MINI REVIEW

Epidemiology of liver failure

Philippe Ichai\textsuperscript{a,b,c}, Didier Samuel\textsuperscript{a,*\textsuperscript{,b,c}}

\textsuperscript{a} Centre hépato-biliaire, hôpital Paul-Brousse, AP—HP, 94800 Villejuif, France
\textsuperscript{b} University Paris-Sud, UMR-S 785, 94800 Villejuif, France
\textsuperscript{c} Inserm, unité 785, 94800 Villejuif, France

Available online 6 May 2011

Summary  The etiology of fulminant hepatitis varies in different countries and at different times. The main causes of fulminant hepatitis are viruses, paracetamol, drugs (other than paracetamol), poisons and 15–30\% remained of undetermined origin. The prevalence of these etiologies varies according to the geographic region and has changed over the past 10 years. Paracetamol has now overtaken viruses (particularly hepatitis B virus) as the leading cause of fulminant hepatitis. Establishing the cause of fulminant hepatitis is an important step in the management of acute liver failure, so that specific therapy can be initiated and any contraindications to liver transplantation be eliminated.

© 2011 Elsevier Masson SAS. All rights reserved.

Fulminant hepatic failure is characterized by a deterioration in liver function and hepatic encephalopathy. Three main definitions have been proposed for fulminant hepatitis (FH) including acute hepatitis complicated by acute liver failure (ALF) with hepatic encephalopathy occurring less than 8 weeks after the onset of jaundice. The definition of FH is important because of its implications to the prognosis. Likewise, there are many causes of ALF and various definitions have been proposed [1—3]. The common points of these definitions are the occurrence of encephalopathy during the course of FH in a patient without previously known hepatopathy and the spontaneous poor prognosis with a mortality rate of 85%.

The main causes of FH are viral infection, drugs, or indeterminate. Early elucidation of the cause of ALF is one reason to refer patients to a specialist center as quickly as possible so that its consequences can be established promptly and appropriate treatment initiated. Another important reason to refer patients is so that they can be considered for emergency liver transplantation. It is only in this setting that the different available prognostic scores can be applied.

Etiology of fulminant hepatitis

There are many causes of FH, which vary with geographic region. The most frequent causes worldwide include viral hepatitis (particularly hepatitis A (HAV) and B (HBV)), medication overdose (in particular paracetamol), idiosyncratic drug reactions, ingestion of toxins and metabolic disorders. In addition to these known etiologies, indeter-
miniate causes of FH account for a large proportion of cases of ALF, despite systematic screening to detect rare viruses, rare causes of drug- or toxin-induced liver failure or other less common causes such as Wilson’s disease, ischemic hepatitis, Budd-Chiari syndrome, Reye’s syndrome and malignancy.

Establishing the cause of FH is important for three main reasons:

- so that specific treatment can be initiated quickly;
- to eliminate contraindications to liver transplantation;
- and to determine the prognosis.

For all of these reasons, early referral to a specialist center is important and all patients should be screened routinely on admission for the usual causes of ALF: viral (anti-HAV IgM, hepatitis B surface antigen (HBsAg), anti-HBc IgM, anti-VCA (EBV) IgM, anti-CMV IgM, anti-HSV1 and two IgM, and anti-HCV antibodies), autoimmune (autoantibody titers, gamma globulin levels), metabolic (serum caeruloplasmin level, 24-h urinary copper, cupropria)

In a survey in the USA carried out between 1998 and 2008, the major etiologies of ALF in 1147 patients were paracetamol overdose (46%), followed by indeterminate cause (14%), drug-related ALF (11%), HBV (7%), other (7%), autoimmune hepatitis (AIH) (5%), ischemic hepatitis (4%), HAV (3%), and Wilson’s disease (2%). In UK, the first cause of FH is paracetamol (60.9%). In our French series, the main causes of ALF, between 1986 and 2006, in 500 patients with deterioration of liver function defined by a prothrombin index less than 50%, with or without encephalopathy, were viral infection in 31%, paracetamol overdose in 20%, drug other than paracetamol or toxins in 18%, unknown origin in 17% and miscellaneous etiologies in 14% [4] (Fig. 1, Table 1). In a study by Bernal et al., including 310 patients from 1994 to 2004, 132 patients (43%) had ALF resulting from paracetamol and 178 (56.5%) from non-paracetamol causes. The non-paracetamol causes were non-paracetamol drug induced (8%), viral (7%), autoimmune (2.5%), pregnancy related (2.5%), Wilson’s disease (1.5%), Budd-Chiari syndrome (5%) and others (1%). Indeterminate causes accounted for 30% [5]. From the European Liver Transplantation Registry, we can determine the causes of FH in patients undergoing liver transplantation. So, the most common causes of transplanted FH between 1972 and 2007 were viral (HAV: 1%; HBV: 15%), paracetamol overdose (8%), drug other than paracetamol (11%), indeterminate causes (48%), and other causes (17%) [6]. However, these etiologies have changed over the past 10 years (Table 2).

HBV infection is a main cause of fulminant hepatitis. HBV-induced ALF may be due to acute hepatitis but also to HBV reactivation in chronic HBV carriers. HBV reactivation can be spontaneous or secondary to chemotherapy or due to escape mutant HBV in patients on nucleotide(s) analogs. HBV ALF is serious and results in death or transplantation in 80% of individuals. HBV ALF is probably secondary to an immune-mediated reaction against HBV. Lamivudine antiviral treatment in patients with acute HBV infection significantly decreases HBV DNA levels but does not result in significantly greater clinical and biochemical improvement compared to placebo [7]. Usually, HBV reactivation evolves to subfulminant hepatitis with a poor prognosis. With antiviral therapy, the incidence and overall morbidity of HBV reactivation decreases significantly. HBV represented around 50% of the causes of ALF until the early 1990s. Since then, there has been a decline in HBV FH in Europe. France has also seen a sharp decline in the number of cases of HBV-induced ALF in the past 10 years [4,8]. Anti-HBV vaccination has probably contributed to this decrease.

HAV is the second most common viral cause of ALF after HBV. However, the incidence of patients undergoing liver transplantation for HAV-related ALF in the UNOS database decreased significantly between 1988 and 2005 in the USA (from 0.7% in 1988—1989 to 0.3% in 1996—1997 and 0.1% in 2004—2005; p < 0.001). The Centers for Disease Control and Prevention (CDC) also reported a similar decrease in incidence of HAV cases between 1993 (24 238 cases) and 2003 (7 653 cases) [9]. However, the incidence of HAV is probably underreported. Furthermore, during 1995 and 2006, the incidence of HAV decreased by 90% to the lowest rate ever recorded (1.2 cases per 100 000 population). The decline was greatest among children and in states where routine vaccination of children was recommended in 1999, while an increasing proportion of cases occurred in adults. One explanation for this decrease in incidence of ALF and fulminant HAV in the USA is the implementation of routine childhood hepatitis A vaccination [10].

HAV-related liver failure is probably due to an excessive host response associated with a marked reduction in viral load. The severity of HAV infection is multifactorial. In a series of 79 patients with acute hepatitis A, age, gender and drug toxicity (paracetamol) were identified as potential contributing factors by Rezende et al. in univariate analysis, whereas in multivariate analysis, the independent variables associated with encephalopathy were a low or undetectable HAV load and a high bilirubin level at admission [11].

Paracetamol overdose is the main cause of ALF in both the UK (60.9%) and USA (46%) [12,13]. Recently, paracetamol overdose has also become a common cause of ALF in countries of Europe [8,12,14,15]. Intentional overdose-related ALF is more frequent in the UK than in North America. In the UK, ALF or fulminant hepatic failure is more often due to an intentional paracetamol overdose whereas in the USA paracetamol hepatotoxicity is usually secondary to an accidental overdose (ingestion of multiple doses of paracetamol for pain relief without suicidal intent). A comparison of 122 subjects with intentional overdose and 131 subjects with unintentional overdose shows many differences [16]. Overall, unintentional overdose subjects were significantly older (median, 38 years) than those who attempted suicide (median, 32 years) (p = 0.002), and used multiple paracetamol-containing preparations more frequently (38% vs. 5%, p < 0.0001). Accidental overdose patients were less likely to report depression (24% vs. 45%, p < 0.0001), have severe (grade 3 and 4) hepatic encephalopathy on admission compared to intentional overdose subjects (55% vs. 39% respectively, p = 0.002). In these two groups of patients, the number listed for transplantation and time to transplantation did not differ. Paracetamol dose was significantly lower in accidental overdose victims (median, 12 g) than in those with a suicidal intent (median, 20 g) (p = 0.009). Chronic alcohol consumption, malnutrition probably played a role in the occurrence or worsening of liver injury. In addition, several studies strongly suggested that therapeutic doses
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Ref</th>
<th>Years</th>
<th>No. of patients</th>
<th>Main etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paracetamol Drug-induced, not paracetamol Viral (HAV, HBV, other) Indeterminate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams R</td>
<td>London</td>
<td>[12]</td>
<td>1973–1993</td>
<td>1257</td>
<td>765 (60.9%) 77 (6%) 329 (26.2%) 60 (5%), 94 (7%), 6 (0.5%) 201 (16%) 86 (6.8%)</td>
</tr>
<tr>
<td>Shakil AO</td>
<td>Pittsburgh</td>
<td>[51]</td>
<td>1983–1995</td>
<td>177</td>
<td>33 (19%) 21 (12%) 55 (31%) 13 (7%), 33 (19%), 9 (5%) 49 (28%) 19 (11%)</td>
</tr>
<tr>
<td>Brandsaeter B</td>
<td>Nordic countries</td>
<td>[21]</td>
<td>1990–2001</td>
<td>315</td>
<td>52 (17%) 31 (10%) 37 (12%) 7 (2%), 25 (8%), 5 (2%) 135 (43%) 53 (17%)</td>
</tr>
<tr>
<td>Ostapowicz G</td>
<td>USAa</td>
<td>[19]</td>
<td>1998–2001</td>
<td>308</td>
<td>120 (39%) 40 (13%) 36 14 (4%), 22 (7%) 17% 9%, NA, 8%</td>
</tr>
<tr>
<td>Farmer DG</td>
<td>UCLA</td>
<td>[52]</td>
<td>1984–2001</td>
<td>204</td>
<td>13% 11% 13% 9%, NA, 8%</td>
</tr>
<tr>
<td>Gow PJ</td>
<td>Australia</td>
<td>[20]</td>
<td>1988–2001</td>
<td>80</td>
<td>29 (36%) 5 (6%) 11 (14%) 119 (33%) 18 (5%), 100 (29%) 35 (44%)</td>
</tr>
<tr>
<td>Samuel D</td>
<td>France</td>
<td>[4]</td>
<td>1986–2006</td>
<td>363</td>
<td>26 (7%) 75 (21%) 119 (33%) 18 (5%), 100 (29%)</td>
</tr>
<tr>
<td>Escorsell A</td>
<td>Spain</td>
<td>[15]</td>
<td>1992–2000</td>
<td>267b</td>
<td>6 (2.2%) 36 (13.5%) 98 (37%) 5 (2%), 11 (4%) 86 (32%)</td>
</tr>
<tr>
<td>Areia M</td>
<td>Portugal</td>
<td>[14]</td>
<td>1992–2006</td>
<td>61</td>
<td>1 (2%) 13 (21%) 14 (23%) 13, 1 16 (26%) 17 (28%)</td>
</tr>
<tr>
<td>Miyake Y</td>
<td>Japan</td>
<td>[22]</td>
<td>1990–2001</td>
<td>80</td>
<td>0 15 (18.7%) 36 (45%) 5 (6.3%), 27 (33.7%), 2 (2.5%) 24 (30%) 8 (10%)</td>
</tr>
<tr>
<td>Mudawi HMY</td>
<td>Sudan</td>
<td>[53]</td>
<td>2003–2004</td>
<td>37</td>
<td>0 3 (8%) 10 (27%) 8 (22%), 2 (5%) 14 (38%) 10 (27%)</td>
</tr>
<tr>
<td>Bernal W</td>
<td>London</td>
<td>[5]</td>
<td>1994–2004</td>
<td>310</td>
<td>132 (42%) 26 (8%) 10 (27%) 8 (22%), 2 (5%) 21 (7%) 92 (30%)</td>
</tr>
</tbody>
</table>

* a 17 tertiary care centers.
* b 20/267 children.
* c B: 77, B-Delta: 16, HBV reactivation: 7.
* d hepatitis B and D.
* e HCV: 2.
* f HEV 2.
of paracetamol might be associated with an increased liver injury in patients with liver failure from other causes liver disease [11,17,18].

Drug-related ALF (not due to paracetamol) is a frequent cause of hepatitis. The incidence varies with geographic country. The incidence is of 2.5% in the UK [12], 13% in the USA [19], 6% in Australia [20], 19.5% in Spain [15], 21% in Portugal [14] 10% in Nordic countries [21], 22% in Japan [22] and 15% in France [8]. In Scottish series, non-paracetamol drugs were implicated in 4.8% (30/625 cases of ALF) of cases. The most common drugs related to ALF were antibiotics (23%) followed by ecstasy (3,4 methyldioxymethamphetamine, MDMA) (20%), antituberculous antibiotics (13%), non-steroidal anti-inflammatory drugs (7%), and aminosalicylates (7%) [23]. Ecstasy is a common cause of FH consumed mainly by young people and taken for its amphetamine-like stimulatory effect, increasing energy and reducing awareness of fatigue [24]. The clinical presentation is hypothermia, hypotension, fits, disseminated intravascular coagulation and rhabdomyolysis associated with severe hepatic damage. Young people with severe hepatitis of unknown origin should be investigated thoroughly.

Figure 1  Etiology and Prognosis of Fulminant Hepatitis in Adults According geographic region.

Table 2  Rare causes of fulminant hepatic failure.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>Calculated N</td>
<td>Total miscellaneous cause</td>
<td>ischemic hepatitis</td>
<td>autoimmune hepatitis</td>
<td>Wilson's disease</td>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>315</td>
<td>48 (15%)</td>
<td>1 (0.3%)</td>
<td>7 (2%)</td>
<td>5 (2%)</td>
<td>16 (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>308</td>
<td>59 (19%)</td>
<td>17 (6%)</td>
<td>13 (3%)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>8 (10%)</td>
<td>—</td>
<td>6 (7%)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>363</td>
<td>77 (22%)</td>
<td>21 (6%)</td>
<td>16 (4.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61</td>
<td>14 (23%)</td>
<td>—</td>
<td>2 (3%)</td>
<td>4 (6.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>267</td>
<td>31 (11.6%)</td>
<td>—</td>
<td>6 (2.2%)</td>
<td>13 (4.9%)</td>
</tr>
</tbody>
</table>
due to the relatively high number of causes of ALF or FH in these individuals. In a large US retrospective cohort study performed from 1987 to 2006, 661 patients were transplanted for drug-induced acute liver failure. The 4 leading implicated drug groups were acetaminophen (n = 265; 40%), antituberculosis drugs (n = 50; 8%), antiepileptics (n = 46; 7%), and antibiotics (n = 39; 6%). The survival probabilities after liver transplantation were significantly lower in patients with antiepileptics induced acute liver failure compared to the others drugs [25]. More recently, in a multicenter, prospective study, drug-induced acute liver failure accounted for 11.1% (133 patients) among 1198 subjects enrolled at 23 sites in United States. 81.1% were considered highly likely by expert opinion, 15.0% probable and 3.8% possible. Over 60 individual agents were implicated and the most common were antimicrobials (46%). Transplant-free (3 weeks) survival was poor (27.1%), but transplantation was successful in 42.1% [26]. Among the patients with drug-induced liver injury, the risk of progressing to death or transplantation was calculated at 11.7% in the series of Andrade RJ et al. The anti-infective group of drugs was the more frequently incriminated and amoxicillin-clavulanate accounting for the 12.8% [27].

Despite intensive investigations and the use of the most modern techniques (PCR methods, molecular techniques, genomic DNA, biochemical), the causes of most cases of FH or ALF remain unknown: 26% in Portugal [14], 12% in Australia [28], 43% in Nordic countries [21], 18% in France.

In addition to viral, drug/toxin (paracetamol or other), and indeterminate causes of ALF or FH, a large number of cases are classified as other causes (Table 2). The main "other causes" include rare viruses (HSV-1 and -2 infection, varicella zoster virus (VZV) infection, parvovirus B19), a fulminant course of Wilson’s disease, Budd-Chiari syndrome, Reye’s syndrome, acute autoimmune hepatitis (AIH), massive malignant infiltration of the liver (liver metastasis, leukemia, lymphoma), hypoxic hepatitis due to cardiac failure, heatstroke, fatty infiltration of the liver, and HELLP syndrome. Overall, the incidence of these rare cases varies from 11—23%. In France, miscellaneous causes included hypoxic hepatitis, Autoimmune Hepatitis (AIH), heatstroke, Wilson’s disease, Budd-Chiari syndrome, Reye’s syndrome, HELLP syndrome, neoplasia, and acute fatty pregnancy. In Nordic [21] countries between 1990 and 2001, the etiology of the majority of cases could not be established. These indeterminate cases of FH represented 43% of patients, followed by paracetamol (17%), viral hepatitis (10.2%), and non-paracetamol drug-induced (10%) [21].

HSV-related hepatitis is a rare cause of FH, and is included most of the time in different reports under "miscellaneous causes". The spontaneous prognosis of HSV-related hepatitis is poor, in spite of the existence of antiviral treatment [29]. Despite the rarity of HSV-1 and -2 related ALF or FH, the diagnosis should always be considered in immunocompetent or immunocompromised patients with high fever, with or without leukopenia, with or without skin or genital lesions, and with or without marked elevations in aminotransferase levels after exclusion of other common causes. HSV hepatitis can follow both recurrent and primary HSV infection in immunocompromised hosts. In immunocompetent hosts, however, only primary infections have been associated with hepatitis. Both HSV types can induce severe or fulminating acute hepatitis although HSV-2 is more frequent. Serological assays are of very limited value for establishing an early diagnosis. Thus, molecular methods (real time PCR) in particular appear the most reliable for diagnosis [30].

As well as HSV, diagnosis of VZV infection must be considered when the classical etiologies have been eliminated in the presence of severe abdominal pain, fever, chills, malaise, fatigue, mild elevation of aminotransferase levels and skin lesions. A definitive diagnosis can be established rapidly by VZV DNA detection in serum by PCR [31]. In the above two cases, histology and immunostaining of transjugular liver biopsy specimens can help to establish or confirm a diagnosis of HSV or VZV hepatitis, which shows nuclear inclusion.

The hepatitis E virus (HEV) is an enterically transmitted RNA virus responsible for large waterborne epidemics of acute liver failure or fulminant hepatitis. The 4 leading causes of acute liver failure or fulminant hepatitis were significant in 7%, and antibiotics (n = 46; 7%), and antiepileptics (n = 39; 6%). The survival probabilities after liver transplantation were significantly lower in patients with antiepileptics induced acute liver failure compared to the others drugs [25]. More recently, in a multicenter, prospective study, drug-induced acute liver failure accounted for 11.1% (133 patients) among 1198 subjects enrolled at 23 sites in United States. 81.1% were considered highly likely by expert opinion, 15.0% probable and 3.8% possible. Over 60 individual agents were implicated and the most common were antimicrobials (46%). Transplant-free (3 weeks) survival was poor (27.1%), but transplantation was successful in 42.1% [26]. Among the patients with drug-induced liver injury, the risk of progressing to death or transplantation was calculated at 11.7% in the series of Andrade RJ et al. The anti-infective group of drugs was the more frequently incriminated and amoxicillin-clavulanate accounting for the 12.8% [27].

Despite intensive investigations and the use of the most modern techniques (PCR methods, molecular techniques, genomic DNA, biochemical), the causes of most cases of FH or ALF remain unknown: 26% in Portugal [14], 12% in Australia [28], 43% in Nordic countries [21], 18% in France.

In addition to viral, drug/toxin (paracetamol or other), and indeterminate causes of ALF or FH, a large number of cases are classified as other causes (Table 2). The main "other causes" include rare viruses (HSV-1 and -2 infection, varicella zoster virus (VZV) infection, parvovirus B19), a fulminant course of Wilson’s disease, Budd-Chiari syndrome, Reye’s syndrome, acute autoimmune hepatitis (AIH), massive malignant infiltration of the liver (liver metastasis, leukemia, lymphoma), hypoxic hepatitis due to cardiac failure, heatstroke, fatty infiltration of the liver, and HELLP syndrome. Overall, the incidence of these rare cases varies from 11—23%. In France, miscellaneous causes included hypoxic hepatitis, Autoimmune Hepatitis (AIH), heatstroke, Wilson’s disease, Budd-Chiari syndrome, Reye’s syndrome, HELLP syndrome, neoplasia, and acute fatty pregnancy. In Nordic [21] countries between 1990 and 2001, the etiology of the majority of cases could not be established. These indeterminate cases of FH represented 43% of patients, followed by paracetamol (17%), viral hepatitis (10.2%), and non-paracetamol drug-induced (10%) [21].

HSV-related hepatitis is a rare cause of FH, and is included most of the time in different reports under "miscellaneous causes". The spontaneous prognosis of HSV-related hepatitis is poor, in spite of the existence of antiviral treatment [29]. Despite the rarity of HSV-1 and -2 related ALF or FH, the diagnosis should always be considered in immunocompetent or immunocompromised patients with high fever, with or without leukopenia, with or without skin or genital lesions, and with or without marked elevations in aminotransferase levels after exclusion of other common causes. HSV hepatitis can follow both recurrent and primary HSV infection in immunocompromised hosts. In immunocompetent hosts, however, only primary infections have been associated with hepatitis. Both HSV types can induce severe or fulminating acute hepatitis although HSV-2 is more frequent. Serological assays are of very limited value for establishing an early diagnosis. Thus, molecular methods (real time PCR) in particular appear the most reliable for diagnosis [30].

As well as HSV, diagnosis of VZV infection must be considered when the classical etiologies have been eliminated in the presence of severe abdominal pain, fever, chills, malaise, fatigue, mild elevation of aminotransferase levels and skin lesions. A definitive diagnosis can be established rapidly by VZV DNA detection in serum by PCR [31]. In the above two cases, histology and immunostaining of transjugular liver biopsy specimens can help to establish or confirm a diagnosis of HSV or VZV hepatitis, which shows nuclear inclusion.

The hepatitis E virus (HEV) is an enterically transmitted RNA virus responsible for large waterborne epidemics of acute liver failure or fulminant hepatitis. The 4 leading causes of acute liver failure or fulminant hepatitis were significant in 7%, and antibiotics (n = 46; 7%), and antiepileptics (n = 39; 6%). The survival probabilities after liver transplantation were significantly lower in patients with antiepileptics induced acute liver failure compared to the others drugs [25]. More recently, in a multicenter, prospective study, drug-induced acute liver failure accounted for 11.1% (133 patients) among 1198 subjects enrolled at 23 sites in United States. 81.1% were considered highly likely by expert opinion, 15.0% probable and 3.8% possible. Over 60 individual agents were implicated and the most common were antimicrobials (46%). Transplant-free (3 weeks) survival was poor (27.1%), but transplantation was successful in 42.1% [26]. Among the patients with drug-induced liver injury, the risk of progressing to death or transplantation was calculated at 11.7% in the series of Andrade RJ et al. The anti-infective group of drugs was the more frequently incriminated and amoxicillin-clavulanate accounting for the 12.8% [27].
Epidemiology of liver failure

Changes in etiology over time

In a recent Spanish study of 267 patients, Escorsell et al. found significant changes in the causes of ALF over time. Between 1992 and 1995, viral infections were the predominant cause of ALF (61/145 cases, 42%). However, between 1995 and 2000, viral etiology decreased to 30% (37/122 cases). In the same period of time, toxic substance or drug-related ALF increased (27% vs. 13% before 1995). However, paracetamol had the lowest increase among these drugs [15]. The same evolution was observed in our experience and in Europe. In 500 patients referred in our department for ALF, the main causes of ALF until 1996 were acute viral hepatitis in 42%, drug- or toxin-related FH in 25%, other etiologies in 11% and indeterminate origin in 22%. After 1996, HBV decreased significantly (15%, p < 0.0001), whereas paracetamol overdose increased significantly (15%) [8].

The USA has followed the same evolutionary trends. In the series of 459 patients reported by Detre et al. [50], between 1987 and 1991, roughly one-third had HBV-related fulminant hepatitis (22.9%), one-third had NANB hepatitis (22.9%), followed in frequency by drug- or toxin-induced liver injury (paracetamol: 4.6%; others drugs: 10.7%); HCV and HAV, respectively. More recently, in another North America series of 308 patients with ALF, paracetamol was the most common cause (39%), followed by indeterminate cause (17%), idiosyncratic drug reactions (13%), HBV and HAV infection (7%), and other causes (24%) [19].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

patients with acute liver failure: 20 year single center experience. Hepatology 2006;37:10A.


