



# Enfermedades Infecciosas y Microbiología Clínica

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## The changing etiology of fever of intermediate duration

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### ABSTRACT

**Background:** Fever of intermediate duration (FID) is a common condition. Currently, its most frequent causes are not well defined.

**Methods:** Prospective study of FID cases attended at a hospital in 2 periods: 1983–1989 and 2004–2005. Blood cultures and serologic studies for *Brucella melitensis*, *Coxiella burnetii*, *Rickettsia typhi*, *Rickettsia conorii*, cytomegalovirus, and Epstein-Barr virus were performed on all patients. Other microbiological, serological, radiological, or invasive procedures were performed according to clinician-in-charge criteria.

**Results:** A total of 505 patients were included from 1983 to 1989, and 179 from 2004 to 2005. A diagnosis was reached in 410 (81.1%) and 109 patients (60.9%), respectively. The cause of FID was an infectious disease in 389 patients from the first period (94.8% of those with a final diagnosis) and 92 from the second (84.4%). Most were systemic infections, 328 (80%) in 1983–1989 and 74 (67.8%) in 2004–2005, followed by focal infections, 9.5% and 16.5%, respectively. Q fever was the most frequent etiology in both periods. In 2004–2005, brucellosis decreased and HIV infection emerged as a cause of FID. The origin of FID was non-infectious in 5.1% and 15.5%, respectively.

**Conclusions:** Q fever is the most frequent cause of FID in southern Spain. Studies over time are needed to identify changes in the etiologic spectrum of this condition. Important viral etiologies, such as HIV infection, may be detected as causes of FID. Further studies are needed to determine the importance of other agents as causes of FID.

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## Cambios en el espectro etiológico de la fiebre de duración intermedia

### RESUMEN

#### Palabras clave:

Fiebre de duración intermedia

Fiebre Q

Brucelosis

Infección VIH

Epidemiología

**Introducción:** La fiebre de duración intermedia (FDI) es una causa importante de fiebre. Las etiologías más importantes no están bien definidas en la actualidad.

**Métodos:** Estudio prospectivo de los casos de FDI atendidos entre 1983–1989 y 2004–2005. Se realizaron cultivos y estudios serológicos para la detección de *Brucella melitensis*, *Coxiella burnetii*, *Rickettsia typhi*, *Rickettsia conorii*, citomegalovirus y virus de Epstein-Barr en todos los pacientes. Se llevaron a cabo otros estudios microbiológicos, serológicos, radiológicos y pruebas invasivas adicionales según el criterio del clínico responsable.

**Resultados:** En el periodo de 1983 a 1989 se incluyeron 505 pacientes y 179 desde 2004 a 2005. Se alcanzó un diagnóstico etiológico en 410 (81,1%) y 109 (60,9%), respectivamente. La causa de FDI fue infecciosa en 389 pacientes del primer periodo (94,8% del total de pacientes con diagnóstico etiológico) y 92 del segundo (84,4%). La mayoría fueron infecciones sistémicas, 328 (80%) en 1983–1989 y 74 (67,8%) en 2004–2005, seguidas de infecciones focales, 9,5% y 16,5%, respectivamente. La fiebre Q fue la etiología más frecuente en ambos periodos. En 2004–2005, la brucelosis disminuyó mientras que la infección por el VIH se mostró como una causa emergente de FDI. El origen de la FDI fue no infeccioso en el 5,1% y el 15,5% de los casos, respectivamente.

**Conclusiones:** La fiebre Q es la causa más frecuente de FDI en el sur de España. Son necesarios estudios prospectivos más amplios para identificar los cambios en el espectro etiológico de esta entidad. Infecciones virales, como la infección por el VIH, deben ser contempladas como causa de FDI.

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## Introduction

Community-acquired fever without a focal condition is frequent in clinical practice. Medical management of this syndrome is based mainly on fever duration. Along this line, there are 3 chronologically distinct types of fever: first, fever of short duration, lasting up to 7 days, is usually due to self-limiting systemic viral infections; the diagnostic and therapeutic approach to this entity is well defined;<sup>1</sup> second, classic fever of unknown origin (FUO), for which the concept, epidemiology, most frequent etiologies, and diagnostic and therapeutic approaches have been extensively evaluated by many authors in several geographic, historic, and population contexts;<sup>2–4</sup> and third, fever higher than 38 °C lasting 7 to 28 days that remains undiagnosed or has associated findings that prompt a diagnostic procedure after performing the patient's history, physical examination, hemogram, serum creatinine determination, urine analysis, and chest radiograph, defined as fever of intermediate duration (FID). This condition has recently been considered a separate syndrome, and constitutes an entity with well-defined etiological features.<sup>5</sup> After various prospective clinical and epidemiological analyses were carried out in southern Spain, an overall diagnostic strategy and empirical treatment for FID was proposed.<sup>6,7</sup>

Nonetheless, over the past few years, certain changes in the incidence of community-acquired infections that were frequent causes of FID have occurred in Spain. One significant example is that the incidence of brucellosis has decreased from 22 cases/100,000 inhabitants in 1984 to 1.7 cases/100,000 inhabitants in 2006.<sup>8,9</sup> Furthermore, new pathogens/diseases may have emerged in the past years and established efficient life cycles in human populations. Lastly, we know that ecological, socioeconomic and health conditions change over time, and these variations can result in potential changes in the emergence-reemergence of endemic infections, and therefore, in the etiological spectrum of FID. Despite these facts, current studies that focus specifically on possible changes in the etiological patterns of FID over time are lacking.

The aim of the present study was to evaluate the etiologies of FID in southern Spain in a prospective study carried out between 2004 and 2005 and compare them with those found in a methodologically similar study performed between 1983 and 1989 in the same geographic area. The study was designed to assess possible changes that would prompt us to redefine the best diagnostic approach and empirical treatment of this common condition.

## Methods

**Setting:** Two prospective studies were carried out in 1983–1989 and 2004–2005 to determine the etiology of FID in patients attended in the Infectious Diseases Department of Virgen del Rocío University Hospital in Seville, southern Spain. Virgen del Rocío is a tertiary hospital that attended a population of 881,454 and 973,200 inhabitants, respectively, in each period, mostly from urban areas (60% and 65%, respectively).

**Inclusion Criteria:** All patients older than 14 years with the following FID criteria were included: 1) fever higher than 38 °C, with no apparent cause and lasting between 1 and 4 weeks; 2) no previous hospital admission or health care-related attention<sup>10</sup> and no underlying immunodeficiency or chronic disease that could cause fever; and 3) no diagnosis following an initial approach, including clinical evaluation, hemogram, urinary sedimentation study, serum creatinine determination and chest radiography. All patients with known HIV infection, intravenous drug users (IDUs), immigrants that had resided for less than one continuous year in Spain, and persons who had traveled internationally in the previous 6 months were excluded.

**Study protocol and variables:** A basic evaluation was performed on all patients. The following data were recorded: demographic and epidemiological data, date on the onset of fever, patient from rural or urban areas, medical history, and results of a thorough physical examination. In addition to the analyses included in the definition, the erythrocyte sedimentation rate (ESR), and alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and bilirubin levels were determined.

Urine cultures were performed and blood cultures (2 samples separated by 30 min, aerobic and anaerobic vials, BACTEC) if the patient had fever higher than 38 °C initially. The following serologic studies were performed (acute and convalescent phases): 1) *Brucella melitensis*: Rose of Bengal (bioMérieux, Lyon, France) and immunofluorescence assay (IFA) (Vitaltech, Sant Cugat, Barcelona, Spain) for quantified IgG and IgM (Bio-Rad, Paris, France), previous inactivation of IgG and rheumatoid factor with Gull-sorb (Meridian, Cincinnati, Ohio, USA); 2) *Coxiella burnetii*, IFA (Virion, Richland, USA in 1983–1989 and Vitaltech in 2004–2005); 3) *Rickettsia typhi* and *Rickettsia Conorii*, IgG IFA (Pasteur Laboratories, Marnes, la Coquette, France until 1986 and bioMérieux from 1987); 4) cytomegalovirus (CMV), complement fixation (Virion in 1983–1989) and enzyme-linked immunosorbent assay (ELISA IgG and IgM, Dade Behring, Barcelona, Spain in 2004–2005), the positive IgM being confirmed by IFA (Meridian); and 5) Epstein-Barr virus, IFA (Meridian in 1983–1989) and chemiluminescence (IgG and IgM, DiaSorin, Vercelli, Italy in 2004–2005) confirmed by IFA (Meridian, IgG e IgM). In the first period of the study (1983–1989) serology for *Leptospira* spp. by IFA (Difco Laboratories, Sparks, USA) was carried out in all cases.

Other laboratory studies were also performed, depending on the clinical features of the patient: 1) auramine-rhodamine staining of sputum and urine cultures for mycobacteria; 2) thyroid-stimulating hormone and free thyroxine; 3) serology for parvovirus B19 in the second period (IFA IgM, Biotrin, Lyon, France); 4) *Toxoplasma gondii* IFA (BioMérieux) and IgG and IgM by ELISA (Dade Behring) in the 2 periods, respectively; 5) HIV by ELISA (Dade Behring) and Western blot (New lav Blot 1, Bio-Rad); and 6) syphilis by quantitative RPR (Biosystems, Foster City, USA) and FTA ABs-IgG and IgM (Bio Mérieux).

All patients were followed-up for at least 1 month after the first visit and until cure, progression to FUO, or death. At the end of follow-up, the definitive diagnosis and hospital admission information were collected.

**Statistical analysis:** A descriptive analysis was carried out using the Epi-Info and SPSS 13.0 statistical packages.

## Results

A total of 505 patients were included in the first period (1983–1989) and 179 in the second (2004–05), with a median age of  $32.6 \pm 17.4$  and  $39.7 \pm 15.8$  years, respectively. In both periods, there was a predominance of males: 404 (80%) in the first and 117 (65.4%) in the second.

The monthly distribution showed a higher incidence of cases between March and November (479 [94.8%] in the first period and 138 [77.1%] in the second) (Fig. 1). In the first period, 42.9% of patients lived in urban areas, and in the second, 57%.

An etiologic diagnosis was attained in 410 patients (81.1%) in the first study and 109 patients (60.9%) in the second study, whereas in 95 (18.8%) and 70 (39.1%) cases, respectively, fever resolved without determining the cause, despite completion of the diagnostic workup (Table 1). The cause of fever was an infectious disease in 389 patients from the first period (77% of the total and 94.8% of those with a final diagnosis) and 92 patients from the second (51.3% and 84.4%, respectively). Most were

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