

# Fulminant hepatic failure: a Portuguese experience

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**Background** Fulminant hepatic failure (FHF) is a rare condition. Several series have been reported either by individual centres or in multicentre studies but, to our knowledge, this is the first report from a Portuguese population and might be a good example of FHF cases in a SouthWestern European population.

**Aims** To present the experience in FHF of a Portuguese Hepatogastroenterological Intensive Care Unit.

**Materials and methods** Retrospective study of 61 cases of FHF consecutively admitted between February 1992 and October 2006. Definition and classification of FHF were those suggested by Trey and Davidson (1970) and O'Grady *et al.* (1993), respectively. Criteria and contraindications for hepatic transplantation (HT) were those proposed by Bernuau *et al.* (1991) and Muñoz (1993), respectively.

**Results** Fifty-seven per cent of patients were women and median age was 37 years (range: 8–73). Most common cause of FHF was indeterminate (26%) followed by viral (23%) and drug-induced (23%), with 51% of cases with a hyperacute evolution. Global HT rate was 54% with criteria

for HT present in 87% of the patients resulting in an applicability rate of 62%. Overall survival was 69% and transplant-free survival was 15%; transplanted patients had survival rates of 70 and 68% at 6 and 12 months, respectively.

**Conclusions** Drug-induced and viral agents were responsible for almost half of FHF cases with a clear predominance of hyperacute presentation. The HT rate was 54% and the applicability rate was 62%. The overall 1 year survival of 69% might reflect the adequacy of the HT criteria used. *Eur J Gastroenterol Hepatol* 19:665–669 © 2007 Lippincott Williams & Wilkins.

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**Keywords:** acute liver failure, fulminant hepatic failure, liver transplantation

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## Introduction

Fulminant hepatic failure (FHF) is a rare condition characterized by a sudden aggression to a healthy person with unknown previous liver disease with the development of coagulopathy and hepatic encephalopathy. In the US there are about 2000 cases per year [1], most of them due to drug-induced liver injury or viral hepatitis [2]. With few exceptions, treatment remains mainly supportive with significant morbidity and mortality owing to the rapid progression to cerebral oedema and multiorgan failure. As liver transplantation has become available, short-term survival has increased and is now higher than 65% [2].

Several series are reported by individual centres and some multicentre series but, to our knowledge, this is the first report from a Portuguese population and might be a good example of FHF cases in a SouthWestern European population.

## Materials and methods

From February 1992 to October 2006, 61 consecutive patients with the diagnosis of FHF were admitted to a Gastroenterological Intensive Care Unit of a tertiary

referral hospital. In the context of FHF, this unit admits patients on a national basis and, in fact, one third of admissions came from outside the regional influence area.

The defining criteria used for FHF were those originally presented by Trey and Davidson in 1970 as 'a potentially reversible condition, the consequence of severe hepatic injury, with an onset of encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of preexisting liver disease' [3]. The patients were subsequently divided according to different time intervals between the onset of jaundice and the development of encephalopathy, as defined by O'Grady *et al.* [4]: hyperacute FHF when encephalopathy occurs within 7 days of the onset of jaundice; acute FHF for cases with an interval between 8 and 28 days from jaundice to encephalopathy; and subacute FHF in cases with encephalopathy that occurs within 5–12 weeks of the onset of jaundice [4].

The indication for liver transplantation in our institution is addressed by the use of the so-called 'Clichy criteria' defined by Bernuau *et al.* [5] in 1991: a factor  $V < 20\%$  in a patient aged  $\leq 30$  years or a factor  $V < 30\%$  in a patient

aged >30 years with coma or confusion. The contraindications for liver transplantation used were those appointed by Muñoz in 1993 [6]: seropositivity for human immunodeficiency virus, active alcohol or drug abuse, advanced cardiopulmonary disease, uncontrolled sepsis, widespread thrombosis of portal and mesenteric veins, irreversible brain damage or improving hepatic function.

## Results

This series of 61 patients with FHF included 26 men and 35 women with a ratio of 1:1.4. The mean age was  $37 \pm 16$  years (range: 8–73).

The most common aetiology (Table 1) was indeterminate FHF responsible for 26% of cases, immediately followed by acute viral (14 cases of hepatitis B infection with one case of hepatitis D coinfection) and drug-induced failure (Table 2), both present in 23% of the cases. There were also cases of mushroom poisoning (three patients) and toxic industrial exposure (three patients) and a group of miscellaneous cases representing 18% of the series, including Budd–Chiari syndrome (four patients), Wilson disease (three patients), autoimmune hepatitis (two cases) and two cases of massive neoplastic hepatic infiltration (one by a Burkitt lymphoma and the other by a neuroendocrine small cell carcinoma) [7–10].

Hyperacute FHF was responsible for more than half (51%) of the cases. Acute FHF was present in 31% of cases with only 18% evolving in a subacute process.

Transplantation criteria were fulfilled in 87% of the patients but only 62% were actually transplanted, as 13 patients had contraindications for the procedure and seven cases failed to get an available organ on time.

The global transplantation rate was 54%, with 33 out of 61 patients being transplanted. If only the group of patients having criteria for transplantation is considered, the global applicability rate of hepatic transplantation (HT) was 62%. In each group the transplantation rates according to aetiology were: toxic, 67%; indeterminate,

**Table 1 Aetiology of fulminant hepatic failure (FHF) cases**

Aetiology	Number of cases	Percentage
Indeterminate	16	26
Viral	14	23
Hepatitis B	13	
Coinfection of hepatitis B and D	1	
Drug-induced	14	23
Toxic	6	10
Mushroom	3	
Toxic industrial exposure	3	
Others	11	18
Budd–Chiari syndrome	4	
Wilson disease	3	
Autoimmune hepatitis	2	
Burkitt lymphoma	1	
Neuroendocrine small cell carcinoma	1	

**Table 2 Pharmacological agents responsible for toxic fulminant hepatic failure (FHF) cases**

Pharmacological agent	No. of cases
Antituberculosis associations	5
Sulfasalazine	2
Nimesulide	2
Fenoxicam	1
Methyldopa	1
Acetaminophen	1
Ciclosporin	1
Valproate sodium	1

**Table 3 Transplantation (transplanted patients per total cases) and applicability rates (transplanted patients per number of cases with transplantation criteria)**

	Transplantation rate (%)	Applicability rate (%)
By aetiology		
Toxic	67	100
Drug-induced	50	50
Indeterminate	56	64
Viral	36	42
By subgroup		
Hyperacute	58	69
Acute	42	50
Subacute	64	64

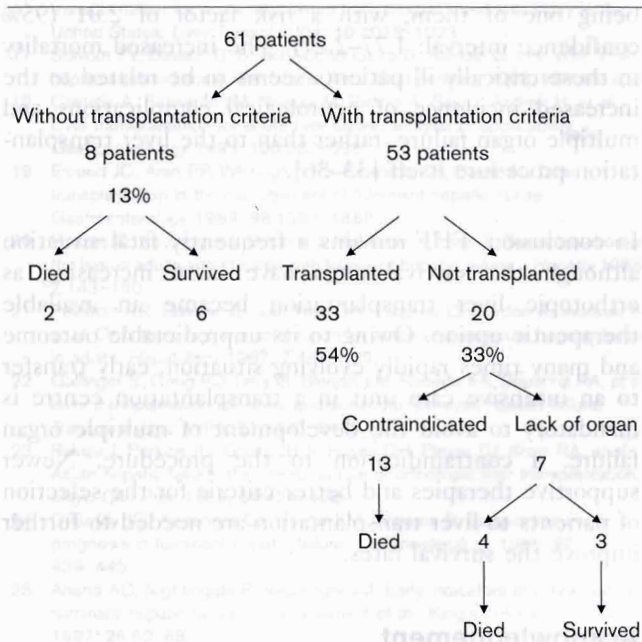
56%; drug-induced, 50%; and viral, 36%. By subgroup the rates were: hyperacute, 58%; acute, 42%; and subacute, 64%. The applicability rates by aetiology and subgroup were respectively: toxic, 100%; drug-induced, 50%; indeterminate, 64%; and viral, 42%; hyperacute, 69%; acute, 50%; and subacute, 64% (Table 3).

Complications were found in 77% of the patients, mainly cardiopulmonary insufficiency (44%), renal failure (41%), cerebral oedema (23%), haemorrhage (15%) and infection (8%).

The global mortality rate was 31%. Considering the aetiology, the mortality rate was higher in viral FHF with 43% of the patients deceased, followed by indeterminate cases with 38% and drug-induced cases with 36%. By subgroups classification, mortality rate was higher in acute cases, with almost half of the patients (42%) dying, with a slightly lower mortality rate in subacute cases (36%) and even lower in hyperacute FHF with just 23%.

The overall survival was 69% with a survival rate of 75% in those patients not fulfilling transplantation criteria and a transplant-free survival of 15%. Survival rate in the transplanted patients was 70% at 6 months (21 in 30 patients) and 68% at 12 months (19 in 28 patients with clinical follow-up). All the 13 patients with transplantation criteria but with contraindications to the procedure died; of the seven patients waiting for transplant but not receiving a graft, four died but three recovered (Fig. 1).

Fig. 1



Algorithm of the study cases.

## Discussion

This study represents the largest FHF series of Portuguese patients ever published. The 61 patients included in our report represent all the FHF cases from our institution since the beginning of the HT programme in 1992.

In this study, there was a slight female predominance of cases (more than 57% of the cases) as also found in the latest large prospective study from 17 centres in the US [2] (in which 73% of the patients were women) and other earlier studies [7–9]. There is no definite explanation for this consistent finding; some authors defend a greater female susceptibility to FHF or a more frequent use of medication by women, but these hypotheses remain to be proven [14].

The main cause of FHF cases was from indeterminate origin, even after an extensive diagnostic workup (including a liver biopsy by transjugular approach if necessary). As reported in other studies, the lack of a clear diagnosis suggests that a nonreported toxin or drug or an unidentified viral agent could be the cause of these FHF cases [15].

The second cause was drug-induced and viral FHF, which each represented 23% of cases. In the literature drug toxicity, and particularly acetaminophen overdose, have replaced viral hepatitis as the leading cause of FHF cases in the US and Europe [2,15], with acetaminophen alone representing 49% of the drug-induced liver injury in the

United Network for Organ Sharing database from 1990 to 2002 [16]. In this series, however, only one patient had a fulminant evolution owing to this agent (Tables 1 and 2).

As in other studies, hepatitis B virus prevails and, in these patients, was responsible for all viral cases, including a coinfection with a hepatitis D virus. In our experience, there were no cases of hepatitis A (which was the second viral agent in the American study) [2] and no cases of hepatitis C, in agreement with the concept that this agent alone does not appear to cause FHF [2,15,17]. Exclusion of a viral aetiology was considered if negative results were obtained to HAV-IgM, HBV-HBsAg, HBV-HBc Ab (IgM and IgG) and HCV, Cytomegalovirus-IgM, Epstein–Barr virus-IgM and herpes simplex virus-IgM antibodies.

Our transplantation rate of 54% is an example of the morbidity of this clinical entity in which orthotopic liver transplant remains the only therapy in cases unable to recover spontaneously. This is a much greater rate than that reported by Ostapowicz *et al.* [2], in which only 29% of the patients received a liver transplant but this discrepancy might be explained by the fact that, in our study, 87% of the patients had criteria for transplantation, whereas in the US study only 44% fulfilled criteria for liver transplantation. In fact, there is a similar rate of transplanted patients per number of cases fulfilling the criteria for transplantation (the applicability rate): 62 versus 66% in Ostapowicz *et al.* [2] study. These numbers are consistent with other series, in which transplantation rates ranged between 30 and 61% and applicability rates between 50 and 85% [18–23].

In the group of seven patients with transplantation criteria but no available organ, four died but three had their liver function improved and recovered. In addition, in the Ostapowicz *et al.* [2] series of the patients waiting for a liver graft, 25% died but 16 patients recovered (35% of those with criteria), even after being placed on the transplantation list. These facts reinforce the need to develop better prognostic factors to accurately determine which patients will spontaneously recover and those who will not survive without a liver graft [2,15].

Many studies have addressed the value of several criteria, the most known and used being the 'Clichy' [5] and the 'King's College' [24] criteria, showing positive predictive values from 70 to 100% and negative predictive values from 25 to 94% [15,25–29]. Although the 'Clichy' criteria were routinely used in this series, more than 80% of the patients presented both criteria and no significant prognostic differences were found.

Of the 13 patients meeting criteria for orthotopic liver transplantation but with contraindications to the

procedure, more than half were due to multiple organ failure already present at admission. As so, an early transfer of these patients to a liver transplantation centre is mandatory as these patients may deteriorate rapidly [15,30].

Complications occurred in 77% of the patients. Cardio-pulmonary insufficiency developed in 44% of the patients, with progression to renal failure in 41%. Specific complications related to the decreasing liver function (like cerebral oedema and haemorrhage) occurred in 23 and 15% of the patients, respectively. Infection occurred in 8% of the patients despite a careful surveillance of infections, with periodic cultures of sputum, urine and blood for bacterial and fungal organisms and the use as a rule of prophylactic antibiotics (usually imipenem or a combination of ceftazidime and vancomycin) and anti-fungals (mainly fluconazole).

The global mortality rate observed was 31%. Mortality rate was higher in viral FHF with 43% of the patients dying, probably because most cases with contraindication to liver transplantation were of viral aetiology.

Considering subgroup classification, the highest mortality rate was in the acute and subacute cases (42 and 36%, respectively), consistent with the original statement of O'Grady *et al.* [24] and also the result of the study of Ostapowicz *et al.* [2] in which these groups of patients presented a lower transplant-free short-term survival. In our hyperacute cases the mortality rate was as low as 23%, clearly lower than the former two groups. These results question the statement of Polson and Lee that these terms 'are not particularly helpful as they do not have prognostic significance distinct from the cause of the illness' [15].

The global survival rate of 69% is very similar to the 67% reported in the last US study [2], with a transplant-free survival of 15%.

The survival rate of the transplanted patients was 70% at 6 months (21 in 30 cases) and 68% at 12 months (19 in 28 patients), higher than the 50% reported by Zieniewicz *et al.* [31]. In their study, Zieniewicz *et al.* reported a per-operative mortality of 45% in patients submitted to liver transplantation for FHF and the mortality rates were much higher in the emergency liver transplantation group (18 cases) owing to FHF in comparison to the group of elective (178 cases) liver transplantation (50 and 47% versus 80 and 74%, at 12 months and 3 years, respectively). This higher mortality risk associated with emergency liver transplantation in FHF cases was also confirmed in the European study reported by Adam *et al.* [32], in which in a 22 089 patients' database from 102 centres in 18 countries, 12 risk factors in liver transplan-

tation were identified, transplantation in a FHF setting being one of them, with a risk factor of 2.01 (95% confidence interval: 1.77–2.27). The increased mortality in these critically ill patients seems to be related to the increased incidence of neurological complications and multiple organ failure, rather than to the liver transplantation procedure itself [33–36].

In conclusion, FHF remains a frequently fatal situation although the survival rates have been increasing as orthotopic liver transplantation became an available therapeutic option. Owing to its unpredictable outcome and many times rapidly evolving situation, early transfer to an intensive care unit in a transplantation centre is mandatory to avoid the development of multiple organ failure, a contraindication to the procedure. Newer supportive therapies and better criteria for the selection of patients to liver transplantation are needed to further improve the survival rates.

## Acknowledgement

Conflict of interest – none declared.

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**Results** Steatosis was found in 95.7% of the patients and significant fibrosis (METAVIR F2-F4) was present in 28.7%. The presence of steatosis could only be predicted by fibrosis, whereas significant fibrosis could be predicted by steatosis and age. Adiponectin levels were significantly decreased (-32%) with the severity of the steatosis. Although overweight chronic hepatitis C patients (body mass index  $\geq 25$  kg/m<sup>2</sup>) had insulin resistance and hypoadiponectinemia, lean chronic hepatitis C patients (body mass index < 25 kg/m<sup>2</sup>) had already significantly higher glycemia and lower adiponectin levels than in controls.

## Introduction

Liver steatosis is observed in 50-75% of patients chronically infected with hepatitis C virus (HCV) [1]. The occurrence of this association is of particular interest because steatosis per se is an important cofactor in accelerating both necroinflammatory activity and liver fibrosis in chronic hepatitis C (CHC) [2,3]. In addition, it has been reported that the incidence of sustained virological response to antiviral treatment could be decreased in the presence of steatosis [4]. Although the causes of steatosis associated with CHC are thought to be influenced by either viral or host characteristics or both, numerous factors involved in its occurrence remain to be determined. It is currently agreed that the occurrence of

steatosis in patients with genotype non-3 infections is mainly related to host metabolic abnormalities such as overweight, insulin resistance and type 2 diabetes mellitus [5,6]. By contrast, a direct effect of HCV on liver faty changes has been documented in genotype 3 infections; steatosis has been shown to be related with viral load and to be improved following sustained virological response to treatment [7]. Overweight, however, with its associated insulin resistance, has also been associated with liver steatosis and fibrosis in patients infected with genotype 3 [8], suggesting that host metabolic characteristics as well as viral characteristics might also be involved in the pathogenesis of their overweight.