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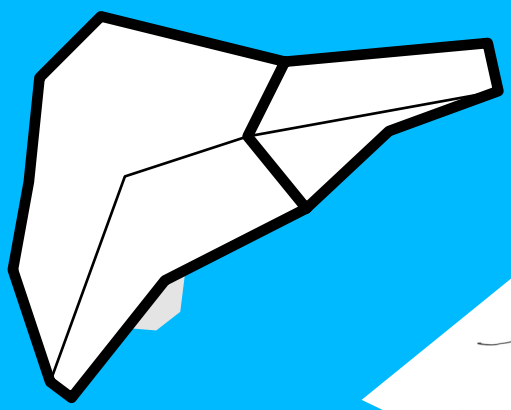

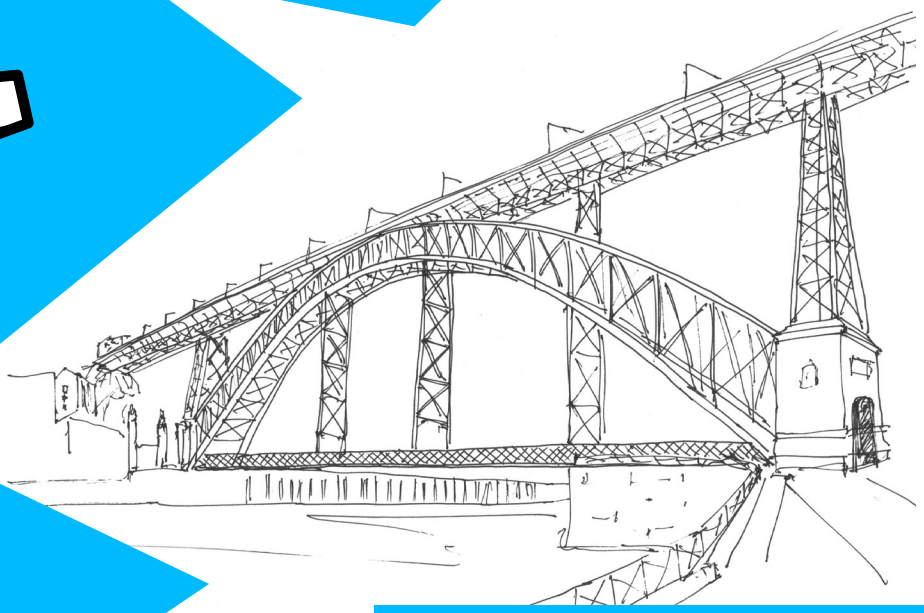

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Editor-chefe | **Pedro Vita**

Editores Associados | **Diana Valadares, Alexandre Pinto, Arlindo Guimas, Filipe Nery, Graziela Carvalheiras**

Arranjo e Design Gráfico | **José Oliveira**

Conteúdo WEB | **Pedro Marcos**

Edição ACIM | **Associação de Cuidados Intermédios Médicos**

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Associação de Cuidados Intermédios Médicos

Despite being a rare clinical entity, acute liver failure (ALF) management raises, worldwide, a major concern due to its quick installation, general and specific approaches, related complications (namely coagulopathy and hepatic encephalopathy), patient allocation and the decision whether transplant or not.

The first approach of the patient with ALF is made in any hospital facilities and so, all the physicians that work in the emergency department must be able to recognize this entity and to start some general and specific treatments (for example, N-acetylcysteine for paracetamol related ALF), as well as when to refer to specialized centers with liver transplant facilities, where severe cases must be quickly referenced and dealt.

In Portugal, there are three liver transplant centers: in Porto (Centro Hospitalar do Porto – Hospital Santo António), Coimbra (Centro Hospitalar Universitário de Coimbra) and in Lisbon (Centro Hospitalar de Lisboa Central – Curry Cabral), where this severe patients are dealt with multidisciplinary teams, namely hepatologists, surgeons, intensivists, anesthesiologists, psychiatrists, well trained nurses, etc.

In order to make a point of situation concerning the approach of ALF in Portugal, ACIM (Associação de Cuidados Intermédios Médicos/ Intermediate Medical Care Association), together with ASCI (Associação de Cuidados Intensivos/ Intensive Care Association) and UTHP (Unidade de Transplante Hepato-Pancreatica/ Hepatic Pancreatic Transplantation Unit of Centro Hospitalar do Porto), and with the scientific support of APEF (Associação Portuguesa para o Estudo do Fígado/ Portuguese Association for the Study of the Liver) promoted the realization of this first monothematic conference “Acute Liver Failure”, framed in a cycle of specific meetings “Current Topics in Intermediate and Intensive Care”, and invited national and international well known speakers that work and are experts on this field.

We sincerely hope that this meeting will, somehow, bring news, raise questions, and promotes the inter-institutional relationship, in order to raise the quality of general knowledge and clinical care to ALF patients.

Be very welcome,

Filipe Nery

On behalf of the Acute Liver Failure – Monothematic Conference organization team

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Etiology and diagnosis of ALF

Etiological heterogeneity in Europe. The Portuguese Reality.

Sandra Lopes

CHUC, Portugal

Key Points

1. Establishing the cause of acute liver failure is an important step in its management, so that specific therapy can be initiated.
2. The etiology of acute liver failure varies in different countries and at different times. A viral etiology (in particular hepatitis B virus) is now less frequent in the West, and paracetamol-induced fulminant hepatic failure is more common.
3. Many patients have less frequent causes of acute liver failure. In addition to known etiologies, indeterminate causes account for a large proportion of these cases.
4. The Portuguese reality: in 2007, Areia M. et al. published the first report from a Portuguese population. Of the 61 cases included, almost half were caused by drugs and viral agents. It may be a good example of acute liver failure cases in a South-western European population. An update of acute liver failure cases admitted to the Gastroenterology Intensive Care Unit of Coimbra University Hospital was made (current until 2013).

Definitions

Acute liver failure (ALF) refers to the abrupt loss of hepatic cellular function in a patient without pre-existing liver disease, with the subsequent development of coagulopathy, jaundice and encephalopathy. In 1970, Trey and Davidson defined fulminant hepatic failure as a "potentially reversible condition, the consequence of severe liver injury, with an onset of encephalopathy within eight weeks of the appearance of the first symptoms and in the absence of pre-existing liver failure" [1].

ALF is a rare but life-threatening critical illness with an incidence of fewer than 10 cases per million persons per year in the developed world, and is seen most commonly in previously healthy adults in their 30s [2, 3]. The syndrome of ALF is not a single clinical entity, and may be precipitated by a wide variety of hepatic insults (Table 1) [4]. Establishing the etiology is vital as this determines in large part the prognosis in ALF. Furthermore, there are specific treatments for certain conditions such as paracetamol poisoning, mushrooms and pregnancy.

Table 1 | List of Different Etiologies of Acute Liver Failure

T VIRAL	
	Hepatitis A, B (±D), C, E
	Haemorrhagic fever viroses
	Cytomegalovirus
	Herpes simplex viroses
DRUGS/TOXINS	
	Dose-related
	Paracetamol
	Carbon tetrachloride
	Amanita poisoning
	Bacillus cereus emetic toxin
	Cyanobacteria microcystins
	Idiosyncratic
	Isoniazid, halothane, troglitazone, bromfenac, multiple other prescription drugs
	Reye's syndrome (salicyclic acid)
	Herbal medicines
METABOLIC/GENETIC	
	Galactosaemia
	Fructose intolerance
	Tyrinosaemia
	Neonatal iron storage disease
	Wilson's disease
	Alpha-1-antitrypsin deficiency
NEOPLASTIC	
	Metastases: breast, melanoma, lung, lymphoma
PREGNANCY-RELATED	
	Acute fatty liver of pregnancy
	HELLP syndrome
	(Haemolysis, elevated liver function tests, low platelets)
VASCULAR	
	Budd-Chiari syndrome
	Veno-occlusive disease
	Ischaemic shock liver
MISCELLANEOUS	
	Autoimmune hepatitis
	Primary graft non-function in liver transplanted patients
	Heat stroke
INDETERMINATE	

Etiology is Different in Different Settings

The most frequent causes worldwide are viral hepatitis (particularly hepatitis A and B), drug overdose (in particular paracetamol), idiosyncratic drug reactions, ingestion of toxins and metabolic disorders [5 - 7]. There is a marked geographical and socioeconomic variation of these etiologies (Table 2) [5 - 7].

Table 2 | Incidence of Different Etiologies of Acute Liver Failure in Various Countries According to the Year (Adapted from Ichai and Samuel[7])

Authors	Country	Years	Number of Patients	Main Etiologies				
				Paracetamol	Drug-Induced, Not Paracetamol	Viral (HAV, HBV, and Other)	Indeterminate	Other
Williams and Wendon[11]	London	1973-1993	1257	765 (60.9%)	77 (6%)	329 (26.2%) 60 (5%), 94 (7%), 6 (0.5%)	201 (16%)	86 (6.8%)
Shakil et al.[46]	Pittsburgh	1983-1995	177	33 (19%)	21 (12%)	55 (31%) 13 (7%), 33 (19%), 9 (5%)	49 (28%)	19 (11%)
Brandsaeter et al.[18]	Nordic countries	1990-2001	315	52 (17%)	31 (10%)	37 (12%) 7 (2%), 25 (8%), 5 (2%)	135 (43%)	53 (17%)
Ostapowicz et al.[16]	United States*	1998-2001	308	120 (39%)	40 (13%)	36 (11.5%) 14 (4.5%), 22 (7%)	53 (17%)	59 (19%)
Farmer et al.[62]	UCLA	1984-2001	204	13%	11%	17% 9%, NA, 8%	59%	
Gow et al.[17]	Australia	1988-2001	80	29 (36%)	5 (6%)	11 (14%)	35 (44%)	
Samuel et al.[4]	France	1986-2006	363	26 (7%)	75 (21%)	119 (33%) 18 (5%), 100 (28%)[‡]	66 (18%)	77 (21%)
Escorsell et al.[14]	Spain	1992-2000	267[†]	6 (2.2%)	36 (13.5%)	98 (37%) 5 (2%), 86 (32%), 7(3%)[§] 5 (2%)	86 (32%)	41 (15%)
Areia et al.[13]	Portugal	1992-2006	61	1 (2%)	13 (21%)	14 (23%) 13, 1, 0	16 (26%)	17 (28%)
Miyake et al.[19]	Japan	1990-2001	80	0	15 (18.7%)	34 (42.5%) 5 (6.3%), 27 (33.7%), 2 (2.5%)[‖]	24 (30%)	7 (9%)
Mudawi and Yousif[63]	Sudan	2003-2004	37	0	3 (8%)	10 (27%) 8 (22%), 2 (5%)[¶]	14 (38%)	10 (27%)

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; HEV, hepatitis E virus; NA, not applicable; UCLA, University of California Los Angeles.
*Seventeen tertiary care centers.
†Twenty children of 267.
‡HBV and HDV.
§HCV: 2.
‖HBV: 77; HBV-HDV: 16; HBV reactivation: 7.
¶HEV: 2.

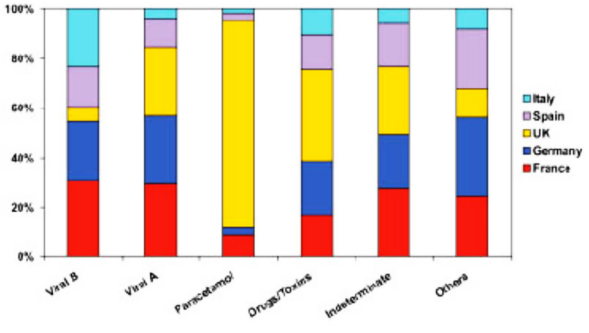
In the East and the developing world, ALF is due mainly to viral infections, primarily hepatitis B but also A and (especially in developing countries) E, as well as other nonhepatotropic viruses. There are relatively few drug-induced cases; antituberculosis therapy represents the major harmful class in these areas [3, 5].

By contrast, more than 65% of ALF in the West is currently thought to be due to drugs and toxins, with paracetamol being the overwhelming leader in the United States (46%) and the United Kingdom (60.9%) [3, 5 - 8]. Recently, paracetamol overdose has also became a common cause of ALF in others countries of Europe (Figure 1) [5 – 7]. An Irish study found that 30% of nonfatal overdoses in that country involved paracetamol, and that survivors reported relative ease of access as a principal reason for choosing that compound [9]. Other European countries such as Denmark and Sweden also report similar numbers of ALF cases due to paracetamol [10].

France, a country that has some restrictions on paracetamol sales, sees comparatively fewer cases, though numbers may have increased in conjunction with an overall increase in sales [9, 11]. The experience from Spain stands out as unique among characterized

Figure 1 |

Etiology of Fulminant Hepatitis in Transplanted Patients in France, Spain, the United Kingdom, Germany, and Italy from 1972 to 2007 (Adapted from Ichai and Samuel[7])



Western populations. A retrospective analysis of 267 cases, from 1992 to 2000, showed that paracetamol was responsible for only a handful of cases [12]. One key difference between Spain and the rest of the West appears to be the lack of paracetamol as an over-the-counter preparation.

The developed world is particularly subject to idiosyncratic drug induced liver injury, because of the large quantity of drugs ingested [4]. The incidence varies with geographic country: 2.5% in UK [8], 10% in Nordic countries [10], 15% in France [11], 19.5% in Spain [12] and 21% in Portugal [13]. The responsible drugs vary by location and prevailing drug use, with antibiotics (most commonly anti-tuberculosis medications), anticonvulsants and anti-inflammatory drugs most frequently implicated (Table 3). Herbal or adulterated traditional or complementary medications are also a notable cause.

In addition to viral, drug (paracetamol or others) and toxic (particularly mushroom) causes of ALF, a large number of cases are classified as other causes (Table 4). This miscellaneous group includes vascular causes (such as ischemic hepatitis, acute Budd-Chiari syndrome and veno-occlusive disease), Wilson disease, autoimmune hepatitis, pregnancy-associated liver failure including the acute fatty liver of pregnancy and HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome and the rapid evolution of metastatic or lymphomatous hepatic infiltration [5 – 7]. Overall, the incidence of these rare cases varies from 11 to 23% [5].

In many instances, the etiology remains unclear despite extensive history taking and laboratory assessment and these cases are termed indeterminate: 18% in France [11], 26% in Portugal [13], 30% in UK [8], 32% in Spain [12] and 43% in Nordic countries [10].

Table 3 | Drugs Implicated in Idiosyncratic Liver Reactions Leading to Acute Liver Failure

Infrequent causes	Rare causes	Synergistic causes
Isoniazid	Carbamazepine	Alcohol and paracetamol
Valproate	Ofloxacin	Trimethoprim and sulfamethoxazole
Halothane	Ketoconazole	Rifampin and isoniazid
Phenytoin	Lisinopril	Paracetamol and isoniazid
Sulfonamides	Niacin	Amoxycillin and clavulanic acid
Propylthiouracil	Labetalol	
Amiodarone	Etoposide (VP-16)	
Disulfuram	Imipramine	
Dapsone	Interferon-α	
Bromfenac	Flutamide	
Troglitazone		
Tolcapone		

Table 4 | Rare Causes of Acute Liver Failure (Adapted from Ichai and Samuel[7])

	Authors					
	Brandsaeter et al.[18]	Ostapowicz et al.[16]	Gow et al.[17]	Samuel et al.[4]	Areia et al.[13]	Escorsell et al.[14]
Year	2002	2002	2004	2006	2007	2007
Number	315	308	80	363	61	267
Total miscellaneous cause	48 (15%)	59 (19%)	8 (10%)	77 (22%)	14 (23%)	41 (15.3%)
Ischemic hepatitis	1 (0.3%)	17 (6%)	—	21 (6%)	—	6 (2.2%)
Autoimmune hepatitis	7 (2%)	13 (4%)	—	16 (4.6%)	2 (3%)	13 (5%)
Wilson's disease	5 (1.5%)	8 (2.5%)	6 (7%)	15 (4%)	3 (5%)	2 (0.7%)
Budd-Chiari syndrome	16 (5%)	5 (1.5%)	2 (3%)	1 (0.3%)	4 (6.5%)	0
Pregnancy-related liver failure	2 (0.6%)	6 (2%)	—	6 (2%)	—	2 (0.7%)
Neoplastic infiltration	2 (0.6%)	4 (1%)	—	5 (1.5%)	2 (3%)	8 (3%)
Heat stroke		6 (2%)	—	1 (0.3%)	—	0
Mushroom ingestion	6 (2%)	—	—	5 (1%)	3 (5%)	10 (3.7%)
Viral other (EBV, HCV, HGV, and parvovirus B19)	3 (1%)	—	—	7 (2%)	—	—
Postsurgery liver failure	5 (1.5%)	—	—	—	—	—
Metabolic liver failure	1 (0.3%)	—	—	—	—	—

Abbreviations: EBV, Epstein-Barr virus; HCV, hepatitis C virus; HGV, hepatitis G virus.

Changes in Etiology over Time

In Spain, Escorsell et al. found significant changes in the causes of ALF over time [12]. 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). The same evolution was observed in French series and in Europe. In 500 patients referred to Hôpital Paul Brousse for ALF, the main causes of ALF, between 1986 and 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%) [11].

The Portuguese Reality

From March 1992 to December 2013, 104 consecutive patients with the diagnosis of ALF were admitted to Gastroenterology Intensive Care Unit of Coimbra University Hospital, a tertiary referral hospital. In the context of ALF, this unit admits patients on a national basis and, in fact, a quarter of the admissions came from outside the regional influence area. ALF was defined as the presence of coagulopathy (prothrombin time >15 s or international normalized ratio ≥1.5), any grade of hepatic encephalopathy within 26 weeks of illness onset, and no history of underlying liver disease.

Our series of 104 patients with ALF included 43 men and 61 women. The mean age was 41.7 years (range 8 to 85). The most common etiology (Table 5) was drug-induced toxicity, responsible for a quarter of cases (Table 6), followed by indeterminate cases in 22%. Toxic-related ALF occurs in 19% of patients: mushroom poisoning (15 cases), toxic industrial exposure (3 cases) and herbal medicine ingestion (2 cases). Acute viral hepatitis was present in 18% of the cases (17 cases of hepatitis B infection with one case of hepatitis D co-infection; one case of hepatitis E in a pregnant woman; one case of hepatitis EBV). There was a group of miscellaneous cases representing 15% of the series, including Budd–Chiari syndrome (four patients), autoimmune hepatitis (four patients), Wilson's disease (three patients), ischemic hepatitis (two patients), massive neoplastic hepatic infiltration (one by a Burkitt lymphoma and the other by a neuroendocrine small cell carcinoma) and a case of HELLP syndrome.

Like in others series, the etiologies of ALF in Portugal have evolved over time. Between 1992 and 1999, viral hepatitis (9/33 cases), drug-related ALF (9/33 cases) and indeterminate origin (9/33 cases), were the major causes, each present in 27% of the cases. The remaining six cases were induced by toxins (five cases) and by massive neoplastic hepatic infiltration by Burkitt lymphoma. After 2000, there was a significant increase of less common causes of liver failure (15/71 cases, 21%) such as autoimmune hepatitis, Budd-Chiari syndrome, Wilson's disease, ischemic hepatitis, HELLP syndrome and massive neoplastic hepatic infiltration due a neuroendocrine small cell carcinoma; drugs-related ALF occurs in 24% (17/71 cases), toxin-related ALF in 21% (15/71 cases), indeterminate in 19.7% (14/71 cases) and with viral hepatitis corresponding to only 14% (10/71 cases).

Table 5 |

Etiology of Acute Liver Failure Cases in Portugal from 1992 to 2013

Etiology	Number of cases	Percentage
Drug-induced	**26**	**25**
Indeterminate	**23**	**22**
Toxic	**20**	**19**
Mushroom	15	
Toxic industrial exposure	3	
Herbal medicine	2	
Viral	**19**	**18**
Hepatitis B	16	
Coinfection of hepatitis B and D	1	
Hepatitis E	1	
Hepatitis EBV	1	
Miscellaneous	**16**	**15**
Budd-Chiari syndrome	4	
Autoimmune hepatitis	4	
Wilson disease	3	
Ischaemic hepatitis	2	
Burkitt lymphoma	1	
Neuroendocrine small cell carcinoma	1	
HELLP syndrome	1	

Table 6 |

Pharmacological Agents Responsible for Drug-related Acute Liver Failure Cases in Portugal from 1992 to 2013

Pharmacological agent	Number of cases
Antituberculosis associations	7
Paracetamol	5
Flupirtine	4
Nimesulide	3
Sulfasalazine	2
Valproate sodium	2
Cyclosporine	1
Fenoxicam	1
Methyldopa	1

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Diagnosis of ALF – Is there a 'good and true' definition?

Dr William Bernal
Reader in Hepatology and Intensive Care Medicine
Liver Intensive Therapy Unit
Institute of Liver Studies
Kings College Hospital
London SE5 9RS
United Kingdom

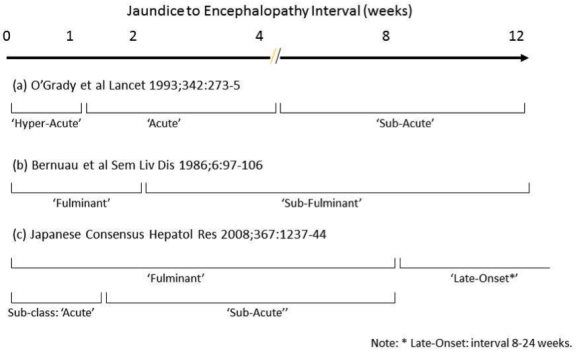
Encephalopathy and ALF

The term 'Fulminant hepatic failure' was first coined in 1970 to describe a 'potentially reversible condition, the consequence of severe liver injury, with an onset of encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease' [1]. Key elements of this definition remain relevant today, particularly the recognition of the central importance of the development of encephalopathy, though classifications have evolved through the observations that prognosis and complications vary in relation to the rate of evolution of illness [2].

More modern definitions therefore seek to quantify the interval between symptom onset and development of encephalopathy and in some the severity of liver injury by degree of coagulopathy. A number of classification systems exist and include (figure 1):

- The 'O'Grady' terminology which is commonly used in adults, and sub-classifies into 3 groups; Hyper-acute, Acute and Sub-acute dependent upon the interval between the development of jaundice and the onset of encephalopathy [3].
- Bernuau and colleagues classify the condition into two categories of 'fulminant' and 'sub-fulminant' disease, with a jaundice to encephalopathy intervals of less than 2 weeks and 2 weeks to 3 months respectively [4].
- Japan consensus criteria subdivide the condition into 'fulminant hepatitis' and 'late-onset hepatic failure' with onset of encephalopathy at respectively less than 8 weeks and 8 to 24 weeks after disease onset. 'Fulminant hepatitis' is further subdivided into 'acute' and 'sub-acute' subtypes [5].

Figure 1. Classification Systems for Acute Liver Failure.



These classifications have direct clinical relevance as they may give clues as to the aetiology of disease, its likely complications and overall prognosis. However, in young children clinical encephalopathy may be absent or occur only late in the course of illness. Working paediatric definitions therefore do not depend on the presence of encephalopathy but only on coagulopathy due to liver injury. An accepted definition is that of "a multi-system disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a patient with no recognised underlying chronic liver disease" [6].

Patterns of Disease

The central place of encephalopathy in all definitions of adult ALF reflects its key prognostic importance, with development indicating critically impaired liver function. Its clinical features cover a spectrum of neurological impairment that ranges from mild disorders of concentration to frank coma. In patients with sub-acute presentations, even low grade encephalopathy may indicate extremely poor prognosis, whereas in hyper-acute disease survival with medical management may be good even in patients developing high grades. Adoption of a single threshold of encephalopathy severity to mark transition from liver 'injury' to frank 'failure' across all presentations and etiologic groups is thus somewhat simplistic.

The aetiology of disease and the clinical phenotype of illness that results are closely linked. Using the O'Grady classification, 'Hyper-acute' liver failure typically results from acetaminophen or acute Hepatitis A (HAV) or E (HEV) virus infection causing liver injury with a week or less between symptom onset and high-grade encephalopathy, in 'Acute' disease this interval is between one and four weeks, typified by acute HBV disease and in 'sub-acute' disease a more indolent presentation is seen with the interval of up to 3 months.

Sub-acute cases typically result from idiosyncratic drug-induced liver injury or are indeterminate in cause and despite less severe coagulopathy and encephalopathy, have consistently worse outcome with medical care alone than those with more rapid clinical course [3].

This variation in presentation does not appear to be solely determined by the causative agent and may be influenced by host factors. For reasons that are currently unexplained, ALF is more common in women and in many aetiologies, survival worsens with increasing age [7]. Sub-acute presentations of HEV and HAV ALF occur only infrequently but are most common in older subjects, with poorer survival than in those with more rapid evolving presentations [8, 9].

Mode of presentation is also linked to the incidence of cerebral oedema and intracranial hypertension (ICH) in patients with high grade encephalopathy. ICH is much more common in patients with hyper-acute than sub-acute disease, reflecting the greater overall severity of multi-organ failure seen in this group and the inability of cerebral osmotic compensatory mechanisms to adapt to very abrupt rises in circulating ammonia. Again, age may influence susceptibility though differences in intracranial CSF volume resulting from lower cerebral volumes in older subjects. In the young, the ability to compensate for cerebral swelling is thus reduced and the threshold for the development of ICH lower [10].

Unresolved Issues

No consensus exists on the severity of coagulopathy or encephalopathy that marks the transition from liver *injury to failure* [11]. A 'fulminant' presentation is now also recognised to occur in some specific forms of previously sub-clinical chronic liver disease - exemplified by some cases of Wilson's disease or reactivation of hepatitis B virus (HBV) infection – but whether this represents true 'acute liver failure' or 'acute on chronic disease' is a subject of contention. This lack of agreement complicates interpretation of research and the application of clinical protocols between centres – both aspects already constrained by the rarity of the condition and its heterogeneous nature. A universally accepted definition of the condition would be a major advance but currently appears unlikely to be agreed.

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Workup diagnosis in the setting of acute liver failure of unknown etiology

François Durand

Hepatology & Liver Intensive Care, Hospital Beaujon, Clichy and University Denis Diderot Paris VII, France

Correspondence:
François Durand, MD
Hepatology & Liver Intensive Care, Hospital Beaujon
100 Boulevard du Général Leclerc, 92110, Clichy, France
Tel : + 33 1 40 87 55 110
E.mail : francois.durand@bjn.aphp.fr

1. Are the manifestations related to acute liver failure or not?

TAcute liver failure (ACLF) is an uncommon condition characterized by an acute deterioration of liver functions resulting in extra-hepatic organ/system failures and/or encephalopathy/brain edema in patients without evidence of prior chronic liver disease. This is a potentially life threatening condition requiring urgent workup. There are various potential causes of ACLF ranging from paracetamol overdose to auto-immune disorders [1].

The first manifestations of severe acute liver injury may be non-specific manifestations (fatigue, mild abdominal pain…), a decrease in prothrombin index or an increase in INR and a marked increase in serum transaminases, reflecting liver tissue damage. Jaundice may be absent. Patients with a marked increase in INR but only a mild increase in serum transaminases (AST/ALT < 5 times normal) are highly unlikely to have acute liver failure. In this context other causes of increased INR (or decrease in prothrombin index) such as diffuse intravascular coagulation or administration of vitamin K antagonists should be carefully checked. Factor V can be useful to differentiate decreased production of coagulation factors by the liver from the effects of vitamin K antagonists but there are important inter-laboratory variations in factor V determination.

ACLF should also be differentiated from decompensation of cirrhosis and acute-on-chronic liver failure (ACLF) which is characterized by the occurrence of organ failure(s) in patients with cirrhosis.

2. If the patient has acute liver failure, check for life-threatening manifestations requiring urgent care

If a diagnosis of acute liver failure can be clearly established, two situations represent life threatening conditions that should be rapidly identified and graded in terms of severity: multiple organ failure and brain edema.

Multiple organ failure is an increasingly common mode of presentation or complication of ALF. Failures may involve the cardio-circulatory system, kidney and lungs (acute respiratory distress syndrome). Each of these failures need appropriate care according to general ICU guidelines (vasopressors, renal replacement therapy and mechanical ventilation). It is sometimes difficult to differentiate ALF resulting from multiple organ failure (shock liver) from ALF as a cause of multiple organ failure.

For unknown reasons, brain edema has become less common than multiple organ failure in the course of ALF [2]. Brain edema is characterized by a progressive increase in intra-cranial pressure that may ultimately result in extreme hypoperfusion and irreversible cerebral anoxia [3]. Transcranial ultrasonography, which is a non-invasive and reliable technique, should be used as a first line investigation each time brain edema is suspected. Specific management is discussed elsewhere.

3. Check for factors with a determinant impact on the outcome

Initial workup should include a rapid assessment of two variables that may have a determinant impact on the outcome: (i) the course of the disease and its manifestations and (ii) previously unknown underlying chronic liver disease.

Patients can be categorized into three groups with respect to the course of the disease: hyperacute (interval from jaundice to encephalopathy ≤ one week), acute (interval between jaundice to encephalopathy from one to 4 weeks) and subacute (interval between jaundice to encephalopathy from 4 to 12 weeks). For any given level of disease severity (coagulopathy, encephalopathy…) the slower the progression the higher the risk of dying with medical management alone [4]. However, a limitation of this classification is that jaundice may be absent, especially in patients with hyperacute ALF.

Previously unrecognized chronic liver disease with extensive fibrosis or cirrhosis should be carefully assessed as it is obviously associated with a worse prognosis. Indeed, underlying chronic liver lesions reduce regeneration capacity. Besides the identification of a cause of chronic liver disease (alcohol abuse, non-alcoholic steatohepatitis, chronic viral hepatitis…), abdominal ultrasound is useful to show evidence for portal hypertension. Importantly, subacute liver failure may be associated with dysmorphic liver and ascites mimicking cirrhosis. Liver biopsy is another useful tool (see below).

4. Identify the cause of acute liver failure

The next step is to identify the cause of ALF. Basically, massive liver cell necrosis/apoptosis without inflammation (such as in paracetamol overdose), acute hepatitis combining hepatocyte destruction and inflammatory infiltrates (such as in viral hepatitis) and acute microvesicular steatosis (such as in acute fatty liver of pregnancy) are the three main mechanisms involved in ALF. Some causes are associated with a single type of liver lesion. Other causes may be responsible for different types of lesions in different patients.

In most Western countries, paracetamol overdose has become the most common cause of ALF [1, 4]. Undetectable serum paracetamol concentration does not exclude paracetamol overdose in patients who have been referred lately. Interestingly, accidental intoxication represents about 50% of paracetamol-induced ALF while the remaining 50% correspond to voluntary intoxication in a suicide attempt.

Causes of ALF cover a wide spectrum including viral infections, idiosyncratic drug toxicity, circulatory changes, malignancies and metabolic disorders, among others. In patients admitted for ALF without clear evidence for a given cause, appropriate diagnostic tests should be performed to cover all possible causes (Table 1).

Table 1 | Causes of acute liver failure and corresponding liver lesions

Cause	Hepatocyte necrosis and/or apoptosis	Inflammatory infiltrates	Inflammatory infiltrates
Paracetamol (acetaminophen) overdose	+	-	-
Hepatitis viruses			
• Hepatitis A virus	+	+	-
• Hepatitis B virus			
Acute HBV infection Acute HBV infection	+	+	-
Acute exacerbation of chronic HBV infection*	+	+	-
• Hepatitis D virus	+	+	-
• Hepatitis E virus	+	+	-
Other viruses			
• Herpes simplex virus 1 and 2	+	±	-
• Varicella-Zoster virus	+	±	-
• Esptein Barr virus	+	-	-
• Human herpes virus 6	+	±	-
• Miscellaneous viruses			
Human parvovirus B19 †	+	±	-
Hemorrhagic fever viruses	+	±	-
Amanita mushroom poisoning	+	-	-
Other toxins			
• Industrial solvents	+	-	-
• Herbal medicines	+	±	-
• Illicit drugs			
Ecstasy	+	±	-
Cocaine	+	±	-
Intravenous buprenorphine	+	-	-
Drug-induced hepatitis	+	±	
Hypoxic liver cell necrosis	+	-	-
Heat stroke	+	-	-
Wilson's disease*	+	-	±
Malignant infiltration of the liver	+	-	-
Auto-immune hepatitis*	+	+	-
Syncytial giant cell hepatitis	+	±	-
Acute fatty liver of pregnancy	±	-	+
HELLP syndrome	+	-	-
Reye's syndrome	±	-	+
Obstruction of the hepatic veins*	+	-	-
Liver transplantation and liver surgery	+	±	-

* underlying parenchymal fibrosis is frequently associated; † the responsibility of this virus is highly uncertain.

Hepatitis B virus (HBV) can be responsible for ALF in two circumstances: acute HBV infection or acute exacerbation of chronic HBV infection [5]. It may be difficult to clearly differentiate acute infection from acute exacerbation when chronic HBV infection was previously unknown. Manifestations and serological profile may be similar. Origin for an area where HBV infection is endemic, recent exposure to immunosuppression, high HBV-DNA level and underlying liver fibrosis argue for an acute exacerbation rather than acute infection. The prognosis of acute exacerbation is worse as compared to that of acute infection.

Hepatitis E infection is an emerging cause of ALF in Western countries [6]. Metabolic syndrome seems to be a predisposing factor for the development of ALF. Serum HEV-RNA may be undetectable because of its short half-life. Determination of HEV-RNA in the stools increases sensitivity.

5. Conditions that should not be considered as a cause of acute liver failure

Alcohol abuse alone never causes ALF. Similarly, CMV infection and EBV infection alone may not be considered as possible causes of ALF. Positive serological tests for these viruses are not evidence that they are the cause of ALF.

6. Acute liver failure of unknown origin vs acute liver failure with too many causes

Despite extensive workup, no cause can be identified in a significant proportion of patients (10-20% in Western countries). Most of these patients with ALF of unknown origin are women, have a subacute rather than acute presentation with marked jaundice, a progressive deterioration in liver function, and a poor prognosis. By definition, auto-antibodies are absent (or present at a non-significant level). Liver biopsy (see below) shows extensive liver cell necrosis with marked inflammatory infiltrates and, occasionally regenerative features.

On the opposite, an increasing number of patients have ALF due the combination of several factors among which it is impossible to determine which (if any) predominates. For instance, patients may develop ALF in a context of absorption of cocaine or ecstasy followed by seizures, hyperthermia, hypovolemia and hypotension. Inadvertent administration of paracetamol is not uncommon in such patients with hyperthermia and may further contribute to liver lesions.

7. The role of biopsy

Liver biopsy may help establish more precisely the diagnosis. It may also help identify additional prognostic factors. Transvenous route is almost always needed because of the decrease in coagulation factors. Due to technical reasons, transjugular may be impossible to perform in patients placed on mechanical ventilation. Therefore, it is recommended to consider biopsy at an early stage, in patients without encephalopathy (but at high risk to progress to acute liver failure) or in patients with early encephalopathy.

When a patient has risk factors for chronic liver disease (alcohol abuse, HCV infection, metabolic syndrome…) not directly related to the cause of ALF, biopsy helps identify and grade underlying fibrosis. Patients with extensive fibrosis are less likely to recover with medical management alone. However, it must be noted that the assessment of mild fibrosis may be difficult in patients with massive liver cell necrosis and trabecular collapse.

In patients with HBV infection, the presence of fibrosis is an argument for acute exacerbation rather than acute infection. However, absence of fibrosis is no evidence that ALF is due to acute HBV infection.

Most patients with auto-immune hepatitis had a silent disease that progressed for years before the onset of ALF. In borderline cases (pathological features suggesting auto-immune hepatitis but no significant increase in auto-antibodies…), the presence of fibrosis argues for auto immune hepatitis.

When ALF due to herpes simplex (HSV) infection is suspected based upon fever, a context of immunosuppression, serum transaminases over 100 times normal…), liver biopsy is very useful, showing lesion almost pathognomonic of this group of infections [7]. Lesions include patchy areas for liver cell necrosis involving the lobules with no or mild inflammatory infiltrates. Viral inclusions can be observed.

Finally, in patients with no obvious cause of ALF, marked deterioration of general status and enlarged liver, biopsy is needed to identify diffuse infiltration by malignant cells (lymphoma, melanoma, poorly differentiated adenocarcinoma…), even when liver parenchyma seems homogeneous on imaging. Malignant infiltration, a rare cause of ALF, is a contraindication for transplantation.

8. Evaluation for emergency transplantation

ALF is often a life threatening condition in a very short term and emergency liver transplantation may be the only life-saving options. Evaluation has four objectives: (i) make sure that mortality is very high (80% or more) with medical management alone, (ii) make sure that the operative risk is acceptable based on age, organ failures and comorbidities, (iii) make sure that the expected result in the long term is acceptable (taking into account comorbidities, factors potentially associated to adherence to immunosuppression, disease recurrence…) and (iv) make sure (whenever

it is possible) that the patient is not too sick to be transplanted (futile transplantation). In contrast to patients considered for elective transplantation, there is very little time for evaluation in ALF. The final decision should be multidisciplinary in a center with a strong experience.

9. Conclusions

Acute liver failure is a multifaceted syndrome which can be related to many causes. These possible causes are widely different in nature. Independent of the cause, the first step is to determine whether the manifestations are basically related to the liver. This is especially relevant in patients presenting with multiple organ failure. The second step, independent of the cause, is to identify life threatening conditions (multiple organ failure secondary to ALF and/or brain edema) that require urgent management in a specialize unit. The third step (which may be intricated with the first step) is to identify the cause. However, it must be noted that ALF, an uncommon syndrome, is generally multifactorial. Patients with paracetamol overdose are more prone to develop ALF if they have predisposing factors such as poor nutritional status or alcohol abuse. Patients with acute viral hepatitis are more prone to develop ALF if they received paracetamol etc… Some causes are evident. Others are much more uncommon and sometimes difficult to ascertain (Wilson's disease, HSV infection…). Therefore, in order to save time, it is recommended to tests a wide number of possible causes at initial workup rather than performing a step by step assessment. Biopsy may be useful either to provide arguments for a given liver disease or to document underlying chronic liver lesions. Imaging is also another important tool. Finally, evaluation for emergency liver transplantation is obviously more difficult than evaluation for elective transplantation.

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Specific treatments

NAC for acetaminophen poisoning and other ALF etiologies

Filipe Nery
Intensive and Intermediate Care Unit
Centro Hospitalar do Porto – Hospital Sto António, Porto, Portugal
filipegaionery@gmail.com

1. NAC and its relationship with Glutathione

N-acetylcysteine (NAC) – C5H9NO3S - is the acetylated precursor of L-cysteine and reduced glutathione (GSH), having a molecular weight of 163,2. NAC possesses a sulfhydryl group (responsible for its characteristic odor). It stimulates GSH synthesis, enhancing glutathione-S-transferase activity, and also promotes liver detoxification and scavenging of free radicals [1]. GSH is synthesized in the cytosol from the aminoacids glycine, L-cysteine and L-glutamate, in a two step reaction requiring the action of γ-glutamylcysteine synthetase and GSH synthetase, being the presence of cysteine rate limiting for the synthesis of GSH [2]. NAC is able to serve as a cysteine donor to GSH formation, increasing GSH levels. GSH has a main important role in human homeostasis as an antioxidant preventing damage to intracellular components, used as a substrate in both conjugation and reduction reactions, by binding to endogenous compounds (limiting and regulating the reactivity of the chemicals, facilitating their membrane transport and elimination from the cell and organism and leading to the formation of essential biological mediators) [3]. The liver is the major site of GSH biosynthesis. It is known that in alcoholics, pools of mitochondrial GSH are depleted as well as in chronic hepatitis C infection [4, 5].

Many clinical applications have been attributed to NAC, either by its role in ameliorating the oxidative stress acting as an antioxidant, either by its other functions as vasodilator by facilitating the production and action of nitric oxide. NAC has been used in chronic obstructive pulmonary disease, prevention for contrast-induced nephropathy, influenza illness, idiopathic pulmonary fibrosis, polycystic ovary syndrome, etc [6].

2. Acetaminophen toxicity and NAC use

In 1966 the first two cases of paracetamol related acute liver failure (ALF) were reported (both patients died) [7]. Nowadays, drug-induced liver injury is the second main cause of ALF worldwide, being paracetamol, in the USA and northern Europe, the leading drug. In the USA, paracetamol is even the commonest cause of ALF [8]. Acetaminophen toxic doses are referred to ingestion of a single dose > 200mg/Kg or 10gr (in adults) [9]. GSH detoxifies N-acetylbenzoquinonineamine (NAPQI), the toxic metabolite of paracetamol to nontoxic metabolites (glucoronide and sulfate conjugates). When ingested in toxic doses, GSH reserves become depleted and NAPQI covalently binds to hepatocellular proteins resulting in cellular necrosis and death with characteristic centrolobular necrosis at the histology level [9, 10].

NAC has been recognized as paracetamol antidote since almost 4 decades ago, property that was soon attributed to its sulphydryl compound, having a positive impact on morbid-mortality, lowering it, being more effective when started sooner (8-10h after ingestion) [9, 11].

3. NAC and non-paracetamol ALF

A benefit with the use of NAC in non-paracetamol ALF has been tried to be established since de early 90's. Harrison *et al*. compared a group of 12 versus 8 patients with paracetamol and non-paracetamol induced ALF and reported an increase in oxygen consumption, microcirculatory blood flow and tissue oxygenation in both groups, although less marked in those with ALF due to other causes than paracetamol [12]. These results were found elsewhere irrespectively of the etiology of the liver disorder [13]. In animal models, it was shown that NAC increases cerebral perfusion pressure [14], having not only antioxidant but also anti-inflammatory properties, attenuating the expression of plasma proinflammatory cytokines [15]. Less severe histopathological injury in CCl4 induced liver injury in mice was found when NAC was co-administered [16].

However, studies concerning the use of NAC in non-paracetamol induced ALF are scarce and generally gather low number of patients.

In 2000, NAC was proposed as a treatment option for all patients with ALF irrespective of the etiology, based on a study made with 7 patients in which it may have led to the prevention of progression to grade III/IV hepatic encephalopathy (HE) and amelioration of the coagulation factors [17].

A retrospective study comparing non-paracetamol ALF in 170 children, showed that when NAC was administered it was associated with a shorter length of hospital stay, higher incidence of native liver recovery without liver transplantation (LT), and better survival after LT [18].

Similar results were found in adults, with NAC non-utilization being an independent predictor of mortality in multivariate analysis [OR=10.3, 95%CI1.6-65.7, p=0.014] [19]. Later on, a benefit of transplant-free survival was found in a prospective study which included 173 patients (81 NAC versus 92 placebo), but only in those with lower grades of HE (I-II), with a 52% rate of survival without grafting [20]. Those patients treated with NAC and early low grade HE had greater improvements in ALT and bilirubin during

the first 4 days of hospitalization [21]. The same Study Group showed not only that NAC administration was an independent predictor of transplant-free survival, but also that lower IL-17 concentration were related to the same effect, postulating that NAC ameliorates the production of IL-17, which was associated with HE progression and a dismal prognosis [22].

NAC has also been found to improve the outcome in the setting of ALF complicating dengue [23] and hepatitis A viral infection in children [24], as well as to improve 1-month survival in the setting of acute alcoholic steatohepatitis when associated to corticotherapy, but not at 6 months [25].

NAC use has been proposed by the AASLD in the setting of non-paracetamol ALF [26], and is a generalized standard of care in many adult and children liver units all over the world.

But there may be differences concerning adult and pediatric populations, as there is recent evidence in a well prospective conducted study that there was no improvement in 1-year survival in non-paracetamol ALF in those children treated with NAC, but more important, that those who were treated with NAC had 1-year LTx-free survival significantly lower, particularly those with less than 2 years old with HE grades 0-1 (p=0,0493) [27].

4. Conclusions

NAC is the antidote for paracetamol induced ALF, and is related to an amelioration of the outcome/ survival, which is more evident when started sooner. For non-paracetamol induced ALF, and in adult population, most centers use it with the same doses as for paracetamol induced ALF, being related to a better outcome specially within a subset of patients with HE grades I-II. In the pediatric population, recent evidence of NAC use in non-paracetamol induced ALF, seems to jeopardize the outcome, particularly in those with less than 2 years old. So, more studies shall be conducted before a definitive statement concerning indiscriminate NAC use in the pediatric population is done.

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Is penicillin and/or silibinin the best approach for mushroom poisoning?

Claire Francoz

Liver Intensive Care Unit and Transplantation, Hepatology, Hôpital Beaujon, Clichy, France

1. Mushroom poisoning: epidemiology, pathophysiology

Of the more than 5000 species of mushrooms, only 50 are poisonous genus. *Amanita* species are the most common toxic mushrooms and poisoning due to A. *phalloides* predominates in Europe countries. These mushrooms grow from late summer to early winter in geographic areas with temperate climate and are found on the ground below trees or in grass, near to trees. They are characterized by a white cap, closed white gills, a white stalk enlarging to a basal bulb and a membranous volva.

Amanita species contain three main groups of toxins: amatoxins, phallotoxins and virotoxins. Amatoxin is the most dangerous. It is heat stable and not destroyed by cooking, neither destroyed by freezing or drying, and eventually remains toxic after prolonged periods of storage. Amatoxins are rapidly absorbed after ingestion and are characterized by enterohepatic recycling. In chronological order, there principal targets are the intestinal mucosa, liver cells and proximal tubules of the kidney.

2. Manifestations and prognosis

Amanita poisoning usually occurs during fall and early winter. It is most frequently an accidental intoxication and several family members who shared a meal are simultaneously intoxicated. Occasionally, voluntary intoxication in an attempt to commit suicide can occur.

After an asymptomatic period of 6 to 12 hours following ingestion, initial manifestations consist in violent abdominal pain, vomiting and profuse cholera-like watery diarrhea. This stage frequently results in hypovolemia and hypotension within a few hours. It is usually associated with a first peak of serum aminotransferases of 10 times the upper limit and renal dysfunction that results from hypovolemia. Diarrhea persists for at least 2 days but is often more prolonged. In the second stage, corresponding to the toxic effect of amatoxin 24 to 48 hours after ingestion, there is a marked increase (or reelevation) in serum aminotransferases, usually above 100 times of upper limit, with AST greater than ALT. Serum bilirubin level is usually normal or mildly increased. Coagulation are markedly decreased (prothrombin index and factor V), reflecting a profound alteration in liver function but which can also result from disseminated intravascular coagulation. In the most severe forms, there are often high arterial lactates level, metabolic acidosis, hyperammonemia and hypophosphoremia. Hemodynamic instability, due to initial vascular collapse and also to acute liver failure, is frequent. At this stage, renal dysfunction is quite constant and results both in hypovolemia but also in direct amatoxin toxicity. Encephalopathy and brain edema occur at the later stages and are associated with an especially poor prognosis unless emergency liver transplantation is performed. There are some peculiarities with respect to encephalopathy in the setting of mushroom poisoning. First, a minority of patients develop very rapidly irreversible shock without developing encephalopathy. Second, in most cases, once encephalopathy occurs, the progression to multiorgan failure is especially rapid and patients often die before liver transplantation. Third, some patients may occasionally recover after a transient period of encephalopathy.

Approximately 10 to 30% of patients die or need emergency liver transplantation after amanita poisoning. In patients with amanita poisoning, Clichy's and King's College criteria for deciding emergency liver transplantation criteria have a poorer accuracy than in other causes of acute liver failure. Specific criteria for mushrooms poisoning recently proposed by Ganzert (association of prothrombin index below 25% of normal and increase in serum creatinine over 106 µmol/L from day 3 after ingestion) are attractive. In a multicenter study, we found that the association of an interval less than 8 hours between ingestion of the mushrooms and the onset of diarrhea, a decrease in the prothrombin index below 10% of normal 4 days or more after ingestion and female sex is quite always associated fatal outcome.

3. Management

3.1. General management

All patients with *A. phalloides* poisoning should be promptly referred to a specialized unit with access to liver transplantation. The initial phase consists in fluid resuscitation to prevent vascular collapse, ischemic liver injury and prerenal azotemia. Any potentially nephrotoxic, hepatotoxic or neurologic agents (including domperidone) should be avoided. Systematic gastric lavage is only useful within the first hour after ingestion. There is no evidence that oral administration of activated charcoal limits toxicity. In the second phase, the management is similar to any acute liver failure. Renal replacement therapy is frequently required due frequent metabolic acidosis and hemodynamic instability.

3.2. Specific treatments

In experimental models, the only treatments suggesting a protective effect are **β-lactam antibiotics** and

silibinin. Silibinin is the major component of silymarin, a standardized extract of the milk thistle seeds and it has been considered as the best antidote. However, evidence for its efficacy remains weak in the literature. Indeed, only small uncontrolled series including patients with various stages of amanita poisoning have been published. Even if silibinin has an excellent safety profile, it seems doubtful that any significant benefit can be expected in the case of acute liver failure. Other agents such as thioacetic acid, L-ascorbic acid or cimetidine have been proposed but are definitely not effective.

N-acetylcysteine (NAC) is widely used in patients with acute liver failure including those with nonacetaminophen causes. NAC improves transplant-free survival in nonacetaminophen acute liver failure and coma grade 1 to 2 and, although these results did not focus on *A. phalloides* poisoning, the systematic administration of NAC should be recommended.

Extracorporeal detoxification. Amatoxins are small and easy dialyzed molecules and theoretically, hemodialysis or hemofiltration could be helpful. However, the benefit of these devices is limited since circulating amatoxins are only detectable in the blood within the first 24 hours following ingestion of mushrooms. There is no evidence that hemoperfusion across charcoal cartridges is superior to conventional filtration. More recently, case reports and small series have suggesting that MARS (Molecular Adsorbent Recirculating System) may be effective in mushroom poisoning. However, no controlled studies have been published and past experience shows that a majority of patients survive without any extracorporeal support. Finally, rather than removal amatoxins and limiting the extent of liver damage, detoxification systems should be viewed as a means for correcting the consequences of *A. phalloides* intoxication.

Liver transplantation. Emergency liver transplantation is the only option in patients who develop fulminant liver failure. In the absence of large series, it remains difficult to establish clear-cut criteria for deciding on emergency liver transplantation. Noteworthy, once patients develop encephalopathy, a key prognostic variable according to usual Clichy's and the King's College criteria, there is a very little time left for bridging them to transplantation. Ganzert's criteria (prothrombin index below 25% of normal and serum creatinine over 106 µmol/L from day 3 after ingestion onwards) may be used but we found in a retrospective study that these criteria are less accurate than King's College criteria. Practical guidelines for deciding emergency liver transplantation are the following: (1) at admission, strongly consider that liver transplantation may be necessary if the interval between ingestion and the onset of diarrhea is under 8 hours (the need for transplantation is unlikely if this interval exceeds 8 hours) and (2) post admission, list for emergency transplantation if the King's College are met and/or the prothrombin index is below 10% (INR over 6) 4 days or more after admission, independently of encephalopathy.

4. Conclusions

Patients with acute liver failure following *A. phalloides* intoxication have a high mortality rate. There is no clear evidence that any pharmacological agent or any extracorporeal detoxification system can help to prevent the extent of liver cell necrosis. The management essentially relies on symptomatic care and the prevention of precipitating factors. Emergency liver transplantation is the only option in patients who develop encephalopathy and/or multiorgan failure. Education about mushrooms characteristics and toxicity is needed to prevent accidental ingestion.

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Nucleo(s)tide analogues for the treatment of ALF due to acute hepatitis B: is there a role?

Rodrigo Liberal

Institute of Liver Studies, King's College London School of Medicine at King's College Hospital, London, UK

rodrigo.liberal@kcl.ac.uk

Hepatitis B virus (HBV) infection is a major global health problem. It is estimated that over 2 billion people have been infected worldwide; of these more than 350 million are chronic hepatitis B surface antigen (HBsAg) carriers [1, 2], indicating that more than 80% of patients spontaneously clear the HBsAg. Rates of clearance increase to higher than 90% figure in those patients who present with clinical evident acute hepatitis [3].

Due to implementation of routine vaccination, most countries have seen a decrease in the incidence of acute hepatitis B [4, 5]. However, there are still some patients who may progress to HBV-related fulminant liver failure [6]. Acute hepatitis B is the most predominant viral cause of acute liver failure in Western countries [7, 8], accounting for 7 to 10% of reported cases of ALF in Europe and for 7% in North America [9, 10].

In a study from Japan, Sato et al identified, between 2007 and 2008, 890 cases of acute hepatitis B among 5.85 million inpatients in a nationwide database; of all cases, 6% (n=53) developed fulminant hepatitis and 4% (n=36) died [11]. A retrospective study from Spain reported 2160 cases of hospitalized patients diagnosed with acute hepatitis B, of which over than 70% of cases were diagnosed in males; the highest rate corresponded to the group aged 20-39 years [12]. Of the 2160 cases, 4% (n=90) died; this rate was 1% in those without fulminant hepatitis and over 50% among the 53 patients who presented with fulminant hepatitis [12]. Taken together, these studies suggest that there could well be a good reason to treat acute hepatitis B.

A multicentre case series of 37 patients treated with lamivudine for severe acute or fulminant hepatitis B and reported that 80 % of the patients survived with full recovery without liver transplantation [13]. None of the patients showed an adverse event. Three patients requiring transplantation despite lamivudine therapy had more advanced disease on admission, of whom one had taken paracetamol while another was already HBV-DNA negative on admission [13]. One year later, Kumar et al reported the results of a randomised clinical trial which aimed to evaluate the efficacy of lamivudine in patients with acute severe hepatitis B. At week 4, HBV DNA levels were significantly lower in lamivudine-treated group compared to the placebo group [14]. In both studies, severe acute hepatitis B was defined by the presence of at least two of the following three parameters: bilirubin levels equal or higher than 10 mg/dL, international normalised ration (INR) equal or above 1.6 or the presence of hepatic encephalopathy [13, 14]. Several other studies have confirmed very high survival rates in patients receiving lamivudine [15, 16], while the outcome without antiviral therapy has remained very poor [17]. Of note, most patients who died or required liver transplantation despite the treatment with lamivudine were started on antiviral therapy at later stages of the disease compared with those patients who have survived. Thus, prompt and timely antiviral therapy seems to be crucial. Whether or not other antivirals are also beneficial in the setting of acute liver failure due to hepatitis B remains to be fully addressed. Nevertheless, a small number of reports have demonstrated the efficacy and safety profile of entecavir in the setting of fulminant hepatitis due to acute hepatitis B [18, 19].

In conclusion, antiviral treatment for patients with acute liver failure due to hepatitis B seems to improve survival, particularly when started before the development of advanced stages of disease. Based on these data, the European Association for the Study of the Liver (EASL) guidelines published in 2012 support their use in the treatment of HBV acute severe or fulminant hepat. [20].

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Other therapeutic approaches

Artificial liver support: When to start, how to use, when to stop

Anibal Marinho

Serviço de Cuidados Intensivos / Centro Hospitalar do Porto

Introduction:

Liver failure constitutes a life-threatening condition which, in most cases, can only be treated by performing a liver transplant.

In the course of liver failure, water-soluble toxins (e.g. ammonia, mercaptans) and albumin-bound toxins (e.g. bilirrubin, bile acids, aromatic amino acids, and fatty acids) may accumulate and cause encephalopathy and multiple organ dysfunction/failure. Most of these compounds related to detoxification field of the liver can be addressed by artificial devices similar to dialysis machines (artificial systems, detoxification devices)

Why Liver Support and not Liver Replacement Therapy?

The biological complexity of the liver is immense and many of the specific processes involved with this organ's multiple functions are not yet fully understood. The liver performs multiple metabolic functions ranging from protein synthesis to gluconeogenesis, metabolism of amino acids, lipids and urea, and the detoxification of drugs and by-products of intermediate metabolism. The liver also acts in the regulation of the immune system and the metabolism of many hormones. While the field of detoxification and partially also of regulation can be addressed by artificial devices, the synthetic function of the liver can only be provided by living cells, usually after a liver transplant.

Most studies until now have focused on improving survival rates; however these devices do not act as liver replacement therapy but only as a bridge to liver transplant. In a renal replacement therapy, renal function is almost substituted by dialysis, so we can show by using various techniques (increased renal dose or prolonging period of dialysis) if these different techniques may improve or not the survival rates of the patients with renal failure.

In patients with liver failure, the most important factor for survival is liver transplant. Artificial liver support devices only delay the time to find a liver donor and improve the condition of the patient until the transplant. So we must not focus on improving survival rates but instead attempt to prove that with these devices we gain time for liver transplant, while a better control of the fluid balance, an improvement in renal function and the encephalopathy can allow for the patient to arrive in the operating theatre in a better condition for a transplant. The key factor for survival is not the liver support technique but period of time to find a suitable donor and the success of the operation. The RELIEF trial - the largest trial to date involving the use of extracorporeal liver support - show that MARS therapy, is a safe procedure, which has significant dialysis effect and improves severe hepatic encephalopathy in patients with cirrhosis and rapid deterioration of their liver function.

When to Start?

Particular areas of uncertainty remain in the timing, mode, intensity and duration of extracorporeal liver support therapy. In the Hellios study, the time elapsed between the precipitating event and the start of treatment had no relationship with treatment outcome.

In the same study, the subgroup of patients with MELD score > 30 had the greatest benefits when using these devices. However, the decision to start liver support should depend not only on the MELD Score but also on the severity of this complex illness. Elevated serum bilirrubin, difficulty in controlling fluid balance and multiple organ failure are also important markers that should be taken into account when making a decision to start liver support.

How to use?

Support systems designed to treat patients with liver failure fall into two main categories, non-cell-based systems, including plasmapheresis, albumin dialysis, and charcoal-based hemadsorption, and systems that incorporate living hepatocytes or hepatic tissue, also known as bioartificial liver support systems.

A systematic review that pooled 12 randomized controlled trials (with a total of 483 patients) using various bioartificial support systems concluded that overall they had no significant effect on mortality compared with standard medical therapy.

Fundamentally we only use non-cell-based systems - MARS and Prometheus – two sophisticated detoxification systems, taking into account the elimination of lipophilic, albumin bound toxins. The two main resulting concepts are albumin dialysis (MARS) and fractionated plasma separation (Prometheus).

Use of these devices is dependent on the severity and progression of the illness but most of the time they are only used for a short period, up to two weeks. Is usually performed once daily for 6 – 8h.

Some studies demonstrates that the reduction ratio for ammonia is clearly lower than for urea (40 vs. 59%), despite comparable clearance (141 vs. 147 mL/min). A higher generation rate in combination with rapid

refilling from the extravascular compartments could explain this phenomenon. Sometimes we extended the Prometheus technique only with SLED which allows a higher ammonia removal associated with a better control of fluid balance.

An important aspect of the Hellios study is that it showed no differences in the number of patients who developed complications that could potentially arise from the application of extracorporeal Prometheus therapy, such as bleeding or infections. This is especially worth to note since extracorporeal therapies are sometimes regarded as risky in patients with liver failure because these patients have frequently a weakened immune system and a high bleeding risk.

When to stop?

As mentioned previously, the key factor for survival is not the liver support technique but period of time to find a suitable donor and the success of the operation. A prolonged period of time to find a suitable donor associated a rapid deterioration of multiple organ failure, can lead to consider this technique as a futile act and inevitably lead to its suspension.

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Systemic repercussion

Cerebral edema: monitoring strategies and general treatment considerations

Javier Fernandez

Chief of Liver Intensive Unit Care, Hospital Clinic, Barcelona, Spain

Acute liver failure is a disorder that can deteriorate multiple organs and systems. It is characterized by the development of liver dysfunction, coagulopathy and encephalopathy. Cerebral edema and intracranial hypertension is a potential life-threatening complication observed in patients with grade III/IV encephalopathy that can lead to fatal herniation. Recent data show that intracranial hypertension is less frequent than previously described (20-30%) probably as consequence of earlier illness recognition, improved ICU care, and use of emergency liver transplantation. The pathogenesis of brain swelling remains controversial. Ammonia plays a pivotal role in the development of cytotoxic brain edema. Its effects seem to be potentiated by the presence of systemic inflammation. Cerebral blood flow is disturbed and generally increased. Onset of encephalopathy and intracranial hypertension can be dramatic with rapid development of asterixis, delirium, hyperreflexia, seizures, extensor posturing and coma. The risk of brain edema and intracranial hypertension increases to 25-35% in grade III hepatic encephalopathy and up to 75% in those reaching grade IV, being the leading cause of death in these patients. Timely recognition and treatment of intracranial hypertension is therefore of paramount importance in the management of patients with advanced encephalopathy to increase their probability of survival until liver transplantation. In patients at risk of intracranial hypertension, insertion of an intracranial pressure-monitoring catheter may be considered to optimize treatment and interventions. Its insertion should be considered only in the subgroup of patients who have progressed to grade III/IV coma. Risk factors for developing intracranial hypertension are hyperacute or acute liver failure, systemic inflammation, hyponatremia, arterial ammonia >150 µmol/L, vasopressor support and presence of pupillary abnormalities. Transcranial doppler is used as a non-invasive alternative to estimate intracraneal pressure and cerebral blood flow, especially in patients with severe thrombocytopenia. Standard treatment measures such as sedation with propofol and osmotic agents (e.g., mannitol, hypertonic saline) are useful first-line interventions. Hyperventilation restores cerebral autoregulation but is only used to treat acute rises of intracranial pressure and for short periods. Barbiturate coma and intravenous indomethacin are options in refractory cases. Therapeutic hypothermia (core temperature: 32-34°C) can be an adjunct therapy in selected patients with uncontrolled intracranial hypertension. Albumin dialysis is used in some centers as a bridge to liver transplantation in patients at high risk of cerebral edema. This therapy decreases serum ammonia concentrations and ameliorates inflammatory response but has not demonstrated beneficial effects on survival.

Infection in the setting of ALF: from prophylaxis to treatment strategies

Richard Moreau [1,2,3,4]

1. Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris;

2. UMR_S 1149, Université Paris Diderot-Paris 7, Faculté de Médecine, Paris;

3. Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, AP-HP, Clichy;

4. Laboratoire d'Excellence (Labex) Inflamex, PRES Sorbonne Paris Cité, Paris; all in France.

Patients with acute liver failure (ALF) have increased susceptibility to infections, principally due to a multiple immune defect: a systemic anti-inflammatory profile, impairment in monocyte antigen presentation capabilities, defect in opsonic systems, impairment of neutrophil phagocytosis/intracellular killing functions; potential bacterial translocation and the need of invasive procedures [1]. Bacterial infections are documented in 50-90% of ALF and develop early (2-5 days) following admission [2]. Invasive fungal infections (predominantly candidiasis) are observed in 32% [3]. Pneumonia, bacteremia and urinary tract infection and accounts for 50%, 25%, and 20% of cases, respectively. The diagnosis of infection is challenging in ALF because a third of patients has no increased neutrophil count, fever or hypothermia. Infection is associated with a worsening of hepatic encephalopathy and intracranial hypertension, and a poorer outcome [4]. Systemic prophylactic antibiotics reduce the incidence of infection and increase the opportunity for liver transplantation [5]. Selective parenteral and enteral antisepsis regimens have no additive effect. Despite this prophylaxis or even use of pre-emptive treatment, the infection rate remains high (29-38%). Intensive care management and prophylactic strategies are responsible of the emergence of Gram-positive organisms and multi-resistant bacteria. Strict measures to reduce the development of in-hospital infection would contribute to improve outcome of patients with ALF.

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Coagulopathy in acute liver failure. Different from cirrhosis = different support?

Ton Lisman

Department of Surgery, Surgical Research Laboratory, University of Groningen, University Medical Center Groningen, The Netherlands.

Introduction

The liver plays a pivotal role in the hemostatic system. It synthesizes most pro- and anticoagulant proteins and a number of proteins involved in fibrinolysis. In addition, the liver synthesizes thrombopoeitin which is the hormone responsible for platelet production. Consequently, in patients with a compromised synthetic function of the liver, profound alterations in the hemostatic system occur. In patients with liver diseases, thrombocytopenia and platelet function defects and low levels of most hemostatic plasma proteins may occur. In addition, endothelial-cell derived proteins, such as the platelet adhesive protein von Willebrand factor (VWF) are elevated in liver disease. In addition to a reduced synthetic capacity of the liver, these hemostatic changes are caused by splenomegaly, clotting factor consumption, and chronic endothelial cell activation. Routine diagnostic tests of hemostasis, such as the platelet count, the prothrombin time (PT) and activated partial thromboplastin time (APTT) are frequently abnormal in patients with liver diseases and indicate a bleeding tendency. However, it has become clear that these widely used tests have no clinical relevance in patients with such complex hemostatic alterations as the patients with a liver disease. Using more modern laboratory tests of hemostasis combined with a reappraisal of the clinical manifestations as a consequence of altered hemostasis, it has been proposed that patients with chronic liver diseases are characterized by a 'rebalanced' hemostatic system. As a consequence of defects in both the pro- and antihemostatic pathways, the net effect of the hemostatic changes in patients with chronic liver diseases is a hemostatic system that remains in balance. This new hemostatic balance, however, is much more fragile as compared to the hemostatic balance in individuals with a healthy liver. This explains the occurrence of both bleeding and thrombotic episodes in patients with chronic liver diseases. The laboratory and clinical evidence of rebalanced hemostasis in patients with chronic liver diseases is summarized in recent review papers [1-3].

Bleeding and thrombosis in patients with acute liver failure

Although the hemostatic changes in different types of liver diseases are similar, they are certainly not identical. Traditionally, patients with acute liver failure (ALF) were perceived to have a more substantial bleeding risk compared to patients with cirrhosis. Indeed, bleeding was common in studies on patients with ALF presented in the 1970's [4]. At that time, around one-third of patients with acute liver failure died with bleeding as the proximate cause of death. In recent series, however, spontaneous and clinically significant bleeding is rare at around 5%, and bleeding very rarely results in death [5]. The reasons for this substantial reduction in bleeding are unclear, but it has to be noted that the intensive care management of patients with acute liver failure has revolutionarized since the 1970's. Similar to the situation in patients with cirrhosis, patients with ALF are not 'auto-anticoagulated'. Thrombotic complications may occur and include thrombosis of CVVH catheters, peripheral venous thrombosis, and portal vein thrombosis. In addition, intrahepatic thrombus formation may occur [6], which may contribute to the progression of the disease (see below). In a recent series of patients with ALF, thrombosis was more frequent than bleeding [7].

Rebalanced hemostasis in patients with acute liver failure

In contrast to patients with cirrhosis, patients with ALF have per definition a coagulopathy, since an INR>1.5 is part of the definition of the syndrome. The decrease in coagulation factor levels in acute liver failure is usually more severe as compared to the decrease in chronic liver diseases. One study has shown mean INR levels on admission of around 4 times normal, and almost 20% of patients had INRs above 5 times normal, which is exceptional in patients with chronic liver disease [8]. In contrast, patients with acute liver failure may have a normal platelet count, which is uncommon in advanced chronic liver failure. Finally, fibrinolytic capacity in patients with acute liver failure is poor, due to elevated levels of PAI-1 and substantially decreased plasminogen levels [9], which is in contrast to fibrinolysis in chronic liver disease which is normal or hyperactive [10].

Recent studies have addressed the consequences of the hemostatic changes in ALF using global tests of hemostasis. Two studies have used thromboelastography to assess the hemostatic status of patients with ALF and found balanced hemostasis in the majority of patients [7, 8]. Interestingly, a proportion of patients were even hypercoagulable using this test which contrasts with the elevated INR and decreased clotting factor levels observed using routine diagnostic tests. Similar to the situation is cirrhosis, the hemostatic balance in ALF remains intact as a result of a concomitant decline in both pro- and antihemostatic pathways. A similar conclusion was drawn in three studies using thrombin generation

assays [8-10]. Many global hemostatic tests such as the PT, APTT or even thrombin generation assays only test part of the hemostatic system. The PT and APTT are only sensitive for levels of procoagulant proteins, which makes these tests unsuitable to test the hemostatic status in patients with complex disorders of hemostasis. Thrombin generation tests are sensitive for some of the anticoagulant mechanisms, but do not take a vital anticoagulant mechanism (the protein C pathway) into account as initiation of this pathway proceeds on endothelial cells (which are of course not present in plasma). Modified thrombin generation tests in which activation of the protein C pathway was facilitated showed normal thrombin generation in patients with ALF. We recently also demonstrated that potential platelet defects in ALF are compensated for by an unbalance in the VWF/ADAMTS13 system. Von Willebrand factor (VWF) is a crucial protein in platelet recruitment to sites of vascular injury, and is present in highly elevated levels in both cirrhosis and ALF. Combined with a decrease in the VWF regulatory protein ADAMTS13, the high VWF levels compensate for platelet defects, as we demonstrated in in vitro models [11, 12]. Thus, the hemostatic status of patients with ALF appears in balance, despite elevated INR and decreased factor levels. Some aspects of the hemostatic system (hypofibrinolysis, VWF/ADAMTS13 unbalance) even suggest a hypercoagulable state.

Management of the coagulopathy of ALF

It has long been common practice to treat the coagulopathy of ALF, specifically by administering plasma to improve the INR. Although in some centers the amount of plasma administered to patients with ALF has decreased immensely, and there appears to be consensus that prophylactic correction of the PT/INR to avoid spontaneous bleeding in patients with ALI/ALF is not indicated [5], it is still common practice in many centers to try to correct the coagulopathy in these patients by infusion of plasma concentrates or recombinant factor VIIa prior to invasive procedures [13, 14]. Prohemostatic therapy is initiated based on the assumption that the prolonged PT/INR is indicative of a bleeding risk. However, as mentioned before, spontaneous bleeding in ALF is rare. Both clinical and laboratory evidence, suggest that hemostasis is preserved in patients with ALI/ALF due to the concomitant decrease of both pro- and antihemostatic drivers. Therefore, prohemostatic therapy should be cautiously used in patients with liver disease for a number of reasons. First, transfusion of blood products is associated with the risk of general transfusion reactions, some of which may even be higher in patients with liver disease [15]. Second, partial correction of the PT/INR requires transfusion of massive amounts of fresh frozen plasma, which carries a significant risk of volume overload, which may exacerbate intracranial hypertension. Third, administration of prohemostatic therapy might result in exacerbation of intrahepatic thrombus formation, which may result in a more rapid progression of the disease (see below). Fourth, whereas the INR is not useful in predicting bleeding in patients with ALI/ALF, it is a useful indicator of recovering or worsening liver function, and this indicator is obscured by administration of fresh frozen plasma or rFVIIa.

Intrahepatic thrombosis and progression of ALF

Animal studies and analyses of patient tissue has demonstrated the deposition of fibrin within the ALF liver [6, 16]. It has recently been shown that intrahepatic clot formation is likely initiated by tissue factor present on hepatocytes [17]. Tissue factor, the natural initiator of coagulation, is normally present in an 'encrypted' form on hepatocytes. This encrypted tissue factor is not capable of initiating coagulation. Acute liver failure, however, results in decryption of tissue factor resulting in massive intrahepatic activation of coagulation. Animal experiments have demonstrated that inhibition of coagulation by for example heparin not only decreases intrahepatic thrombus formation, bus also decreases progression of disease [16]. This indicates that intrahepatic activation of coagulation may be an active player in the progression of ALF, and may be a target for therapy. In patients with cirrhosis, a similar mechanism occurs [18], and it was recently demonstrated that anticoagulation with low molecular weight heparin delays disease progression in patients with cirrhosis [19]. Whether such interventions may be applicable to patients with ALF awaits further studies.

Conclusion

Our understanding of the coagulopathy of ALF has increased substantially in the past decade. In contrast to traditional concepts, patients with ALF appear to have a balanced hemostatic system and may have the bleeding diathesis suggested by the elevated INR. Conservative management of the coagulopathy of liver disease is indicated as correction of the elevated INR likely does not reduce bleeding. Administration of plasma may be harmful and obscures a critical indicator of spontaneous recovery and prognosis. Patients with ALF may even be hypercoagulable, and evidence from experimental animal models suggests that intrahepatic coagulation contributes to disease progression. Many of the aspects of hemostasis in patients with cirrhosis are also true for patients with ALF.

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Liver transplantation

Acute Liver Failure. When to list: different etiologies, different timings? Shall we use incompatible donors?

Sofia Ferreira

Hepatic and Pancreatic Transplantation Unit, Centro Hospitalar do Porto, Hospital Sto António, Porto, Portugal

Acute liver failure (ALF) is a clinical syndrome with very high mortality. Wlodzimirow et al, revised 103 studies and observed that they used 41 different definitions of ALF [1]. Four components are constant but also accounted for the differences: presence and/or grading of hepatic encephalopathy (HE); the interval between onset of disease and occurrence of HE; presence of coagulopathy and pre-existing liver disease. Despite various definitions in the literature, the occurrence of HE during the course of the disease appears to be a landmark of a critical progression. Therefore, early prediction of HE is essential for guiding the correct moment of referral to a specialized center. Takikawa et al described a model which includes bilirubin, PT, age and etiology, that can predict with high sensitivity (although low specificity) the occurrence of HE in patients with severe acute hepatitis unrelated to paracetamol [2].

Once ALF is installed, anticipating the natural prognosis of a patient is one of the most challenging tasks in hepatology critical care [3], leading to the identification of those patients that will survive without liver transplant, and those who must be transplanted or die. There are four key determinants of the prognosis of acute liver failure: etiology, rate of progression of the disease, age of the patient, laboratory markers of disease severity [4]. The highest rate of spontaneous survival is seen in patients with hyperacute liver failure, greatest derangement of coagulation and highest incidence of cerebral edema. The worst survival is seen in patients with sub-acute liver failure with modest derangement of coagulation parameters and relatively little risk of cerebral edema [5].

There are some prognostic models that can assist in the decision of when and in whom to proceed to a liver transplant. However, it never substitutes an experimented clinical judgment by the multidisciplinary transplant team. An ideal score should be simple, objective, multiphasic, dynamic, sensitive, specific, adjusted to the improved spontaneous survival rates and avoid futile transplantation. There is not such a perfect instrument.

The most used and studied scores are the Kings College Criteria (KCC) [6] and the Clichy Criteria for viral etiology [7]. There are several others scores that can be helpful, some of them developed for use in different contexts, like MELD [8], SOFA [9] and APACHE II [10].

Kings College Criteria

Paracetamol-induced ALF
Arterial pH <7.30 after fluid resuscitation
OR all of the following features:
Prothrombin time >100 s (international normalized ratio >6.5)
Serum creatinine >259 µmol/l (3.4 mg/dl)
Grade 3 or 4 hepatic encephalopathy
Non-paracetamol-induced ALF
Prothrombin time >100 s (international normalized ratio >6.5)
OR any three of the following features:
Non-A, non-B viral hepatitis, drug-induced or indeterminate etiology of ALF
Time from jaundice to hepatic encephalopathy >7 days
Age <10 years, or >40 years
Prothrombin time >50 s (international normalized ratio >3.5)
Serum bilirubin >297.6 µmol/l (17.4 mg/dl)

Clichy Criteria

Grade 3 or 4 encephalopathy AND	Age < 30 years and Factor V< 20%
	Age >30 years and factor V< 30%

None of the scores has simultaneously high sensitivity and specificity. Giving primacy to sensitivity, favors the individual, but with the risk of an "unnecessary" liver transplant, subjecting the patient to major surgery, lifetime immunosuppression and a graft is lost that could be used in another patient. On the other hand, giving primacy to specificity, could lead to fail the identification of a patient that is going to die without transplantation, "protecting" as result the pool of organs.

The KCC in non-paracetamol-induced ALF has 80-90% specificity and 60-70% sensitivity. KCC perform best in groups with high grade encephalopathy and in historically earlier studies, suggesting that modern medical management of ALF may modify performance of KCC [11].

Cholongitas et al compared the performance of different scores in paracetamol- induced ALF. The authors observed that the KCC criteria had the highest specificity (83%) but the lowest sensitivity (47%), and the SOFA score had the best discriminative ability [9]. They concluded that for patients with paracetamol-

induced ALF, the SOFA score performed better than the other prognostic scores, and this reflected the presence of multiorgan dysfunction. The authors also found that lactate level was significantly associated with the SOFA score. In paracetamol-induced ALF, a severe acidosis that does not correct after fluid resuscitation, is an indication to proceed to transplant, even in the absence of encephalopathy [6].

It should be reminded that the KCC was not formulated as a static model but as a dynamic one, with serial determinations, to alert clinicians to the potential for deterioration.

The decision to proceed to an emergency liver transplant should also consider the post- transplant results, in order to avoid a futile treatment. *Barshes* et al identified four risk factors at the time of listing: age superior to 50 years, body mass index≥ 30kg/ m2, history of life support and serum creatinine >2mg/dl [12]. The low- risk group has a 5-year survival of 81%, and the high-risk group a 5-year survival of 42%. The graft characteristics also impacts post-transplant survival. Factors with equivalent level of increased risk are donor age > 60 years, non-ABO compatibility, steatosis and non- whole organs [13]. *Germani et al* reported a 57% mortality or graft loss at 1 year if matched a recipient > 50 years with a donor > 60 years [14].

In Europe, nearly 2/3 of liver transplants for ALF were performed using an identical donor/recipient ABO group match, whereas an incompatible ABO matching was used between 1.7% and 7.3% of cases. The mortality or graft loss in incompatible ABO matching is 61% at 1 year and if the donor is > 60 years and the recipient is male, mortality or graft loss at 1 year is 80% [14]. In more recent years, more aggressive immunosupression protocols, use of plasmapheresis, splenectomy, rituximab and basiliximab, in different combinations according to the center, has led to improved incompatible graft and patient survivals [15, 16]. There will always be situations in which the severity of the patient will justify the use of an ABO incompatible graft but, it really should be avoided to sum of other adverse factors.

Conclusion: Acute liver failure is still a dramatic clinical entity. Spontaneous survival is improving as are post-transplant results. Etiology is determinant in clinical evolution and prognosis. Considering emergency liver transplant is a crucial component in the care of these patients, but the timing to list is a quite difficult task. A dynamic clinical evaluation with the indispensable help of prognostic scores is the more important tool assisting this decision. In some severe and occasional cases, ABO- incompatible graft can be an option, with the use of aggressive immunosuppression protocols, according to each center.

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In selective indications some patients with acute liver failure requiring liver transplantation can be successfully treated by auxiliary orthotopic liver transplantation.

Jacques Belghiti and Safi Dokmak

Hospital Beaujon, Paris, France; University Paris 7.

The main causes of acute liver failure (ALF) leading to consideration of patients for liver transplantation (LT) are drug- or toxin-induced hepatic injury including. In the majority of cases, patients who were previously healthy can recover without liver parenchymal sequelae. Severe forms progress to multisystem failure including cerebral oedema, which can cause death within a few hours or a few days. In this situation, LT is the only effective treatment that can substitute metabolic and excretory function of the liver. LT is indicated when severe encephalopathy (confusion or coma) is associated with an important decrease of the coagulation factors (factor V < 20%). LT is an established treatment for ALF. Nevertheless, a significant minority of patients with ALF who fulfill transplant criteria would have had complete morphological and functional recovery of their liver if they had not undergone LT. These considerations have led to the concept of auxiliary liver transplantation, which does not exclude the potential for spontaneous regeneration of the native liver and eventual withdrawal of immunosuppressive drugs. Auxiliary liver transplantation consists of implanting a healthy liver graft placed orthotopically while leaving a part of the native liver. The greater experience with partial grafts and the favorable outcome reported in some European series using auxiliary partial orthotopic liver transplantation (APOLT), have revived interest in this approach.

APOLT requires that both the graft and the recipient's liver being reduced. Size reductions are performed on opposite sites (removing right segments of the recipient's liver and left segments of the graft or exceptionally the other way round) so that after transplantation, the patient has an approximately normal overall liver volume. The surgical procedure consists of three main steps. In the recipient procedure, a frozen section biopsy of the native liver is performed eliminating the presence of fibrosis (that would otherwise suggest that poor regeneration of the native liver is expected) and the presence of viable hepatocytes. A right hepatectomy of the native liver is performed in order to prepare a space large enough to accept a right graft. The parenchymal transection step tends to be easier and bloodless in patients with fulminant liver failure. Meanwhile, another team reduces the donor liver to a size compatible with its implantation beside the partially resected native liver. Two types of auxiliary grafts can be used to perform APOLT: a right liver (segments 5–8) or a left liver (segments 1–4). It is possible to use a right graft from a living donor. Orthotopic donor liver implantation is performed included orthotopically. The right graft is placed in the right hypochondrium so that both cut surfaces of the graft and of the native liver are face-to-face. The caval anastomosis is a large end-to-side caval anastomosis between the suprahepatic stump of the graft's inferior vena cava (IVC) and the recipient's vena cava. The portal vein anastomosis is performed on the right side of the PV just above the head of the pancreas. An end-to-side is performed between the graft's and the recipient's portal vein. The graft is subsequently revascularised and haemostasis is completed on the cut surface of the graft. The graft's coeliac axis is anastomosed end-to-side to the infra-renal aorta. Due to the high risk of biliary fistula we have abandoned Roux-en-Y hepatico-jejunostomy and bile flow is restored through a end to end biliary anastomosis with the cystic duct or end to side with the recipient common bile duct. Intra-operative ultrasound is mandatory to assess the patency of all vascular anastomoses. The right subphrenic space is usually drained. We have recently showed that this challenging procedure can become a routine procedure using a right graft drained by a large caval anastomosis perfused by end to side portal anastomosis and with an arterial flow on the aorta. More important the biliary drainage should avoid bilio-enteric anastomosis in order to reduce dramatically the risk of biliary fistula. The occurrence of stenosis could be stented though endoscopic approach.

Because patients with APOLT are at increased risk, we believe that this procedure should not be performed earlier than standard OLT (i.e. should be indicated using the same criteria as those in use for conventional OLT). Best candidates are young patients aged < 50 years, without evidence of chronic liver disease and without severe haemodynamic instability. In addition, because the amount of hepatocytes provided with this technique is lower than could be anticipated using the standard technique, only ABO-compatible, non-steatotic grafts harvested from young donors with normal liver function tests should be used.

Conventional immunosuppression is started peroperatively. After discharge of the patient, the graft is monitored by computed tomography (CT), hepatobiliary scintigraphy and, when necessary liver biopsy. When, on the basis of histological, scintigraphical and morphological data, there is evidence of sufficient regeneration of the native liver, immunosuppression can be discontinued progressively aiming to induce progressing chronic rejection with subsequent atrophy of the graft.

Special anesthetic difficulties during liver transplantation for Acute Liver Failure

Simão Esteves

Serviço de Anestesiologia, Liver Transplant Team, Centro Hospitalar do Porto, Hospital Sto António, Porto, Portugal

Introduction

Acute liver failure (ALF) is a relatively rare condition associated with a rapid deterioration of liver function which is characterized by the presence of coagulopathy (INR<1.5) and any degree of encephalopathy, occurring within 26 weeks of onset of the symptoms, in patients without previous history of hepatic disease. Patients with Wilson's disease, autoimmune hepatitis or vertically acquired Virus B hepatitis diagnosed within the previous 26 weeks and the described clinical picture, will be also considered as having acute liver failure.

Acute liver failure will be classified as hyperacute if symptoms appeared less than 7 days before, acute if symptoms appeared between 7 and 21 days and subacute or subfulminant if symptoms appeared between 21 days and 26 weeks.

As an infrequent clinical condition with several grades of severity, guidelines for ALF management are usually not based in randomized clinical trials but on expert opinions that reflect revision of the published literature and personal opinions. Most of this literature is based on description of management of small series of patients usually from a single centre. Regarding the anesthetic management of patients with ALF submitted to liver transplantation literature is even scarcer.

Since the beginning of our liver transplant program in 1996 we had 43 liver transplants (LT) in patients with acute liver failure which represents 4.5% of total transplants.

Our most prevalent causes for ALF were autoimmune hepatitis (11 cases), toxic/drug hepatitis (10 cases) and Wilson's disease (8 cases). Patients with diagnosis of ALF should be early transferred to a liver transplant centre, to begin specific therapy, to exclude possible contraindications and to evaluate the opportunity to list patients for liver transplantation.

Most of patients with ALF, at least at more advanced stages, should be treated in intensive care environment as this condition has many similarities with multiple organ failure, and this level of care must be seen as a window of opportunity to those patients while waiting for liver transplantation or spontaneous recovery.

Management of ALF and liver transplantation

Liver transplant is typically different in acute and chronic indications. In ALF, portal hypertension is not usually present and so hepatectomy is relatively easier. Hemorrhage during dissection of the liver, in the absence of portal hypertension, tends to be minimal, but the presence of clinically important coagulation disorders may contribute to increased blood loss. On the other hand, previous hemodynamic instability associated with normal portal circulation may turn caval clamping in a challenge with reduced venous return and reduced cardiac output aggravating hemodynamic instability. This phenomenon could be partially reduced if preserving receptor caval technique (piggyback) is adopted by surgical team, allowing for some inferior vena cava flow return to the heart or by the use of veno-venous by-pass.

Early mortality in liver transplant for ALF is higher than in chronic liver diseases. The severity of the clinical situation on the moment of transplant with the presence of SIRS, sepsis and even multiple organ failure certainly contributes for these poor results. The urgency of the situation makes acceptance of "marginal" and incompatible livers more likely and this can also account for poor outcome. It could also happen that undiagnosed neurologic irreversible damage contributes to mortality.

In addition to specific therapies dependent on the etiology of acute liver failure, there are some common management principles to all patients that must be taken, and discontinuation of all non-essential medications, especially if etiology is unknown, is one of them as they may be the cause acute liver failure.

The anesthetic care during liver transplantation should be an adapted extension of care provided in ICU. As previously referred, there is limited experience of anesthesia for these patients and so management is based on personal "expertise". Patients can be presented for transplantation in unpredictable clinical condition; from the less serious to the extremely ill patient. Fortunately, most of those patients are relatively young and previously healthy, because frequently is not possible to make the usual workup of pre-transplant evaluation and patients are submitted to liver transplantation without clear and sufficient information about their previous clinical status.

The main differences between patients submitted to liver transplant for ALF and "chronic" indications are related with the clinical situation of the patient on the moment of transplantation. Patients may be presented in the operating room (OR) in different conditions some of them not usually present in chronic indications.

Airway and ventilation

- Airway management in liver transplant should always be regarded as a potential problem because of associated risk of regurgitation and aspiration. As those patients frequently went to transplant already intubated and ventilated these potential risk is usually not present.
- On the other hand, previous long ventilation periods may be associated with pulmonary infection and other respiratory problems that may difficult or aggravate oxygenation during surgery.
- Protective ventilation strategies using low tidal volumes, PEEP and recruiting maneuvers should be adopted, something that is also common to other indications for LT

Cardiocirculatory status

- Hemodynamic disturbances are very common in patients with ALF. Although most of the times young and previously healthy, patients with ALF usually suffer from hemodynamic abnormalities that resembles sepsis with high cardiac output a low systemic vascular resistance. As this hemodynamic profile is also common in LT for chronic liver disease we usually use the same kind of approach in acute and chronic indications for LT.
- PiCCO is used as the standard hemodynamic monitor. We gave special attention to parameters that can guide fluid management, pulmonary function and cardiac function.
- Maintenance of an adequate hemodynamic status is crucial, especially in patients with intracranial hypertension and renal dysfunction. Patients may need adequate fluid replacement that is usually done with normal saline.
- If, even with adequate intravascular volume, patients remain hemodynamically instable, inotropic and pressor support should be given. The most common given drug for this purpose is noradrenalin, but in cases of refractory hypotension vasopressin (or vasopressin analogues) could be administered.
- In cases of severe hypotension refractory to amines and vasopressin the hypothesis of adrenal failure (absolute or relative) should be addressed and supraphysiological doses of hydrocortisone administered.

Infection/Sepsis

- Sepsis, whatever is origin, is one of the main causes of death in patients with ALF.
- Respiratory, urinary and catheter-associated infection should be actively monitored and treated while waiting for transplantation. Although prophylactic antibiotics have not shown to improve outcomes, cultures should be performed regularly and treatment promptly initiated if any suspicion of infection.
- In the absence of previous antibiotic treatment standard antibiotic prophylaxis is administered.

Neurological status

- Hepatic encephalopathy (HE) is a diagnostic criterion for ALF and special care must be addressed to treat this situation in order to prevent cerebral edema and impaired cerebral circulation, which may contraindicate liver transplantation.
- Pathogenesis is multifactorial, osmotic disturbances mediated by ammonia and impairment of blood-brain barrier that leads to loss of auto-regulation of cerebral blood flow are among the major causes.
- As encephalopathy progresses patients must be submitted to endotracheal intubation and controlled ventilation in order to maintain normal or slightly reduced PaCO2 and most of patients will be presented in OR in this situation.
- There is a lot of controversy about monitoring intracranial pressure (ICP) in patients with encephalopathy grade 3 or 4, with people arguing that it is not possible to control ICP without knowing it, and others saying that monitoring ICP will put the patients on an inacceptable risk of cerebral bleeding. Anyway, if the ICP is not monitored one must be aware of subtle neurologic alterations and repeated cerebral CAT scanning may be necessary before taking patients to OR, in order to prevent futile transplants.
- If intracranial hypertension is diagnosed mannitol boluses may be used as 1st line therapy in conjunction with short periods of hyperventilation.
- Induction of moderate hypernatremia (145-155 mEq/L) with administration of hypertonic saline may also help to control elevated ICP.
- Reduction of cerebral metabolism promoted by barbiturate or propofol infusion and or moderate hypothermia, may be considered as a bridge to transplantation in patients with refractory elevated ICP and should be maintained during LT.

- During liver transplantation ICP should be closed monitored. If patients had no ICP monitor, additional intraoperative neurological monitoring should be instituted. Cerebral oximetry with INVOS monitor or oxygen saturation of jugular bulb can be added to our standard approach with BIS monitoring, in order to detect and treat further cerebral flow reductions.

Coagulation disturbances

- INR > 1.5 is one of the diagnostic keys of ALF. Traditionally ALF had been seen as a condition associated with severe coagulation disorders and bleeding tendency secondary to impaired synthesis of coagulation factors by the liver.
- The fact is that although there is reduced synthesis of procoagulant factors there is also reduced synthesis of anticoagulant and fibrinolytic factors, reduced clearance of activated factors and distinct function and amounts of platelets, which makes ALF a complex coagulopathy disease.
- Recent studies with thromboelastography, thrombin generation tests and clot lysis assays showed that there is probably a rebalance of coagulation in ALF that promotes equilibrium between coagulation and anticoagulation and makes hemorrhage less common that would be expected by standard coagulation tests.
- These data are supported by the fact that clinical observations show low bleeding rates and the assumption that replacement therapy must only be done in the presence of spontaneous hemorrhage or prior to some invasive procedures.
- During LT use thromboelastography (TEG) or thromboelastometry (ROTEM) should be used to guide coagulation therapy. These monitors provide diagnostic clues for factors deficiency, platelets deficits or dysfunction and fibrinolysis, making oriented component therapy more accurate.
- On the absence of such information correction should not be provided to treat isolated abnormal classical coagulation tests. Administration of plasma, platelets, factor concentrates or antifibrinolytic drugs should be guided by a comprehensive approach between anesthesiologist and surgeon, relating abnormal tests with the presence of hemorrhage not surgery related – oozing and absence of clot formation.

Metabolic dysfunction

- Hypoglycemia is the most common metabolic disturbance but phosphorus, magnesium and potassium deficits could also be present and may require supplementation.

Clinical Cases

Clinical Case | 1

Diana Valadares

Intensive and Intermediate Care Unit, Centro Hospitalar do Porto, Hospital Santo António, Porto, Portugal

Introduction (patient information and chief complaint): 48-year-old woman, lawyer, single, caucasian presents to the hospital complaining of jaundice.

History of present illness: She began with jaundice 10 days previously to hospital admission and malaise, without abdominal pain, acholic stools or pruritus. 3 months earlier she refers inflammatory arthralgia (hands, shoulders and knees) without arthritis or weight loss. She took ibuprofen (600mg/day) and paracetamol (3g/d) during 3 days for knee pains, one week before jaundice started. She denied taking other drugs, ingestion of mushrooms, alcohol or herbal tea. She denies recent trips or vacations. She went to a general doctor and made same exams, including viral markers. However she became more asthenic and jaundiced and went to a hospital wards.

Past medical history: renal colic 2 years ago. She denies allergies or any medications. Review of systems: no other symptoms besides the ones related with chief complaint or history of present illness.

At hospital admission she was awake, oriented in space and time, coherent speech. No flapping. Icteric skin and sclerotics. Apiretic. Hemodinamically stable. Pulmonary and cardiac auscultation: normal. Abdomen: no pain or tenderness.

Laboratory data: Hb 10,1g/dL; WBC 10 250/uL; platelets 150 000/uL; Total bilirubin: 19mg/dl; direct bilirubin: 15mg/dl; AST 334U/L; ALT 345U/L; Alkaline phosphatase: 77U/L; g-GT:25U/L; DHL: 200U/L. RNI: 2,3. Negative viral markers (HCV, HBV, HAV and HEV)

Normal renal function and urinalysis. Beta-HCG negative. Abdominal ultrasound: slight increase in liver dimensions (155mm larger axis), homogeneous echostructure without focal lesions. Normal gallbladder. There is no intra or extrahepatic biliary ductal dilatation or abdominal ascites. Homogeneous splenomegaly (145mm). Permeable portal and supra-hepatic veins. The patient was admitted to an internal medicine ward. At 5th day, she developed fever and flapping and laboratory data were: bilirubin: 22mg/dl; direct bilirubin: 20mg/dl; AST 346U/L; ALT 343U/L; RNI 2,6. She was transferred to the medical intermediate care unit to our hospital (tertiary hospital with liver transplantation facilities).

Clinical Case I 2

Pedro Vita
Intensive and Intermediate Care Unit
Clinical Immunology Unit
Centro Hospitalar do Porto, Hospital Santo António, Porto, Portugal
Biomedical Sciences Institute, University of Oporto, Porto, Portugal

Introduction (patient information and chief complaint): A 19-year-old caucasian woman with a history of medular hypoplasia presents to the emergency room complaining of fever (> 38ºC), mild aching pain in the lower right quadrant and malaise of 3 days duration.

History of present illness: She denies any other symptoms. She was self-medicated paracetamol (a total of 5g in 3 days), but denies any other medication. She drank small amount of green tea and denies any alcohol or drugs use.

Past medical history: Medular hypoplasia - diagnosed when she was 11-years-old, resulting in pancytopenia and also B-cell and T-cell lymphopenia, waiting for bone marrow transplant and in the last 3 years on a regular program of packed red cell transfusion (on average every 2 months).Recurrent axillar lymphadenitis - occurring in the last 5 months, treated with courses of antibiotics (flucloxacillin).Genital human papillomavirus infection with chronic cervicitis, cervical metaplasia and condylomata acuminata - diagnosed 5 months ago and condylomata were treated in the day before chief complaints started.

Allergies: She denies any allergies.

Medications: Danazol 200mg qod

Review of systems: No other symptoms besides the ones related with the chief complaint or past medical history related.

Physical examination findings on emergency room admission: Awake, alert and oriented in space and time. Resting quietly. Overweight and hirsutism. Feverish (38,2ºC).Hemodinamically stable.No signs of respiratory distress.Pulmonary auscultation: normal.Cardiac auscultation: normalAbdomen: no rebound tenderness.Pain during palpation of right inguinal region.Genital examination by a Gynecologist described as normal.

Laboratory data: CBC: Hb 15,1g/dL; WBC 3,170/uL; lymphocytes 570/uL; platelets 59,000/uL. Chemistry: Bilirrubin 0.46mg/dL; SGOT/AST 653; SGPT/ALT 938; LDH 754; Alkaline phosphatase 88; G-GT 70; C-reactive protein: 127mg/L. Urinalysis: normal. Beta-HCG negative. Abdominal and pelvic ultrasound: slight increase in liver dimensions (158mm larger axis), homogeneous and smooth echotexture without focal lesions. Multiple gallstones (largest - 11mm). Gallbladder otherwise unremarkable. There is no intra or extrahepatic biliary ductal dilatation. There is no abdominal ascites. Uterus and anexa unremarkable. No free pelvic fluid is seen in the cul-de-sac. Presence of non-specific reactive infracentimetric adenomegalies in the right inguinal region. Chest Rx: normal.

The patient was admitted to an internal medicine ward.
Evolution in the first 24h: No new complaints. Pyrexia inspite of antipiretic. No signs of encephalopathy. No evidence of blood loss. CBC: Hb 15.1g/dL; WBC 2,570/uL; Platelets 18,000/uL. Increase in elevated liver enzymes: SGOT/AST 4184; SGPT/ALT 5947; Total bilirrubin 1.02mg/dL. Coagulopathy: RNI 2.16. Hiponatremia 129mmol/L. CRP 227mg/L. Viral markers; HBsAg, anti-HBs, anti-HBc, anti-HCV and HIV-1/2 negative.

The patient was transferred to the medical intermediate care unit.

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