp.	5 (13.8)
Salmonella typhi	3
Enterobacter spp.	4 (11.1)
Staphylococcus aureus	4 (11.1)
Aeromonas hydrophila	1 (2.8)
Klebsiella pneumoniae	1 (2.8)
Proteus mirabilis	1 (2.8)
Burkholderia pseudomallei	1 (2.8)
Total	36 (100)

Discussion

This observational study was the first prospective and systematic study designed to find out the causes of AUFI in Thailand. Ten participating hospitals were located in the north, northeast, central, east and south of Thailand. It took almost one and a half years to design, consult experts in infectious diseases and clinical epidemiology and prepare the participating hospitals for the study. However, there were certain limitations with regards to patient enrollment and data collection. Some eligible patients did not agree to be hospitalized and followed up. At night, there may be inadequate hospital personnel to carry out the enrollment process at some 30-bed community hospitals. Children less than two years old were excluded since most of the diseases are self-limited and are mostly due to viruses. Moreover, it

Table 4. Demographic data, diagnosis and underlying diseases of the 13 fatal cases

No	Sex	Age(yr)	Residential location	Diagnosis in the study	Cause of death and underlying disease
1	F	62	North	Dengue fever, influenza, murine typhus	Septicemia and cardiomegaly
2	F	9	East	Unknown	Encephalitis and ARDS
3	M	54	Central	*S. aureus* bacteremia	Pneumonia, renal failure, alcoholism, cirrhosis of liver
4	M	61	North	Unknown	Septicemia and pancytopenia
5	M	73	North	Unknown	Nosocomial pneumonia
6	F	74	North	Unknown	Diabetes mellitus and sepsis (meningitis?)
7	M	35	North	Unknown	Septicemia and hemoglobinopathy
8	M	23	North	Unknown	Septicemia, right renal stone and cirrhosis of liver
9	M	44	North	Unknown	Cirrhosis of liver, UGI bleeding, fever and jaundice
10	F	21	Central	*S. aureus* bacteremia	Pneumonia and mitral regurgitation
11	F	23	South	Unknown	*Klebsiella* liver abscess
12	F	60	North	Unknown	Subarachnoid hemorrhage
13	M	22	South	Unknown	Acute respiratory distress syndrome

M = male, F = female

would be difficult to collect adequate volume of blood from children. A few serum specimens were lost while they were being transported from study sites to the National Institute of Health of Thailand in Bangkok. Thus, the total number of enrollments was less than 2,000 cases as had been expected and only 1,137 case record forms with serological results were available for final analysis. The serological diagnostic techniques were conventional and standard in our country at the time of study initiation. Laboratory results were interpreted using the preset criteria without knowledge of individual clinical data. A few patients who simultaneously demonstrated two or three positive tests diagnostic for separated diseases could be explained by the cross-reaction among the methods rather than the presence of simultaneous dual or triple infections. However, further testing was not designed to confirm which diagnosis was truly correct since the result of the present study was intended to be preliminary. A final draft of the study was completed and submitted to the authority of the Ministry of Public Health several years ago but its content has not been published until now.

Although the cause of AUFI was not revealed in the majority (61.3%) of the cases, their clinical manifestations resembled those of upper respiratory infection (URI) or infectious diseases included in the study of AUFI[12].The authors admit that some unknown causes of acute self-limited febrile illness could operate in patients who belonged to the groups of unidentifiable cause or URI. For example, *Bartonella henselae* infection has never been reported in Thailand though it is prevalent in other countries[13]. The clinical features in some pediatric and adolescent cases are fever and sore throat without lymphaden-opathy[14]. Other tick-borne diseases reported in the United States have never been diagnosed in Thailand[15] and accurate diagnosis has been hampered by the lack of serological methods. Thus, these cases were certainly missed and may have been misdiagnosed as viral URI or included in the group of unidentifiable cause in the present study. However, the authors believe this is a rare situation and no diagnostic test for the diseases is included. For those infections that were included in the hypothesis and diagnostic tests by serological methods were available, a few of them may have been undiagnosed. In case of dengue infection, only in its advanced and severe form as seen in acute dengue hemorrhagic fever and dengue shock syndrome where petechiae and hypotension develop that any general physician can diagnose the infection correctly. However, the disease usually presents in its mild to moderate form as acute dengue fever where clinical manifestations give no clue to the diagnosis. Most of the cases were self-limited if their clinical courses ended uneventfully. The only means to diagnose dengue fever relies solely on the serological test. Since the sensitivity and specificity of the serological test for diagnosis of mild and moderate forms of dengue fever do not approach 100 percent, some cases of dengue fever in the present study were missed or falsely diagnosed. This situation was also applied to other infections solely diagnosed by serology. Thus, the etiologies of the unknown cause of the AUFI could be viral URI or the infectious diseases that were being studied but the diagnostic tests were not included or not sensitive enough to diagnose all the infections. In a future study, if newer diagnostic tests for viral URI and the anticipated causes of AUFI as well as those causes discovered from the present study were included, the study will shed more light on the cause of AUFI in this unknown group[16-17]. A high sensitivity and specificity of the newer rapid assays in early infection are also needed. Their ease of use, and stability in field settings probably will result in more accurate diagnosis of all causes of AUFI. Other causes of true pyrexia of unknown origin such as malignancy and auto-immune diseases should contribute to a very small portion of the unknown cause in the present study since the illnesses were mostly self-limited and fever was not prolonged. The authors have envisaged from the beginning that missed and false diagnosis existed to a certain degree but was not large enough to interfere with the value or compromise the objective of the study.

Fortunately, most of the AUFI group recovered soon and only thirteen cases (1.1%) developed fatal outcome at the end of the follow-up period. Two of them were found to have *S.aureus* bacteremia. The cause of fever was still unknown in eleven cases. An exploration into their case records showed various underlying illnesses that might have contributed to fever and death in some cases such as obscured malignancy (Table 4). These cases had prolonged hospitalization and needed more aggressive investigations to find the cause of fever and treated accordingly. Nevertheless, if the known underlying diseases in eight cases were accepted as the causes of AUFI and excluded from the study, the mortality rate of AUFI in the present study was approximately 0.42 percent. This figure is still higher

than the rate reported by the national surveillance system for acute PUO. Discrepancy in the mortality rate might be due to difference of case definition for AUFI in the present study and acute PUO in the national surveillance. In addition, not all cases of AUFI especially those with mild form of AUFI, were enrolled into the present study.

The present study showed that the etiologies of AUFI in 471 cases (38.7%) were identifiable and coincided with previous reports from local or tropical countries[18-24]. Influenza, scrub typhus and dengue fever were the three most common identifiable causes and predominated during the rainy season. Although the transmission routes of the three diseases are different, one common factor is the rain that facilitates the transmission of the diseases by providing breeding places for mosquitoes, a moist atmosphere to promote droplet or airborne tranmission. The rainy season also brings people to work in the farm and garden or keeps people sheltered under the same roof. Trees and shrubs are abundant and grow better and thus, provide a space for chiggers to bite animals and humans while treking into the garden or forest. Leptospirosis is found all year round without an outbreak since there was no environmental risk factor i.e., flooding during the present study[25]. In recent years when flooding occurred in many northeastern provinces, the number of cases with leptospirosis soared over that of scrub typhus. The authors believe the causes of AUFI can be diagnosed with confidence in many cases by obtaining accurate data from history, physical examination and simple investigation. For example, recent travel to endemic areas of scrub typhus, malaria, leptospirosis can never be overemphasized and ascertained. Injected conjunctiva, rash or generalized erythema or petechiae are instant clues to the diagnosis of scrub typhus or leptospirosis or dengue hemorrhagic fever. Finding an eschar is a real bonus to both the physician and patient. Onset of fever within one week associated with rapid rising of azotemia or pulmonary hemorrhage and hemoptysis after a flood or the rainy season should make one think of leptospirosis. Hematocrit rising to over 48 % together with a platelets count of less than 100,000 per cu.mm. or the presence of atypical lymphocytes of over 5 % are highly suggestive of dengue hemorrhagic fever. Nausea and vomiting with or without hepatomegaly and elevated liver enzymes should arouse one's suspicion of dengue fever as well[6]. Malaria should always be ruled out by blood smear and thick film whether or not there is a history of traveling to endemic area. In cases with rash or hyperemia or injected conjunctiva, finding of leukocyte and red blood cell counts of over 2-4 times the upper normal limits without any bacteria in the urine is highly suggestive of systemic vasculitis and glomerulitis that supports the diagnosis of leptospirosis or scrub typhus[26]. Blood culture should be performed to detect primary bacteremia or enteric fever especially in the elderly[27] or in some cases who do not exhibit any positive physical signs or laboratory findings as mentioned above. The rest of the diagnosis of AUFI depends on clinical clues as to what diagnosis is entertained and a work-up plan is individually organized. Unfortunately, community-based hospitals, especially health stations located at the peripheries of the provinces do not have well-equipped laboratories that are capable of performing all the serological tests or radio-imaging necessary for the diagnosis of most etiologies of AUFI. Thus, a management plan for AUFI is needed to provide assistance both for the treatment and prevention of AUFI at community-based hospitals. In addition, empiric and proper antimicrobial initiation is very cost-effective and can ameliorate fever very soon in cases with scrub typhus or leptospirosis. Thus, a combination of investigation and treatment of the so called "therapeutic diagnosis" for certain infections is integrated in the management based on the result of the present study.

Before a management plan is proposed, therapeutic option of the common causes of AUFI based on the result of the present study need to be considered. Leptospirosis, scrub typhus and murine typhus were frequently found among the known etiologies of AUFI (38.7%). These infections respond promptly to a three-day course of doxycycline. Ceftriaxone is an antibiotic of choice for enteric fever or typhoid fever. Primary bacteremia is often caused by *E.coli, Salmonella* spp., *S.aureus, streptocoocus* all of which are susceptible to ceftriaxone. Gentamicin may be added to ceftriaxone for those cases with severe community-acquired sepsis. Other causes such as viral URI or dengue fever usually run a 5-7 day course of fever and subside in the next few days. Hence, a wait-and-see and symptomatic treatment with analgesics are more appropriate for the latter. A management scheme is proposed that includes a thorough taking of history, recent traveling and physical examination. Complete blood count and platelets count in case of thrombocytopenia, thick film for malaria, urinalysis to detect microscopic

hematuria and pyuria, serum BUN or creatinine and transaminases are initial and optimal investigations that help clinicians properly manage most cases with AUFI. Chest X-rays may be followed if there is a clinical sign suspicious of abnormal pulmonary infiltration and hilar adenopathy or the initial investigations turn fruitless. In areas where tuberculosis is endemic, a chest CT scan might be included in the diagnostic work-up for detecting tuberculous mediastinal adenothpathy[28].

The following is an example to illustrate the application of the management plan. Those cases who present with intermittent spiking or high fever, myalgia, sore throat, coryza, dry cough or petechiae in an apparently healthy and unvaccinated person with influenza vaccine should be managed by close follow-up without antimicrobial administration. From the national statistics, this group comprises nearly half of the children or teenagers who are diagnosed as viral infection and are rarely associated with significant mortality. The initial manifestations of dengue fever are fever not responding to antipyretics, fatigue, anorexia with normal complete blood count. Some cases develop nausea, vomiting, mild hepatomegaly and elevated transaminase enzymes. However, the urinalysis is normal throughout the clinical course unless there is bleeding in the urogenital system. Until the illness enters days 3-5, the hematocrit is rise together with the presence of abnormal lymphocyte and thrombocytopenia. For working persons who exhibit injected conjunctiva, erythema or rash, eschar, doxycycline 200 mg given immediately and followed by doxycycline 100 mg. orally twice per day for three consecutive days should be tried. If the fever subsides within the first three days after therapeutic diagnosis is started, then diagnoses of leptospirosis or scrub typhus or murine typhus should be highly suspected. Rapid recovery from other symptoms of the three infections can also be expected within three days of doxycycline administration. Initial urinalysis that reveals trace to one plus amount of protein, 2 to 4 times the upper normal limits of the number of red blood cells and white blood cells and/or presence of casts is very helpful and an additional clue to the diagnosis of leptospirosis and rickettsial infections. For those who do not fit within the above clinical manifestation and are highly suspicious of enteric fever or primary bacteremia, ceftriaxone combined with gentamicin should provide an optimal coverage for the anticipated micro-organisms that are involved in enteric fever or primary bacteremia. If one can not distinguish scrub typhus or leptospirosis from primary bacteremia, ceftriaxone combined with doxcycline can be empirically used. In these cases, serological tests should be performed simultaneously while the patients are being treated with the antimicrobials.

To improve the utilization of the Annual National Statistical Report on AUFI cases, firstly the authors propose to using "AUFI" instead of acute PUO. Though there is no consensus about the definition of AUFI, most agree with the criteria used in the present study. Fever ranges from 3 to 14 days with generalized symptoms and the result of the physical findings compatible with active systemic infection. Initial complete blood count is normal and urinalysis finding does not support the diagnosis of urinary tract infection due to bacteria. Chest X-ray is optional and normal if performed. Secondly, those AUFI who presented with rhinorrhea and/or sore throat with erythematous nodules on posterior pharyngeal wall should be diagnosed as viral URI and discriminated from AUFI. This step is easy and practical and should reduce the huge number of "old" AUFI to a level that is more sensitive to change when an endemic or outbreak of the diseases grouped in "new" AUFI occurs. By cutting the background of the "old" AUFI due to viral URI, change of endemic or epidemic of dengue fever, influenza and rickettsial infection will be relatively better reflected in the report. An outbreak of leptospirosis can be indirectly detected by the presence of its severe form that is composed of abnormal urinalysis, pulmonary hemorrhage and elevated serum BUN and creatinine within the first week of fever during the flooding or rainy season. The authors believe by distinguishing viral URI from AUFI, the annual number of cases with AUFI will be reduced and more time will be used for disease prevention and control.

Conclusion

The etiologies of AUFI remains unknown in the majority of AUFI. Rickettsial infection, influenza and dengue fever are the three most common known causes in a tropical country like Thailand. Serological methods are mandatory to diagnose the cause and support the management of cases with AUFI since clinical criteria alone are insufficient to identify all etiology. Close follow-up with symptomatic treatment is a strategy to manage many cases with viral infections or viral URI. Doxycycline and/or ceftriaxone combined with gentamicin are proposed as the cost-effective empiric antimicrobials of choice

for the therapy of AUFI due to leptospirosis, scrub typhus, murine typhus and primary bacteremia. However, antimicrobial therapy should be wisely selected according to the likelihood of each treatable infection as suggested by history, physical examination, complete blood count, urinalysis,chest X-rays, serum levels of BUN, creatinine and transaminases enzymes. Finally, distinguishing viral URI from AUFI by clinical criteria is another means to improve the utilization of the national annual report on AUFI.

Acknowledgements

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สาเหตุของไข้เฉียบพลันที่ไม่ทราบสาเหตุในประเทศไทย

อมร ลีลารัศมี, จันทร์เพ็ญ ชูประภาวรรณ, มงคล เจนจิตติกุล, สุทธิพล อุดมพันธุรัก

คณะผู้วิจัยได้ศึกษาหาสาเหตุของไข้เฉียบพลันที่ไม่ทราบสาเหตุในด้านโรคติดเชื้อที่โรงพยาบาลต่างจังหวัด ๑๐ แห่งที่ตั้งอยู่ตามภาคต่าง ๆ ของประเทศไทยระหว่างวันที่ ๑ ตุลาคม พ.ศ. ๒๕๓๔ ถึงวันที่ ๓๐ กันยายน พ.ศ. ๒๕๓๕ เกณฑ์การรับผู้ป่วยเข้าไว้ในการศึกษามีดังนี้คือ อายุมากกว่า ๒ ปี วัดไข้ได้สูงกว่า ๓๘.๓ องศาเศลเสียสภายใน ๒๔ ชั่วโมงที่ผ่านมา ระยะเวลาที่มีไข้อยู่ระหว่าง ๓ วันถึง ๒ สัปดาห์ การชักประวัติ และการตรวจร่างกายไม่สามารถบ่งชี้ถึงโรคติดเชื้อที่เกิดเฉพาะที่อวัยวะใดอวัยวะหนึ่ง ผลการตรวจเลือด การตรวจหาเชื้อมาลาเรีย ปัสสาวะ ภาพถ่ายรังสีทรวงอกไม่บ่งชี้ว่าเกิดจากเชื้อก่อโรคชนิดใดชนิดหนึ่ง ผู้ป่วยที่เข้าเกณฑ์ดังกล่าวถูกรับไว้ในโรงพยาบาลและได้รับการตรวจเพิ่มเติมตามแบบแผนที่ได้วางไว้หรือตามที่ผู้รักษาเห็นสมควร ผู้ป่วยได้รับการติดตามภายใน ๓๐ วันหลังจำหน่ายจากโรงพยาบาล

ผลการศึกษาพบว่ามีผู้ป่วยเข้าร่วมโครงการ ๑,๒๔๐ รายแต่มีข้อมูลในรายงานที่สามารถนำมาวิเคราะห์ได้ ๑,๑๓๗ ราย ตรวจพบสาเหตุของไข้ได้ร้อยละ ๓๘.๗. แบคทีเมียพบได้ร้อยละ ๓.๒. แบคทีเรียที่พบบ่อย ๕ อันดับแรกคือ E. coli, streptococci, Salmonella spp., Enterobacter spp., S.aureus. การตรวจทางน้ำเหลืองพบสาเหตุจากโรคสครับ ทัยฟัส ๙๑ ราย (ร้อยละ ๗.๕) ไข้หวัดใหญ่ ๗๓ ราย (ร้อยละ ๖.๐), ไข้เดงกี ๗๐ ราย (ร้อยละ ๕.๗), มิวรีนทัยฟัส ๖๕ ราย (ร้อยละ ๕.๓), ไข้รากสาดน้อย ๒๓ ราย (ร้อยละ ๑.๙), โรคติดเชื้อไวรัส chikungunya ๑๔ ราย (ร้อยละ ๑.๑), เล็ปโตสไปโรสิส ๑๔ ราย (ร้อยละ ๑.๑), เมลิออยโดสิส ๑๑ ราย (ร้อยละ ๐.๙). ผู้ป่วยถึงแก่กรรม ๑๓ รายหรือร้อยละ ๑.๑

โดยสรุป ตรวจไม่พบสาเหตุของไข้ถึงร้อยละ ๖๑.๓. สครับ ทัยฟัส ไข้หวัดใหญ่ และไข้เดงกี เป็นโรค ๓ อันดับแรกที่พบบ่อยในผู้ป่วยกลุ่มนี้โดยเฉพาะในฤดูฝน คณะผู้วิจัยได้เสนอแบบแผนการดูแลรักษาผู้ป่วยที่เป็นไข้เฉียบพลันที่ไม่ทราบสาเหตุโดยเน้นการรักษากลุ่มที่เป็นแบคทีเมียและโรคติดเชื้อที่ตอบสนองดีต่อยาต้านจุลชีพและแนวทางการรายงานภาวะนี้