Infectious fever of unknown origin and acute undifferentiated febrile illness with particular epidemiological importance

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Abstract

Aim: Fever represents a very common syndrome among patients requesting hospitalization. Today, in the context of the dynamic changes affecting infectious diseases in the global era, the clinical-epidemiological binomial evaluation (as seasonal epidemics, occupational exposure, travel) is important in terms of etiologic diagnosis.
Methods: This study included 323 patients hospitalized at the Infectious Diseases Service of the University Hospital Center "Mother Teresa" in Tirana, during a five-year period (from 2011 to 2016). The age group of the patients varied from 14 to 79 years. Patients were hospitalized by the reference system or through the emergency triage. Each patient was equipped with a specific clinical file which included epidemiological survey, anamnesis, clinical examination and biological, biochemical, microbiological and serological tests.
Results: Of the 323 patients observed from January 2011 to December 2016, we recorded 14 different clinical entities of particular importance to public health, especially epidemiological.
The infectious diseases were 14 entities of which 10 were conventional, 3 emergent and 1 re-emergent. The Acute Undifferentiated Febrile Illness (AUFI) resulted in 127 cases with Leptospirosis (54.9%), Encephalitis 26 (11.2%), Measles 1 (0.4%), Hemorrhagic Fever 44 (19.0%), Pulmonary Tuberculosis 14 (6.0%), Varicella 8 (3.4%) and Hepatitis 11 (4.7%). The Infectious FUOs resulted in: Brucellosis 31 (33.6%), HIV-AIDS 8 (8.69%), Malaria 2 (2.17%), Rickettsiosis 1 (1%), Borreliosis 1 (1%), Tubercular Meningitis 5 (5.43%), Leishmaniosis 44 (47.8%). The seasonal distribution of these pathologies was the same for 5 clinical entities and with some characteristics for the others with predominance in May-June and September-October.
Conclusions: Our study evidenced that the pathogenic spectrum of Febrile Syndromes is considerable in transitional Albania.

Keywords: acute undifferentiated febrile illness, infectious fever of unknown origin, public health.

Introduction

Although febrile syndrome has been conventionally labeled as an indicator of infectious diseases, it is often difficult to identify an infectious etiologic agent. Febrile syndromes are often identified with an infectious disease with or without epidemiological referrals. But more often, in clinical practice, we are faced with acute or prolonged fever with unrecognized etiology. We struggle with the same problem for both clinical variants, the etiologic cause. Both clinical manifestations and epidemiological data play a crucial role in regard to this. Fever of an unknown origin (FUO) in adults is defined as a temperature higher than 38.3° C (100.9 F) that lasts for more than three weeks with no obvious source despite the accurate one week investigation (1-9).

In the last 60 years, there have been many researches on the various causes of fever. Early diagnosis are provided sooner taking into account the improvements of the serological and imaging tools, changing of the definition of FUO, and the development of the patterns of the disease (10).

In fact, our clinical experience has demonstrated that important infectious pathologies can clinically manifest, even though for a short period of time, as acute unknown fever (11-14); we are referring to the first important hours for the diagnosis of a difficult clinical case where the proper clinical infective traits have not yet been prominent.

The etiologic diagnosis in these cases seems to be determined by every hour the patient passes under the medical triage. However, this does not minimize the importance or the diagnostic orientation of acute unknown fever (4,5,13).

Major parts of the febrile syndromes are diagnosed based on the symptoms or visible infectious foci during objective examination. Usually, simple tests like hemocytogram or uroculture are necessary to establish a definitive diagnosis.

Viral pathologies (e.g., upper respiratory tract infections) are responsible for most of these self-limited cases that are usually solved within two weeks. If the temperature persists, a more detailed diagnostic investigation should be undertaken.

Even though some prolonged febrile syndromes appear to be manifestations of serious pathologies, most of them can now be diagnosed and treated.

Methods

The study included 323 patients hospitalized at the Infectious Diseases Service of the University Hospital Center "Mother Teresa" in Tirana during a 5-year period from 2011 to 2016. The age group of the patients varied from 14 to 79 years. Patients were hospitalized by using the reference system or by the emergency room as FUO or AUFI. All patients with FUO met the following well-known criteria:

- 38 degree or higher fever;
- duration of fever for more than 3 weeks;
- infirmity to establish the etiologic diagnosis during a 1 week triage.

AUFI patients were characterized by the presence of high fever without a precise preclinical diagnosis. Patients with attributes of specific patterns that could generate an acute febrile syndrome were excluded.

The patients that participated in the study were equipped with:

- epidemiological survey;
- clinical, anamnesis, and semiotic examinations;
- biological / biochemical data (biochemical balance and hematological examination);
- algorithms of etiologic diagnosis (microbiological investigations such as hemocultures, coproculture, uroculture, tampon cultures from various inflammatory sites, sero-diagnostic research such as Vidal, Wright, Weil-Felix, Elisa for Hepatitis, HIV, Hemorrhagic Fever, Leptospira, Leishmaniosis, Borreliosis, direct observation, microbial culture and gamma interferon for tuberculosis.)
- Imaging - radiological, eco, ct, RMI searches.

The above mentioned data/tests were applied to the patients rationally according to epidemiological, clinical, biological and imaging criteria.

Based on the above data/tests, we built the etio-nosological diagnosis of febrile syndromes and ranked them according to the identified infectious nosologies.

Results

The 323 patients who participated in the study were observed aiming the rapid etiologic diagnosis. This implies a careful assessment not only of clinical and laboratory data, but also of other factors such as age, seasonality, M: F ratio. Overall, 323 patients observed from January 2011 to December 2016 manifested 14 important clinical entities. The Acute Undifferentiated Febrile Illness resulted in 127 cases with Leptospirosis (54.9%), Encephalitis 26 (11.2%), Measles 1 (0.4%), Hemorrhagic Fever 44 (19.0%), Pulmonary Tuberculosis 14 (6.0%), Varicella 8 (3.4%) and Hepatitis 11 (4.7%). The Infectious FUOs resulted in: Brucellosis 31 (33.6%), HIV-AIDS 8 (8.69%), Malaria 2 (2.17%), Rickettsiosis 1 (1%), Borreliosis 1 (1%), Tubercular Meningitis 5 (5.43%), Leishmaniosis 44 (47.8%).

The most frequent age groups for these nosologies were 25-34 and 45-54. The male / female ratio demonstrated a male dominance with a 6.6: 1 ratio and frequent seasons for some of the pathologies resulted in summer and autumn (May-June and September-October) while other pathologies demonstrated a uniform distribution over the four seasons. Lethality was encountered in 5 infectious nosologies: malaria 1 case, hemorrhagic fever 3, HIV / AIDS 3, meningitis 1, encephalitis 4, leptospirosis 9, Leishmaniosis1. Conventional Infectious Diseases dominated most of the Febrile syndromes with 81.4% compared to the emergent ones 21.8% and the re-emergent 5.7%.

Table 1. Acute undifferentiated febrile illness

No.	Diagnosis	No. of cases	M/F ratio	Median age	Seasonality	Lethality
1	Leptospirosis	127	13:1	45-54 55-64	May - June September-October	9
2	Measles	1	1:0	25-34	June	0
3	Encephalitis	26	1:1	25-34	Uniform	4
4	Haemorrhagic fever	44	8:1	25-34	May - June July - August	3
5	Pulmonary tuberculosis	14	1.5:1	15-24	January-February-March	0
6	Varicella	8	1:1	25-34	May - June	0
7	Hepatitis	11	1.2:1	25-34	Uniform	0

Figure 1. Cases with AUFI (N=231)

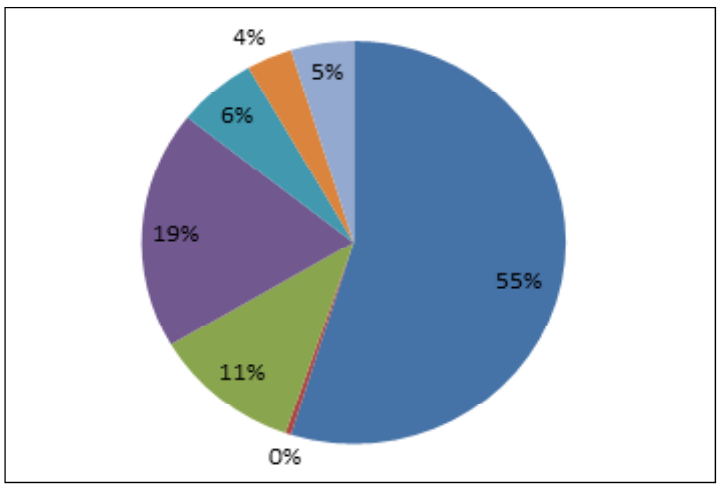
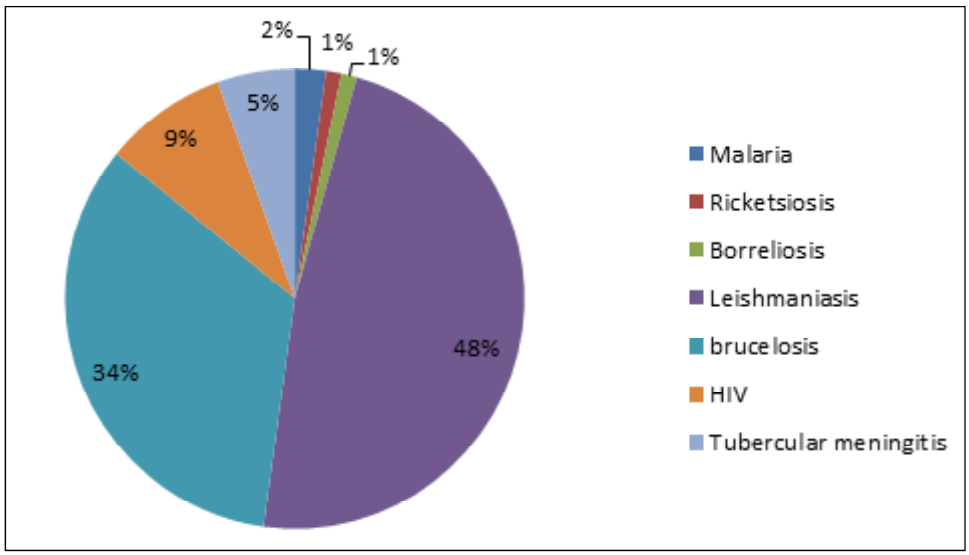


Table 2. Infectious FUO

No.	Diagnosis	No. of cases	M/F rate	Median age	Seasonality	Lethality
1	Malaria	2	0	25-34 35-44	April-June September-October	1
2	Riketsiosis /murine typhus	1	0	15-24 45-54	June - July September - October	0
3	Borrelisis	1	1.2:1	45-54	September - October	0
4	Leishmaniosis	44	2:1	25-34	May- June September-October	1
5	Brucellosis	31	3:1	15-24 45-54	April – June	0
6	HIV	8	3:1	25-34 45-54	Uniform	11
7	Tubercular meningitis	5	1.2:1	15-24 35-44	Uniform	35

Figure 2. Cases with FUO (N=92)



Discussion

The role and impact of Infectious Diseases to Public Health Institute is very important and has some specific indicators: their risk of proliferation by causing limited epidemic outbreaks or true epidemics; high risk of causing organ damage to affected subjects or even death; compliance for national and international epidemiological sanitary legislation based on WHO specific protocols.

Usually, in clinical practice, a special epidemiological

and declarative significance is given to acute diseases or syndromes manifested by exanthema, acute respiratory syndrome (Influenza –like syndromes), toxic-infections (vomiting or diarrhea) etc. Our practice has shown that febrile syndrome can contain in itself infectious pathologies of particular importance to public health.

Both, our material and results look very interesting in terms of the optic of this study. For our country, such vision of infectious diseases as presented in this study is a novelty. However, even in terms of international literature, such studies are scarce and incomplete.

From the above results, there are several clinical and epidemiological phenomena of febrile syndromes, of which we will focus on the following:

Prolonged febrile syndromes resulted in 7 nosologies, each of them representing a different level of risk to Public Health. According to their specific epidemiological importance, we ranked them as below: Leishmaniosis 44 cases, brucellosis 31 cases, HIV / AIDS infection 8 cases, tubercular meningitis 5 cases, malaria 2 cases, borreliosis1 case, rickettsiosis 1.

Their etiological structure included three microbial agents: 4 species of bacteria (Brucellasp, Mycobacterium Tuberculosis, Rikettsiesp, Borreliaspp); Viruses (HIV 1) and protozoa (Plasmodium falciparum and P.oval).

Under the clinical-epidemiological optic they can be distinguished as follows:

The infectious febrile illnesses, due to the importance of lethality and epidemiology:

Malaria evidenced to different types:

- Malaria falciparum, which is very significant for the life of patients due itssignificant lethality rate 29%, but also very important epidemiologically as well, because it can condition the creation of autochthonous focuses in our country;
- Malaria Oval, whose importance for public health is mainly epidemiological.

Visceral leishmaniasis where the two above-mentioned phenomena such as lethality that reaches up to 92% in untreated cases (15) and epidemiological as well, regarding the endemic focus of this protozoa.

Brucellosis, where the clinical and epidemiological aspects as above are also important (16,17) Rickettsiosis and Borrelioza, whose importance is mainly on the epidemiological aspect.

Neuro-tuberculosis where two phenomena come together; the same as Malaria.

HIV/AIDS Infection, which continues to be very problematic both in clinical and epidemiological terms.

AUFI (Acute undifferentiated Febrile Illness) also resulted very interesting in the optics we are discussing. We found 7 etiologic sounds associated with infectious diseases of different species (bacteria 2 and virus 5).

Even in these cases, one or both of the above-mentioned clinical and epidemiological events could be identified.As a result, we can say that:

Hemorrhagic fever is of great clinical significance because complications and mortality are significant. The epidemiological significance is very high, and at the same time the possibility of human epidemic outbreaks a very problematic phenomenon (18,19).

Measles and Varicella are acute infectious febrile syndromes of special epidemiological importance, since their spread and infection pathway are a major cause of outbreaks or epidemics.

Leptospirosis is also a clinically important bacteriosis, manifested in very severe and lethal forms (20) and also epidemiologic as well since the leptospirosis outbreaks and epidemics result in large and public health risks.

Viral encephalitis is also a major two-folded problem: clinical because the syndromes with which it appears may be very severe and may be lethal and epidemiological as they may be associated with causes that have prominent proliferation or viral emergency agents,as in the case meningoencephalitis by WNV (21-23).

Pulmonary tuberculosis is well known for its clinical and epidemiological significance (24).

Viral febrile hepatitis is also important in the clinical aspect, because it can serve as shelter for fulminant forms, with mortality reaching over 90%. From the public health point of view, even a sporadic case

may be followed by epidemic outbreaks as it happened in 2007 in Tirana (25).

It is obvious that the Febrile Syndromes (both acute undifferentiated febrile illness and fever of unknown origin) have important attributes regarding both personal and public health.

Regardless the fact that Albania is one of the countries where disease control and vaccination are fairly regular, inconveniences may occur for different reasons.

All the arguments mentioned above must be taken into account for the acceleration of the diagnosis that would enable appropriate and timely epidemiological measures regarding the febrile infectious diseases, in order to protect the public health by not giving absolute credits to vaccination.

The data of our study clearly confirm that the febrile syndromes, beside the clinical-biophysical and imaging examinations, require another powerful diagnostic component: the epidemiological one, where the contributions of qualified epidemiological consultants are crucial.

Conflicts of interest: None declared.

References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine 1961;40:1-30.
2. Durack DT, Street AC. Fever of unknown origin – reexamined and redefined. Curr Clin Top Infect Dis 1991;11:35-51.
3. de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of Unknown Origin (FUO): I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine 1997;76:392-400.
4. de Kleijn EM, van Lier HJ, van der Meer JW. Fever of unknown origin (FUO): II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. Medicine 1997;76:401-14.
5. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, Mudde AH, Dofferhoff TS, Richter C, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine 2007;86:26-38.
6. Vanderschueren S, Knockaert D, Adriaenssens T, Demey W, Durnez A, Blockmans D, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. Arch Intern Med 2003;163:1033-41.
7. Saltoglu N, Tasova Y, Midikli D, Aksu HS, Sanli A, Dündar IH. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. J Infect 2004;48:81-5.
8. Ergonul O, Willke A, Azap A, Tekeli E. Revised definition of 'fever of unknown origin': limitations and opportunities. J Infect 2005;50:1-5.
9. Mackowiak P, Durack D. Fever of unknown origin. In: Mandell GL, Douglas RG, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and practice of infectious diseases. 5th ed.Philadelphia: Churchill Livingstone; 2000:623.
10. Cutler SJ, Fooks AR, van der Poel WH. Public health threat of new, reemerging, and neglected zoonoses in the industrialized world. Emerg Infect Dis2010;16:1-7.
11. Joshi R, Colford JM, Reingold A. Nonmalarial acute undifferentiated fever in a rural hospital in central India – Diagnostic uncertainity and overtreatment with anti malarial agents. Am J Trop Med Hyg 2008;78:393-9.
12. Thangarasu S, Natarajan P. A protocol for emergency department management of acute undifferentiated febrile illness in India. Int Journal of Emer Med 2011;4:57.
13. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors - an experience from a tertiary care hospital in South India. Trop Doct 2010;40:230-4.
14. Kashinkunti MD, Gundikeri SK, Dhananjaya M. Acute undifferentiated febrile illness- clinical spectrum and outcome from a tertiary care teaching hospital of north Karnataka. Int J Biol Med Res 2013;4:3399-402.
15. Campos R, Santos M, Tunon G, Cunha L, Magalhães L, Moraes J, et al. Epidemiological aspects and spatial distribution of human and canine visceral leishmaniasis in an endemic area in northeastern Brazil. Geospat Health 2017;12.
16. Rubach MP, Halliday JE, Cleaveland S, Crump JA. Brucellosis in low-income and middle-income countries. Curr Opin Infect Dis 2013;26:404.
17. Bouley AJ, Biggs HM, Stoddard RA, Morrissey AB, Bartlett JA, Afwamba IA, et al. Brucellosis among hospitalized febrile patients in northern Tanzania. Am J Trop Med Hyg 2012;87:1105-11.
18. Puca E, Pilaca A, Pipero P, Kraja D, Puca EY. Hemorrhagic fever with renal syndrome associated with acute pancreatitis. Virol Sin 2012;27:214-7.

19. Hjelle B, Jenison SA, Goade DE, Green WB, Feddersen RM, Scott AA, et al. Hantaviruses: clinical, microbiologic, and epidemiologic aspects. Crit Rev Clin Lab Sci 1995;32:469-508.

20. Anderson DC, Folland DS, Fox MD, Patton CM, Kaufmann AF. Leptospirosis: a common-source outbreak due to leptospires of the grippotyphosa serogroup. Am J Epidemiol 1978;107:538-44.

21. Goulenok T, Buzelé R, Duval X, Bruneel F, Stahl JP, Fantin B. Management of adult infectious encephalitis in metropolitan France. Med Mal Infect 2017;47;206-20.

22. Boucher A, Herrmann JL, Morand P, Buzelé R, Crabol Y, Stahl JP, et al. Epidemiology of infectious encephalitis causes in 2016. Med Mal Infect 2017;47:221-35.

23. Fillatre P, Crabol Y, Morand P, Piroth L, Honnorat J, Stahl JP, et al. Infectious encephalitis: Management without etiological diagnosis 48 hours after onset. Med Mal Infect 2017;47:236-51.

24. Krupa R, Zielonka TM, Hadzik-Blaszczyk M, Wardyn KA, Zycinska K. Lung Lesions During Fever of Unknown Origin. Adv Exp Med Biol 2017. doi: 10.1007/ 5584_2017_37.

25. Silva-Díaz H, Chávez-Orosco TD, Mera-Villasis KM, Aguilar-Gamboa FR, Valderrama-Ayén MY.Acute Hepatitis A in patients with febrile illness in a hospital in the northern region of Peru. Rev Peru Med Exp Salud Publica 2016;33:177-8.