Experiences in rapid diagnosis of Brucella bacteremia using the Bact/Alert 120 system

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Brucella species are slow growing, small gram-negative non-motile coccobacilli.[1] The organism is strictly aerobic, nonencapsulated, and catalase and oxidase positive; it does not ferment carbohydrates and has variable urease activity.[1-4] Brucellosis is usually transmitted to humans by direct contact with infected animals or by ingestion of unpasteurized diary products. In addition, occupational exposure of abattoir workers, veterinarians, and laboratory technicians may result in transmission of the disease through contaminated aerosols.[4] All the 6 members of the genus are, in fact, serovars of a single species of which 4, namely, *Brucella abortus, B. suis, B. canis*, and especially *B. melitensis* are able to cause human infections.[4]

Brucellosis some how is common in our area. In our laboratory, blood cultures from suspected cases performed with the Bact/Alert 120 system (Organon Teknica) yield a positive signal, generally within 3-5 days. A 5-10 ml blood sample was used for blood cultures media inculcation. Aerobic blood cultures media was used. Gram stain of the blood culture medium reveals either gram-negative coccobacilli or no definite organisms. These positive broths were then subcultured into Trypticase soy agar medium with 5% sheep blood, a chocolate agar plate, a MacConkey agar plate, and urea slant. Inoculated isolator tubes were processed in a type III biological safety cabinet following the manufacturer's recommendations. Presumptive identification of Brucella species was performed on the basis of a typical microscopic picture showing small gram-negative coccobacilli; positive oxidase, catalase and urease tests; and negative sugar fermentation. API 20NE bacterial identification system (bioMerieux) tests were carried out to rule out any possibility of misidentifying this bacterium as *Moraxella phenylpyruvica*.[3] Confirmation was carried out by agglutination test with specific antiserum.[5] Over the last 2 years, our laboratory received 55 blood cultures from suspected cases of brucellosis. Six blood cultures were positive for brucellosis by the previously described method. Comparative data were obtained from our serology department by carrying out the serial dilution antibody test on those 55 blood cultures. Confirmatory results were obtained.

In summary, our experiences in the microbiological diagnosis of brucellosis that, it can be carried out in 2-5 days using the Bact/Alert system, which indicates a more rapid detection of Brucella than has been shown in previous reports. In an area of endemic of brucellosis, a positive and early direct urease test for signal positive blood culture broths containing gram-negative coccobacilli or no visible organisms may provide a presumptive diagnosis of brucellosis.

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Fever of unknown origin. *Experience of a large tertiary care hospital in Saudi Arabia*

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Fever of unknown origin (FUO) is a common problem in medical practice and encompasses a broad spectrum of diagnostic possibilities. In 1961, Petersdorf and Beeson[1] published their classic article on FUO and established the criteria that have effectively delineated this entity: 1. an illness of at least 3 weeks duration; 2. measured temperature greater than 38.3°C on several occasions, and 3. no established diagnosis after one week of hospital investigation. The definition and appropriate

evaluation continues to provoke controversy. In recent years, there have been several suggestions to modify and introduce new categories and causes of FUO, furthermore, the definition has been altered to 3 outpatient visits without a diagnosis being reached or 3 days of hospital investigation.[2,3]

The spectrum of diseases causing FUO appears to change with time and seems to be determined by geographic and economic factors. Many studies of patient with FUO have been performed around the world using classic definition of Petersdorf and Beeson[1] while others used different criteria.[2,4,5]

King Fahad National Guard Hospital is a 700 beds tertiary care hospital located in the Central region of the Kingdom of Saudi Arabia (KSA), it provides multilevel health care for National Guard soldiers and their extended families. The purpose of this study was to review all cases with FUO admitted to our hospital over the study period to define the categories of the disease in our patients and to determine the clinical presentation, methods of diagnosis, and disease outcome.

In this study, we included all adult patients admitted with the diagnosis of FUO, and as there was no International Classification of Diseases code for FUO, we reviewed the charts of all patients presented to King Fahad National Guard hospital over the period between January 1991 and September 2002 with admitting and discharge diagnosis of fever. The classic definition of FUO by Petersdorf and Beeson[1] was used as the only eligible criteria and we excluded children younger than 12 years, nosocomial infection, and immunocompromised patients. The causes of FUO were classified into 5 groups: 1. Infection 2. collagen-vascular disease 3. neoplasm 4. miscellaneous and 5. no diagnosis. The following data were extracted from the files; demographic data, method of investigation, the final diagnosis and follow up. Out of 320,618 admissions over the study period, we identified 300 patients with either admission or discharge diagnosis of fever; only 20 (6.6%) patients met our eligibility criteria. There were 11 (55%) men and 9 (45%) women, with mean age of 41 years (range from 16-85 years). The mean duration of hospitalization was 22.4 days (range from 9-60 days). Invasive procedures helped to establish the diagnosis in 5 patients (25%). Etiology of FUO was established in 17 (85%) of the cases, whereas the diagnosis could not be established in 3 patients (15%) 2 of them recovered spontaneously during follow-up and one died with no established diagnosis. Infections were found in 7/20 (35%) patients, miscellaneous disease 5/20 (25%), neoplasms in 3/20 (15%) and collagen vascular disease in 2/20 (10%). Of all infectious causes, tuberculosis was the most common cause 3/7 (42%). **Table 1** summarizes the underlying etiology of FUO and method of diagnosis. The duration of follow-up was longer than 2 years in one (5 %) patient, longer than 1 year in 5 (20%) and longer than 6 months in 10 (50%) patients. Four (20%) patients died during the hospitalization period, the cause of death was not established in 3 cases (15%) and was considered as related to the underlying disease, while the fourth case was related to anaplastic B-cell lymphoma. The initial approach to patients presenting with fever is

Table 1 - Etiology of fever of unknown origin and methods of diagnosis.

Etiology	N	(%)	Method of diagnosis
Infection	**7**	**(35)**	
Tuberculosis	3		Empirical therapy
Infective endocarditis	1		Blood culture
Viral	2		Observation
Human immunodeficiency virus	1		Serology
Neoplasm	**3**	**(15)**	
Intestinal shwanoma	1		Laparotomy and surgical pathology
Anaplastic B-cell lymphoma	1		Mediastinoscopy and lymph node biopsy
Hemophagocytic syndrome	1		Bone marrow biopsy and aspiration
Collagen-vascular disease	**2**	**(10)**	
Systemic Lupus Erythematosus	1		Pleural tap and subsequent serological test
Still's disease	1		Clinical diagnosis and empirical therapy
Miscellaneous	**5**	**(25)**	
Drugs	3		Withdrawal of offending agent
Kikushi	1		Lymph node biopsy
Spleen infarction	1		Ultra sound and computed tomography scan of abdomen
No diagnosis	**3**	**(15)**	
Total	**20**		

not uniform but included a comprehensive history, physical examination and appropriate laboratory testing such as complete cell count, differential, sedimentation rate, electrolytes, liver and kidney profile, blood culture and chest-x-ray.[4] As the underlying process develops, new diagnostic clues may become apparent, therefore, the history and physical examination should be repeated and new investigations should be ordered. Equally important is to know the common causes of FUO and their related frequencies in the population served.[5] The most common causes of FUO are infections (13-60%), collagen vascular diseases (10-30%); neoplasm (7-31%), miscellaneous (5-22%) and no definitive diagnosis (9-25%).[1-4] In our study, the causes of FUO were infections (35%), miscellaneous (25%), neoplasms (15%), collagen vascular diseases (10%), and no definitive diagnosis in (15%). Similar to many studies[1-5] infections was the most common cause of FUO in our study and tuberculosis was the most common of all infectious causes (3 of 7 cases [42%]). Investigations failed to confirm the diagnosis of tuberculosis but all responded to empirical anti-tuberculous treatment. The utilities of empiric therapy such as anti-tuberculous medications have not been studied in the management of patients with FUO. However, this was not an uncommon practice. Some authorities recommend careful observation if patient is clinically stable and if an extensive work-up performed has failed to establish a cause. However, empirical therapy is a reasonable option in countries where tuberculosis is prevalent, or in seriously sick patients with no established cause or if the patient is at high risk of invasive procedures.[6] In the 3 cases with tuberculosis in our study, all work-up including, radiological imaging, and invasive procedures were negative. Due to the rapid response to anti-tuberculous therapy, we believe they have disseminated tuberculosis as a cause of FUO. Brucella has been reported as one of the causes of FUO in developing countries particularly when the presentation is atypical.[3] Due to the high prevalence of brucellosis in our population, it was our practice that all patients who are admitted to our hospital with febrile illness are screened for brucellosis. This explains why, in our study, no single case of brucellosis has been diagnosed as a cause of FUO. Miscellaneous causes were the second most important cause of FUO (25%) in our study, contrary to other studies where either collagen vascular disease or neoplasms were the second common cause of FUO. The small number of subjects in our study could explain this or more likely is due to the advanced, sophisticated serological diagnosis of collagen-vascular disease and the availability of advance imaging techniques, which make the diagnosis of collagen-vascular disease and neoplasm more feasible.[4] In our study drug-fever was the most important cause in the miscellaneous group, followed by Kikushi disease and spleen infarction. The diagnosis of drug fever was made by a therapeutic trial of stopping the suspected drug. Most patients will defervesce within 72 hours of substituting the culprit drug, although some may not recover for weeks to months. The etiology of fever could not be established in 3/20 (15%) in our study, this was not different when compared with earlier studies where the numbers of undiagnosed cases have increased ranging from 9-30%.[1,3-5] Two cases were diagnosed as a viral infection based on compatible clinical presentation and the attending physician's impression. Both cases, however, recovered spontaneously. The prognosis in FUO depends on the underlying disease. It is usually worse for neoplastic disease and better in most cases with no established diagnosis. As a result, this study differs from others that was carried out in developed countries but quite similar to other that was carried out in developing countries where infection, particularly tuberculosis as the most common causes.[3,6,7] Miscellaneous causes were the second most important cause of FUO in our study. Furthermore, establishing the etiology of FUO in the Saudi population may provide a guide to future multicenter prospective studies.

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