


TABLE 26-1 ETIOLOGY OF FEVER OF UNKNOWN ORIGIN (FUO) OVER THE PAST 20 YEARS: FINDINGS FROM LARGE FUO STUDIES

First Author (Country, Year of Publication)	No. of Patients (Recruitment Period)	Percentage of Cases Due to Indicated Cause				
		Infections	Noninfectious Inflammatory Diseases	Neoplasms	Miscellaneous	Unknown
Western Countries						
De Kleijn et al. (Netherlands, 1997)	167 (1992–1994)	26	24	13	8	30
Vanderschueren et al. (Belgium, 2003)	185 (1990–1999)	11	18	10	8	53
Zenone et al. (France, 2006)	144 (1999–2005)	23	26	10	15	26
Bleeker-Rovers (Netherlands, 2007)	73 (2003–2005)	16	22	7	4	51
Mansueto et al. (Italy, 2008)	91 (1991–2002)	32	12	14	10	32
Efstathiou et al. (Greece, 2010)	112 (2001–2007)	30	33	11	5	21
Total	772	22	23	11	9	36
Other Geographic Locations						
Tabak et al. (Turkey, 2003)	117 (1984–2001)	34	29	19	4	14
Saltoglu et al. (Turkey, 2004)	87 (1994–2002)	59	18	14	2	7
Ergonul et al. (Turkey, 2005)	80 (1993–1999)	52	16	18	3	11
Chin et al. (Taiwan, 2006)	94 (2001–2002)	57	7	9	9	18
Colpan et al. (Turkey, 2007)	71 (2001–2004)	45	27	14	6	9
Hu et al. (China, 2008)	142 (2002–2003)	36	32	13	5	14
Kucukardali et al. (Turkey, 2008)	154 (2003–2004)	34	31	14	5	16
Ali-Eldin et al. (Egypt, 2011)	93 (2009–2010)	42	15	30	0	12
Total	838	43	23	16	4	13

use of antibiotics, and the availability of new diagnostic techniques. The proportion of cases caused by intraabdominal abscesses and tumors, for example, has decreased because of earlier detection by CT and ultrasound. In addition, infective endocarditis is a less frequent cause because blood culture and echocardiographic techniques have improved. Conversely, some diagnoses, such as acute HIV infection, were unknown four decades ago.

 **Table 26-1** summarizes the findings of several large studies on FUO conducted over the past 20 years. In general, infection accounts for about 20–25% of cases of FUO in Western countries; next in frequency are neoplasms and noninfectious inflammatory diseases (NIIDs), the latter including “collagen or rheumatic diseases,” vasculitis syndromes, and granulomatous disorders. In geographic areas outside the West, infections are a much more common cause of FUO (43% vs 22%), while the proportions of cases due to NIIDs and neoplasms are similar. Up to 50% of cases caused by infections in patients with FUO outside Western nations are due to tuberculosis, which is a less common cause in the United States and Western Europe. The number of FUO patients diagnosed with NIIDs probably will not decrease in the near future, as fever may precede more typical manifestations or serologic evidence by months in these diseases. Moreover, many NIIDs can be diagnosed only after prolonged observation and exclusion of other diseases.

In the West, the percentage of undiagnosed cases of FUO has increased in more recent studies. An important factor contributing to

the seemingly high diagnostic failure rate is that a diagnosis is more often being established before 3 weeks have elapsed, given that patients with fever tend to seek medical advice earlier and better diagnostic techniques, such as CT and MRI, are widely available; therefore, only the cases that are more difficult to diagnose continue to meet the criteria for FUO. Furthermore, most patients who have FUO without a diagnosis currently do well, and thus a less aggressive diagnostic approach may be used in clinically stable patients once diseases with immediate therapeutic or prognostic consequences have been ruled out to a reasonable extent. This factor may be especially relevant to patients with recurrent fever who are asymptomatic in between febrile episodes. In patients with recurrent fever (defined as repeated episodes of fever interspersed with fever-free intervals of at least 2 weeks and apparent remission of the underlying disease), the chance of attaining an etiologic diagnosis is <50%.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for FUO is extensive, but it is important to remember that FUO is far more often caused by an atypical presentation of a rather common disease than by a very rare disease. **Table 26-2** presents an overview of possible causes of FUO. An atypical presentation of endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis are the more common infectious disease diagnoses. Q fever and Whipple’s disease are quite rare but should always be kept in mind as a cause of FUO since the presenting symptoms