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Recent trends in the distribution of causative diseases of fever of unknown origin

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Summary Fever of unknown origin is a challenging diagnostic problem and the aim of this research was to analyze trends in the distribution of its causative diseases. This retrospective study makes a comparison between two different clinical series of patients from two different periods: 227 from period 1 (1998–2002) and 602 from period 2 (2008–2012). There were fewer infections (31.72% vs.16.45%) and more miscellaneous causes (5.29% vs. 13.12%) in the period 2 series, whereas no significant differences in autoimmune diseases, malignancies and undiagnosed cases were found. Adult onset Still's disease and lymphoma occupied the largest proportion in autoimmune diseases (75.00%) and malignancies (89.81%), respectively. Interestingly, the autoimmune diseases group, instead of infections, was found to be the leading category of the causative diseases in fever of unknown origin, which is contrary to previous reports. Further, adult onset Still's disease and lymphoma were suggested to be valued more highly in view of the large and rising proportions found in this study. These trends could support the diagnosis and treatment of fever of unknown origin better in the future.

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Abbreviations

FUO	Fever of unknown origin
AID	Autoimmune diseases

Introduction

Fever of unknown origin (FUO) is one of the most difficult diagnostic challenges. The first revision of criteria was established by Petersdorf and Beeson in 1961. At that time FUO was defined as body temperature above 38.3 °C (101 °F) on several occasions that lasts for over 3 weeks, and no diagnosis was made after 1 week of hospital admission [1]. The definition was modified by Durack and Street in 1991, and they suggested two major changes: the required duration of investigation changed from "1 week of hospital" to "3 inpatient days or 3 outpatient visits", and the FUO was further classified into classical FUO, nosocomial FUO, neutropenic FUO, and human immunodeficiency virus (HIV) associated FUO [2]. Among these four categories of FUO, the classical FUO is the most common and is considerably complicated [3]. Previous literature sources have reported over 200 causes of FUO, a classification of 5 categories: infections, malignancies, autoimmune diseases (AID), miscellaneous causes, and undiagnosed is generally used. Even though there have been remarkable developments in the diagnosis of FUO by modern imaging techniques and laboratory tests, many causative diseases and the varying distribution of the causes make the diagnosis complicated. In addition, the distribution of diseases causing FUO varies in different periods and geographical regions. For example, the proportion of infectious diseases in developing countries

Table 1 General background information of patients in the study

Years	Number of cases	Median age (years, range)	Sex ratio	Diagnostic rate (%)	Case fatality rate (%)	
					Diagnosed FUO	Undiagnosed FUO
1998–2002	227	35 (13–79)	1.34:1	75.77	3.49	10.91
2008–2012	602	41 (15–85)	1.46:1	71.40	3.38	14.89

occurred at comparatively higher levels while AID occupied a larger proportion of occurrences in developed countries [4, 5]. Moreover, there was a decreasing temporal trend in the proportion of infectious diseases from the same region [6, 7]. Furthermore, other complex interactions, such as demographics, economic factors, and population mobility also contribute to trends in the distribution of the causative diseases of FUO. Thus, studies on the temporal trend in specific regions, especially in China, are of great importance; however, to our knowledge, there is a lack of large-scale studies investigating the recent trends, because it is difficult to extract an adequate number of patient cases that meet the criteria of FUO. Therefore, a comprehensive investigation is needed.

The West China Hospital is the second largest hospital in China and it has established extensive cooperation with other institutions. In the present study, therefore, we acquired comprehensive and large-scale data from the Center of Infectious Diseases, West China Hospital, Sichuan University, China. The aim of this study was to analyze recent trends in the distribution of causative diseases of classical FUO. Hopefully, the present study could help establish more applicable qualitative criteria and a uniform classification to support the diagnosis and treatment of FUO better in the future.

Material and methods

Selection and description of participants

In this retrospective study, medical records of patients with a diagnosis of FUO in the Infectious Disease Center of West China Hospital were extracted from two periods: period 1 from 1 January 1998 through 31 December 2002, and period 2, from 1 January 2008 through 31 December 2012. The criteria of Durack and Street for classical FUO was adopted in this study. Patients meeting all of the following criteria were included in this study: 1) fever with axillary temperature ≥38.3 °C at least twice over a ≥3-week period, 2) unknown cause after 3 outpatient visits or during 3 days of hospitalization, 3) not diagnosed with immunodeficiency before fever onset and 4) no confirmed human immunodeficiency virus (HIV) infection before fever onset. This study was approved by the ethics committee of West China hospital and was conducted according to the 1975 Declaration of Helsinki. The present study did not increase the patient's medical expenses or pain and all research materials and results were used for research purposes. The requirement for informed consent was waived by the Medical Ethics Committee as the present study was an observational, retrospective study using a database from which the patients' identifying information had been removed.

Statistical analysis

Statistical analysis of the data was carried out using SAS 9.3 software. The χ^2-test of significance was used to assess differences in constituent ratios in the two series. A p-value <0.05 was considered significant.

Results

Baseline characteristics

Two clinical series of cases were enrolled in this study, which included 227 cases from period 1 (1998–2002) and 602 cases from period 2 (2008–2012). The period 1 series included 130 men and 97 women, with a median age of 35 years (range 13–79 years), the diagnostic rate was 71.40% and case fatality rate was 6.15%. The period 2 series included 357 men and 245 women, with a median age of 41 years (range 15–85 years), the diagnostic rate was 75.77% and case fatality rate was 5.73%. There were no significant differences between the data in the two series (Table 1). Furthermore, in period 1 series, the case fatality rate of diagnosed FUO was 3.49% while it was 10.91% in undiagnosed FUO and the χ^2-test analysis showed the difference was of significance (p = 0.009). In period 2 series, the case fatality rate of diagnosed FUO was 3.38% while it was 14.89% in undiagnosed FUO and the difference was also statistically significant (p = 0.043).

Distribution of causative diseases of FUO in different series

Comparing the period 1 series with the period 2 series of cases we observed that there were fewer infections (31.72% vs. 16.45%, $p < 0.05$) and more miscellaneous causes (5.29% vs. 13.12%, $p < 0.05$) in period 2, whereas no significant differences ($p > 0.05$) in AID (22.03% vs. 23.92%), malignancies (16.74% vs. 17.94%), and undiagnosed cases (24.23% vs. 28.57%) were found between the two series (Fig. 1; Table 2).

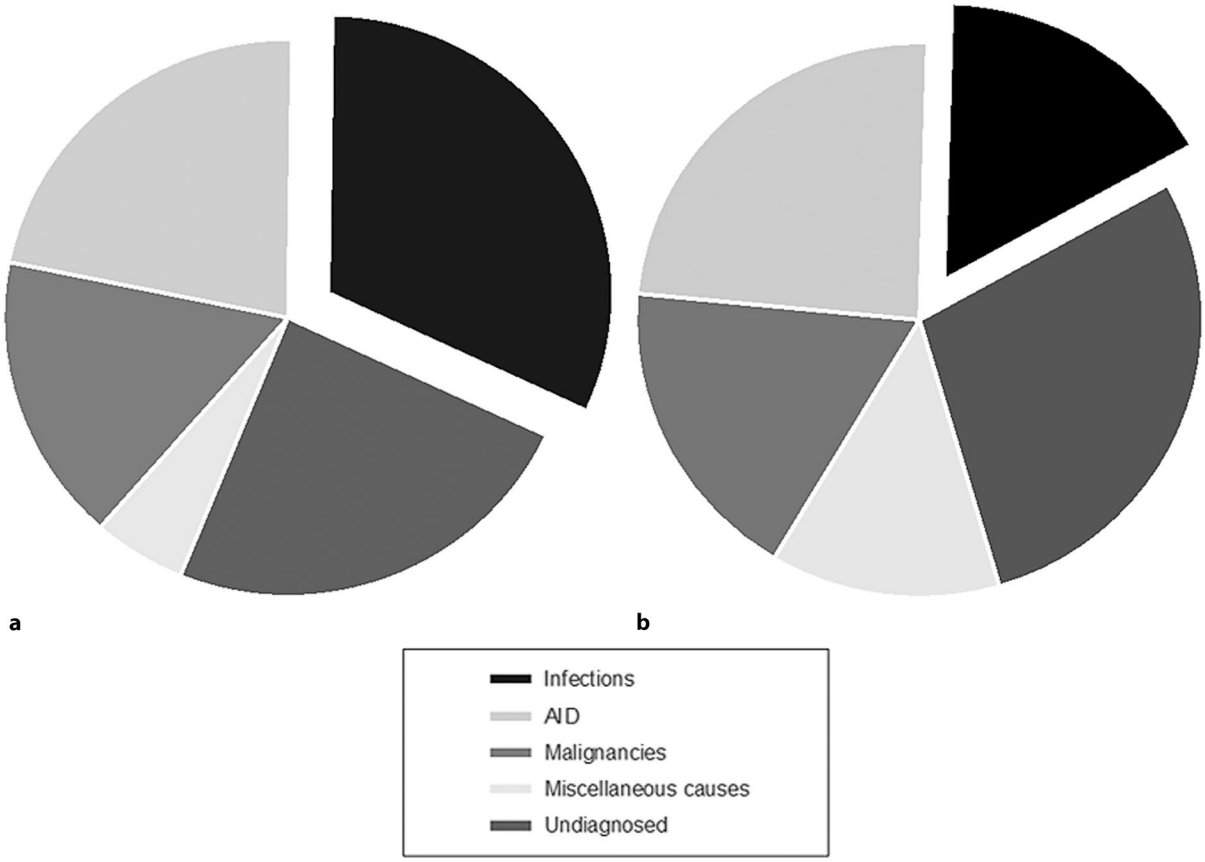

Fig. 1 Distribution of the different disease categories. **a** Period 1 series enrolled cases during 1998–2002, the number of causative diseases in different category groups is analyzed. Data are shown as a pie chart with percentages. **b** Period 2 series enrolled cases during 2008–2012, the number of causative diseases in different group of categories is analyzed

Table 2 Distribution of the different disease categories

Causes	1998–2002 (%)	2008–2012 (%)	*P*-value
Infections	31.72	16.45	0.000
AID[a]	22.03	23.92	0.566
Malignancies	16.74	17.94	0.686
Miscellaneous causes	5.29	13.12	0.001
Undiagnosed	24.23	28.57	0.211

Data shown are percentages. Statistical significance is examined using χ^2-test to assess the difference of constituent ratios in the two series
$P < 0.05$ is considered statistically significant
[a]Autoimmune diseases

Distribution of pathogens causing infections in different series

Further analysis of the distribution of the pathogens that caused infections shows that in period 1 bacterial pathogens accounted for 84.72%, viruses for 6.94%, fungi for 5.55% and parasites for 2.78%. In the period 2 series, bacterial pathogens accounted for 78.79%, viruses for 8.08%, fungi for 7.07% and parasites for 6.06%; however, none of the differences found between the two series were statidtically significant.

Distribution of causative AID diseases in different series

Among the AID grouping of causative diseases, there was higher incidence of adult onset Still's disease (38.00% vs. 75.00%, $p < 0.05$), lower incidences of systemic lupus erythematosus (24.00% vs. 6.94%, $p < 0.05$) and rheumatoid arthritis (12.00% vs. 1.39%, $p < 0.05$) in the period 2 series. Other incidences of causes, such as rheumatic fever, nodular panniculitis, Behcet syndrome, mixed connected tissue, and polymyositis were all decreased in period 2, but there were no significant differences between the two series.

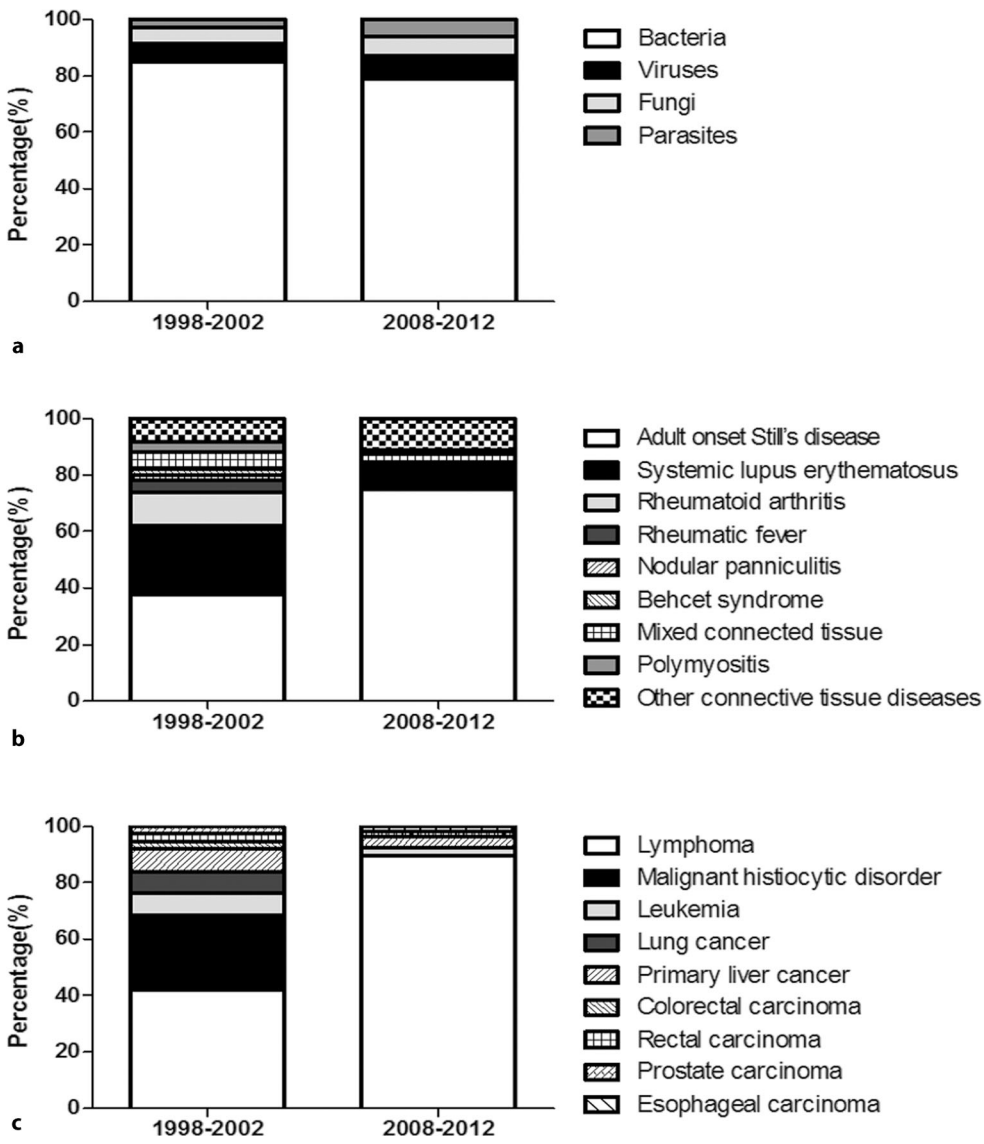

Fig. 2 Distribution of causative diseases in major category groups. **a** Among causative diseases in infections group, the number of patients caused by different pathogens is analyzed. **b** Among causative diseases in AID group, the number of patients with different causes is analyzed. **c** Among causative diseases in malignancies group, the number of patients with different causes is analyzed

Distribution of causative malignancies diseases in different series

As for causes in the malignancies grouping, more lymphoma (42.11% vs. 89.81%, $p< 0.05$) was found in period 2 series, whereas the proportion of malignant histiocytic disorders (26.32% vs. 0.00%, $p < 0.05$) and lung cancer (7.89% vs. 0.00%, $p < 0.05$) in malignancies was decreased. Furthermore, proportions of leukemia, primary liver cancer, colorectal carcinoma, rectal carcinoma, prostate carcinoma and esophageal carcinoma were all decreased in period 2, but there was no significant difference between the two series (Fig. 2; Table 3).

Discussion

In this large retrospective study, the proportion of infectious diseases significantly decreased, while the proportions of adult onset Still's disease in the AID grouping of disease and lymphoma in the malignancies category significantly increased in the period 2 series. Case fatality rates in undiagnosed FUO were significantly higher than those in diagnosed FUO in both two period series. In addition, instead of infections, AID became the primary category.

Comparing trends found in the present study to previous research results [8–11], it is worth noting that infections comprised an extraordinarily low proportion. This trend is in accordance with the increasing use of antibiotics in China during this period. Previous research in 2013 reported that each Chinese person consumes 138 g of antibiotics per year, 10 times that consumed in the USA. Approximately 75% of patients with seasonal influenza are estimated to be prescribed antibiotics, and the rate of antibiotic prescription for inpatients is 80% [12]. With a relatively large amount of users of antibiotics in China, empirical use of antibiotics is also increasing year by year. It is notable that empirical use of antibiotics was

Table 3 Distribution of causative diseases in major category groups

	1998–2002 (%)	2008–2012 (%)	*P*-value
Pathogens in infections group			
Bacteria	84.72	78.79	0.326
Viruses	6.94	8.08	0.782
Fungi	5.55	7.07	0.934[a]
Parasites	2.78	6.06	0.524[a]
Causative diseases in AID[c] group			
Adult onset Still's disease	38.00	75.00	0.000
Systemic lupus erythematosus	24.00	6.94	0.001
Rheumatoid arthritis	12.00	1.39	0.005[a]
Rheumatic fever	4.00	1.39	0.274[b]
Nodular panniculitis	2.00	0.00	0.258[b]
Behcet syndrome	2.00	0.00	0.258[b]
Mixed connected tissue	6.00	2.78	0.540[a]
Polymyositis	4.00	1.39	0.274[b]
Other connective tissue diseases	8.00	11.11	0.533
Causative diseases in the malignancies category			
Lymphoma	42.11	89.81	0.000
Malignant histiocytic disorders	26.32	0.00	0.000[a]
Leukemia	7.89	2.78	0.182[b]
Lung cancer	7.89	0.00	0.017[b]
Primary liver cancer	7.89	3.70	0.549[a]
Colorectal carcinoma	2.63	0.00	0.260[b]
Rectal carcinoma	2.63	0.00	0.260[b]
Prostate carcinoma	2.63	1.85	1.000[b]
Esophageal carcinoma	0.00	1.85	1.000[b]

Data shown are percentages. Statistical significance is examined by using χ^2-test to assess the difference of constituent ratios in the two series
$P < 0.05$ is considered statistically significant
[a]χ^2-value adjusted by continuity correction
[b]χ^2-value adjusted using Fisher's exact test
[c]Autoimmune diseases

recommended in the Chinese guidelines for clinical use of antibiotics in 2015. According to the guidelines, antibiotics could be used before acquiring results of bacterial culture and drug sensitive test when patients were diagnosed with infectious diseases, then the antibiotics therapy should be modified basing on pathogen detection and drug sensitivity test; however, the empirical use of antibiotics was not mentioned in another version of guidelines in 2004. Thus increasing use of antibiotics could help explain why the infections comprise an extraordinarily low proportion in FUO in the period 2 series (2008–2012). Furthermore, it is noteworthy that in period 2 series, 528 out of 602 (87.71%) patients were found to receive empirical antibiotic therapy, the finding that a large proportion in period 2 series received empirical treatment of antibiotics is consistent with the phenomenon of increasing use of antibiotics in China. Moreover, other factors such as effective regional social capital investments in sanitary measures and improved diagnostics over time could also explain the significant downward trend between the two different series.

The leading category of the causative diseases of FUO in the period 2 series was AID. Among them the increase in the proportion of adult onset Still's disease is noteworthy. There could be two reasons, one is that improved diagnostics were helpful in the diagnosis of AID, thus, the proportions of many diseases in the AID category decreased, so that it made the shift of proportion of adult onset Still's disease. For example, the proportion of systemic lupus erythematosus declined because the new criteria such as the new SLICC classification criteria worked well [13] with current immunological serology in diagnosing systemic lupus erythematosus before meeting the definition of classical FUO. The other reason is that adult onset Still's disease is a systemic inflammatory disorder of unknown etiology and obscure mechanism [14–16]. Symptoms such as a triad of daily fever, arthritis, and rash can be found, increases in the erythrocyte sedimentation rate, C-reactive protein (CRP) levels and neutrophilic leukocytosis are frequent. Nevertheless, none are specific; however, recent studies reported that serum ferritin level is correlated with disease activity with a 80% sensitivity and 41% specificity with a fivefold increase

[17–20]. What is more, the diagnosis of adult onset Still's disease needs an exclusion of other diseases [21], even though the diagnostic criteria of Yamaguchi et al. [22] have proven to be the most sensitive [23] the process of exclusions prolong the diagnosis. In addition, it is reported that the chronic progression was correlated with a poor functional prognosis [24].

Among causative diseases in malignancies category, the proportion of lymphoma significantly increased with decreased trends in the proportions of solid tumors. It was due to the widespread use of imaging techniques that helped in establishing the early diagnosis of solid tumors; however, lymphoma remains difficult to diagnose for its irregular fever type with a long duration. Thus, further evaluation is often delayed. Moreover, compared with lymphoma patients in the non-FUO group, patients presenting with FUO encountered more rapid and poorer prognosis [25]. Extranodal tissue biopsy and lymph node biopsy [26], positron emission tomography-computed tomography (PET/CT), and abdominal laparotomy are valuable in diagnostics. It has been reported that the most noteworthy is the contribution of PET/CT [27, 28], which is cost effective in the FUO diagnosis process at an early stage [29].

The proportion of miscellaneous causes significantly increased in the two series possibly because of emerging new diseases and the application of aggressive medical treatment, especially antibiotics, in the early phases of diseases.

Previous studies have reported a high percentage of undiagnosed causes of FUO [30, 31], and the present study also found a relatively high proportion. This may be attributed to the fact that our hospital is a tertiary referral center, which means that many patients receive initial treatment in a primary hospital before. In addition, our study found a higher case fatality rate in undiagnosed FUO than in diagnosed FUO, which may be attributed to longer duration of fever and the lack of effective etiological therapy, indicating the importance of definite diagnosing of FUO.

Some limitations in the present study should be recognized. The diagnosis of classical FUO was made by the attending physician at a specific time, and selection bias was inevitable with consideration of the long time spans of this retrospective study. In spite of that, this study did apply the strict selection criteria of classical FUO to reduce the selection bias.

Conclusion

In the present study, the primary causative diseases of FUO varied from infections to AID and AID and malignancies became the two leading causes of FUO. Moreover, adult onset Still's disease and lymphoma both occupied the largest and rising proportion in AID and malignancies categories, respectively. They should be highly valued in the differential diagnosis of FUO. Further prospective studies on correlations between specific factors, such as and the diagnosis of FUO will be required. In addition, follow-up studies on discharged patients for the outcomes, especially, for adult onset Still's disease and lymphoma are needed.

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Conflict of interest J. Shang, L. Yan, L. Du, L. Liang, Q. Zhou, T Liang, L. Bai, and H. Tang declare that they have no competing interests.

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