Gastroenterol Hepatol. 2017;40(9):649.e1–649.e6

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

SPECIAL ARTICLE

Contributions to our understanding of fulminant hepatitis from the Liver ICU of Hospital Clínic Barcelona: Historical review☆

Aportaciones al conocimiento de la hepatitis fulminante realizadas por la Unidad de Cuidados Intensivos Hepática del Hospital Clínic de Barcelona: revisión histórica

Antoni Mas

Consultor Senior (jubilado), Jefe de la Unidad de Cuidados Intensivos 'Dr. Josep Terés' (1989-2013), Servicio de Hepatología, Instituto de Enfermedades Digestivas y Metabólicas, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain

Received 8 June 2017; accepted 14 June 2017
Available online 4 November 2017

The Hospital Clínic de Barcelona's (HCB) Hepatology Intensive Care Unit (ICU), which was later renamed the Hepatology and Gastroenterology Intensive Care Unit, was opened at the end of 1971. For many years it was the Hepatology Department's cornerstone of teamwork and cohesion, directed by Juan Rodés (deceased). Every morning, the on-call doctor would inform the rest of the department staff of what had occurred the previous evening and night. The complications of admitted patients would be discussed, deaths analysed and treatment changes proposed.

With the founding of the institutes, the department became the ICU of the Institute of Gastrointestinal and Metabolic Diseases. Despite these name changes, within HCB it has always been known as the ''Liver ICU''. To celebrate its 40th anniversary and in tribute to its driving force, founder and first director, the hospital decided to rename it the ''Dr Josep Terés ICU''.

The unit was initially set up to treat gastrointestinal bleeding and other serious complications affecting cirrhotic patients. Since the launch of the HCB's liver transplant programme in 1988, the unit has also been responsible for the immediate post-operative care of transplant recipients. Following the aforementioned restructuring of the hospital into institutions, the number of patients attending the medical and surgical departments under the remit of the institutions soared. An analysis conducted for the 40th anniversary found that 60% of patients attended hepatology and 40% gastroenterology. The proportion of medical/surgical patients was split evenly (50% each).[1]

As part of the critical pathological process of patients with liver disease, so-called acute liver failure (ALF), fulminant hepatitis or fulminant hepatic failure represents the most serious and complex paradigm of the disease with the highest mortality rates within the field of hepatology.[2] Until urgent liver transplantation established itself as the treatment of choice for acute liver failure, mortality for this disease in Spain exceeded 75%.[3] Although the condition is not particularly prevalent, the unit quickly became a liver disease referral centre in Spain because of its unique characteristics (the only unit in Spain dedicated specifically to treating severe liver disorders and run by hepatologists).

☆ Please cite this article as: Mas A. Aportaciones al conocimiento de la hepatitis fulminante realizadas por la Unidad de Cuidados Intensivos Hepática del Hospital Clínic de Barcelona: revisión histórica. Gastroenterol Hepatol. 2017;40:649e1–649e6.

E-mail address: antonimasordeig@gmail.com

Most acute liver failure studies come from English-speaking countries, where the syndrome is much more common than in Spain or Latin America. This is due in part to the fact that paracetamol overdosing, which causes ALF, is very common in English-speaking countries and rare in Latin countries.[3,4] Despite its low prevalence, our experiences of this syndrome are soon to be published. The aim of this article is to analyse our contribution to the study of ALF over the last 45 years. It is also a small tribute to Joan Manuel Salmerón, who died suddenly, and Juan Rodés, who worked for many years at our unit.

The description of the different studies published has been organised into the following sections: aetiology and pathogenesis; conventional treatment; general aspects and epidemiology of ALF in Spain; urgent liver transplantation and potential utility of artificial liver support systems; and general reviews.

Epidemiology, aetiology and pathogenesis

The causes of ALF are extremely varied. An aetiological diagnosis is in many ways essential as it determines the prognosis, the specific treatment (if such treatment exists) and the indication for liver transplantation.

The first-ever study of 51 ALF cases treated at the unit was published in 1985.[3] Dr Miquel Navasa was the primary author of the paper. He was responsible for reigniting the ICU's interest in this syndrome after a period of some despondency (due to the high mortality and poor outcomes with conventional treatment).

The most common cause of ALF in this initial series was acute hepatitis B virus (HBV) infection (22 cases). Two facts were particularly striking: the lack of paracetamol overdose cases, which is a common cause of this syndrome in English-speaking countries, and a failure to identify the aetiology in a high proportion of cases (43%).

Following the identification of new potential causes (primarily new hepatitis viruses), this finding (ALF of unknown or cryptogenic origin) led to the future analysis of frozen serum samples deriving from ALF patients. Various studies found that the hepatitis C virus could not have been responsible for the vast majority of cryptogenic ALF cases (in fact, only two cases in the last 30 years presented hepatitis C virus RNA in serum). Furthermore, no signs of hepatitis G virus infection or transfusion-transmitted virus (TTV) infection were detected.[5,6] Some authors had suggested that these cases could be attributed to HBV with ''cryptic'' replication. One study by Soguero et al. (unpublished data) in 12 patients with cryptogenic fulminant hepatitis treated at our unit found no HBV DNA or hepatitis C virus RNA in serum or liver tissue, as recorded in an analysis on cryptogenic liver disease.[7]

We routinely perform transjugular liver biopsies in patients with ALF. Thanks to the collaboration of Dr Jaume Bosch and Dr Juan Carlos García Pagán, this option is available to us at all times to suit the urgency of the situation. In some cases, such as acute Budd-Chiari syndrome, the haemodynamic study performed before the transjugular biopsy establishes both the diagnosis and the specific treatment. Likewise, Dr Miquel Bruguera's interpretation of urgent liver biopsies has enabled us to ascertain the aetiology of the condition and to prescribe the appropriate treatment in a matter of hours: chemotherapy for lymphoma infiltration or other tumours, immunosuppression in the event of signs suggestive of autoimmune hepatitis, haemodynamic stabilisation if there are data to suggest that shock was the cause of ALF, etc.

We have diagnosed some very rare causes of ALF. Knowledge of these aetiologies may be of importance in certain aspects:

- We have found an increased prevalence of ALF caused by tuberculosis drugs.[8]
- Two cases of ALF due to the hepatitis A virus in adults enabled us to highlight the importance of vaccination for anyone travelling to endemic areas.[9,10]
- From 1980 to 1985, we recorded an increased caseload of ALF due to the hepatitis D virus (HDV) associated with the addition of IV drugs or sexual contact amongst drug addicts, and we described their characteristics.[11]
- We reported cases of ALF caused by medicines and illegal drugs: disulfiram, phenelzine, ecstasy and cocaine.[12–16]
- We diagnosed two cases of liver failure due to heatstroke. One presented with symptoms of liver disease after running a marathon on two separate occasions.[17] The other developed ALF, that required an urgent liver transplantation, also after strenuous physical exercise.
- Together with Dr Bernau et al., we published a small series of ALF attributed to Reye's syndrome in adults. This paper emphasised the possibility of aggravating encephalopathy with the administration of neurotropic drugs, as has been demonstrated in other aetiologies, as well as an apparently improved prognosis in this scenario compared with other causes of ALF.[18]
- We collaborated in a study conducted in hospitals in the Barcelona area on clinically significant drug-induced liver injury, including ALF. 126 cases were identified. The drugs most commonly associated with severe hepatotoxicity were tuberculosis drugs, amoxicillin-clavulanic acid, erythromycin, chlorpromazine, nimesulide and ticlopidine.[19] Although no further cases of ALF were detected, an extension of this study identified other cases of hepatotoxicity attributable to therapeutic doses of paracetamol, as reported in alcoholic and malnourished patients, despite these conditions not manifesting in the affected patients.[20]

In terms of studying the potential physiopathological mechanisms, in 1990 we analysed the degree of viral replication in HBV- and HDV-induced ALF, in collaboration with Dr Buti et al. With the technology available at that time (molecular hybridisation), we detected HBV DNA or HDV RNA in just 14% of cases (four of 29).[21] These data suggested that in HBV- and HDV-induced ALF, rather than high viraemia, the severity of hepatic injury was due to the patient's exaggerated immune response. This also explained the low viral reinfection recurrence after liver transplant in this scenario.[22] In another analysis, we reported how an acute exacerbation of chronic HBV infection can mimic ALF with positive HBsAg and anti-HBc IgM,[23] which was later reported more extensively in Asia. The collaboration of José María Sánchez-Tapias (Hepatology Department) and Josep Costa (Microbiology Department) has been key to analysing the various aspects of viral acute liver failure.

Cerebral oedema with intracranial hypertension is one of the more serious complications of ALF. Together with Joan Córdoba (deceased) of Hospital de la Vall d'Hebron, we published a study on the activation of the ''matrix metalloproteinase-9'' released by the necrotic liver in the possible pathogenesis of cerebral oedema.[24]

In the first decade of this century, we led an ALF study in Spain. Until then, only global data concerning the prevalence, aetiology and clinical course of this syndrome in the United States had been available, published by the Acute Liver Failure Study Group.[25] Data from 17 hospitals, responsible for the care of approximately half the Spanish population, were collected. The most common aetiology was once again ''cryptogenic'' (32%), followed by HBV (28%) and drugs (19.5%). Paracetamol was only responsible for 2% of cases. This confirmed the findings of our individual study published 20 years previously. It also enabled the prevalence of ALF in Spain to be estimated (1.4 cases per million population/year).[26]

A new subsequent analysis performed on 87 ALF cases diagnosed at our unit (2001–2010) identified certain changes in aetiology: slight increase in paracetamol-induced cases (8%), increased number of other drug-induced cases (31%) and lower prevalence of cryptogenic cases (16%). One surprising finding was the continued prevalence of HBV-induced ALF despite the longstanding implementation of vaccination programmes. This can be explained by the rise in the non-vaccinated emigrant population.[27]

Clinical manifestations and conventional treatment

ALF mortality is very high unless an urgent liver transplantation is performed, peaking at 78.4% according to the study by Navasa et al.[3] The most common causes of death were so-called extrahepatic complications. In cases of fulminant/hyperacute liver failure, the predominant causes of death are cerebral oedema/intracranial hypertension with tonsillar herniation and brain death, while in subacute cases, the cause of death tends to be multiple organ failure, often associated with bacterial or fungal infection. The aforementioned study identified signs of cerebral oedema in 45% of cases, with the death of all but one patient. Whether or not an intracranial pressure monitor should be inserted to monitor this complication is a subject of much debate, but we have routinely inserted monitors ever since Miquel Navasa secured the collaboration of the neurosurgery department.[28]

Renal failure was also a common complication identified in 55% of cases, with a mortality rate of 89%.[3] In fact, the first study that we published on ALF was a description of the characteristics of renal failure in 1974. At that time, HCB's Hepatology Department had started renal function studies in patients with cirrhosis, enabling us to analyse the prevalence and characteristics of this complication in ALF. We were able to identify two types of renal failure in a small patient sample: the first due to sustained hypotension with data suggestive of acute tubular necrosis; and the second affecting two thirds of patients with indistinguishable characteristics of what was known at the time as ''functional renal failure in liver cirrhosis'', which has since been renamed hepatorenal syndrome.[29]

Patients with ALF, particularly those with subfulminant/subacute liver failure, often develop ascites secondary to portal hypertension. Performing a transjugular liver biopsy to obtain a sample of hepatic tissue enabled the portal venous pressure gradient to be determined in 25 patients with ALF. Portal hypertension was a very common finding and its gradient was associated with ascites or renal failure, as well as hyperdynamic circulation.[30] Furthermore, patients with ascites may develop spontaneous bacterial peritonitis, similar to cirrhosis patients. It is important to identify any spontaneous bacterial peritonitis before recommending an urgent liver transplant.[31]

ALF treatment is traditionally divided into general therapeutic measures, treatment of extrahepatic complications and aetiology-specific treatments. The studies published by our unit concerning the various therapeutic aspects of ALF are summarised below.

- In the 1980s it was hypothesised that the clinical course of some forms of viral hepatitis-induced ALF was due to an endogenous interferon production deficiency. A study performed at our unit on 12 consecutive patients ruled out this hypothesis, which never went on to be confirmed.[32]
- Like all extrahepatic complications, bacterial and fungal infections are common in ALF and are associated with high mortality. In the study by Navasa et al., all patients with sepsis died.[3] In an uncontrolled study, selective intestinal decontamination was associated with a small risk of infectious complications, particularly by Gram-negative bacteria.[33]
- Since the study published by the US acute liver failure study group on the administration of N-acetylcysteine, which found a correlation between its administration and improved prognosis in patients with grade 1 and 2 encephalopathy secondary to non-paracetamol-induced ALF,[34] most authors recommend its use. It should be noted that the administration of this drug may modify the prothrombin time, thereby affecting the prognostic assessment and distorting the potential indication for an urgent liver transplant.[35]

Urgent liver transplant

The advent of the urgent liver transplant has changed the prognosis of this syndrome. Thanks to our experience in ALF, in the pre-transplant era we were a referral centre in Spain until urgent liver transplantation became available at all transplant units. In 1991, we published an analysis of the first 18 months of the liver transplant programme, in which 11% of the indications were for ALF.[36] Even in more recent times, the rate of liver transplantation for acute liver failure in adults at HCB (10.8% from 2001 to 2016) (Spanish liver transplant activity dossier, 2016, Spanish National Transplant Organisation [ONT]) continues to be higher than in the other Spanish transplant units: 4.6% of all transplants from 1984 to 2011 (Spanish National Transplant Organisation [ONT], 2013).

In this regard, we must mention the programme's first head of surgery (Dr Josep Visa, recently deceased), Dr Luis

Grande, who joined another centre many years ago and Dr Josep Fuster, who is still at our hospital. Dr Juan Carlos García-Valdecasas has been responsible for liver transplantation since the retirement of Dr Visa, and his interest and dedication to the programme from the outset has been key to its success, including liver transplant for ALF. The Anaesthesiology Department plays a vital role in the intraoperative management of liver transplantation, including ALF-specific aspects. Until her retirement, Dr Pilar Taurà had long been our contact person, playing a key role, together with other anaesthesiology colleagues, in the intraoperative management of liver transplantation.[37] The contribution of our colleagues at the Hepatology Department in the overall management of ALF and urgent liver transplantation—Antoni Rimola and Miquel Navasa, who are specifically responsible for transplantation—is also worthy of special mention.

Urgent liver transplantation for ALF in our geographical area presents certain unique characteristics compared to other areas: on the one hand, greater and quicker accessibility to transplant thanks to the high rate of organ donation—more than two thirds of patients receive a transplant in less than 24 hours after ''alert 0'' is triggered—and, on the other hand, the aforementioned aetiology of ALF, which differs from that seen in most developed countries where paracetamol overdose is prevalent, where its prognosis is better and where transplantation tends to be contraindicated in cases of underlying psychiatric disorders. These aspects were analysed in a study published in 1993 of our experience in the suitability of transplant for ALF. Using our urgent transplantation criteria, we divided the patients (n = 62) into three groups: 21% that did not meet the transplantation criteria, with 100% survival, 34% that met the transplantation criteria but with various contraindications either upon admission or identified while the patient was on the waiting list, with a mortality rate of 94%, and, lastly, 45% that met the transplantation criteria without any contraindications, with 79% survival.[38] In 2010, we published a new analysis on this topic entitled 'Liver transplantation for acute liver failure: A Spanish perspective'.[39]

Our experience in liver transplantation for ALF led us to contribute to the drafting of a consensus statement for liver transplantation indications in Spain in 2003.[40]

Artificial liver support

There are two kinds of artificial liver support systems: blood purification, by means of the physicochemical mechanisms of toxins that accumulate in the body in the event of severe hepatocellular disease; and biological, which are charged with live and metabolically active liver cells connected to the patient's blood or plasma circulation.

Joan Manuel Salmerón published the first case of ALF treated with a biological system in Spain.[41] This patient was participating in a randomised multicentre study conducted in various European countries and in the USA, which compared conventional treatment with conventional treatment plus plasma infusion sessions in patients with ALF or primary graft failure after liver transplantation with a system containing porcine hepatocytes. The other participating site in Spain was Hospital Reina Sofía of Cordoba. The primary endpoint of the study (superior survival in the bioartificial liver support system group) was not achieved, probably because the most important prognostic factor was the chance of receiving an urgent liver transplantation.[42]

The utility of albumin dialysis systems, particularly the Molecular Adsorbent Recirculating System (MARS), has also been evaluated in patients with ALF. A French multicentre study in ALF patients with an indication for urgent transplantation, and with no contraindications, found no significant differences between the control group and the MARS group. In these patients, liver transplantation was performed very quickly after inclusion in the study (less than 18 h on average), making it difficult to assess the efficacy of the system as a ''bridge'' therapy prior to transplantation.[43]

A significant proportion of patients (34% in our suitability study) with ALF and an indication for urgent liver transplantation present with contraindications, such as advanced age, previous comorbidities or ALF-related complications, resulting in a very poor prognosis.[38] This is why it seemed reasonable to assess the potential utility of the MARS system in these patients. A survival rate of 41% in 17 consecutive patients with these characteristics was achieved with MARS.[44] Recent retrospective studies conducted by other investigators show that MARS reduces the need for urgent transplant for ALF with excellent survival.[45] Further clinical trials that compare conventional treatment versus conventional treatment plus MARS are needed in order to confirm these findings.

Conclusions

Over our 45-year history, the Dr Josep Terés ICU of the Hospital Clínic de Barcelona Institute of Gastrointestinal and Metabolic Diseases has made numerous contributions that we consider to be relatively significant in the study of acute liver failure. It has surely been the most productive unit in this field outside of the English-speaking world. Reviews and editorials,[46,47] as well as chapters in internal medicine, hepatology and intensive care medicine books,[48–59] have been published based on our experience in this syndrome.

Our studies have been conducted in a variety of settings: within the ICU, in collaboration with our colleagues from the Hepatology Department to which the unit belongs, with other hospital departments, primarily Surgery and Anaesthesiology, as well as collaborative national and international multicentre studies.

It should be noted that these contributions have only been possible thanks to the invaluable support offered by the nursing staff who, throughout the years and with great professionalism, have always understood that advancing our knowledge requires clinical and translational investigations to be conducted which, more often than not, and particularly in this type of patient, place excess burden on the care providers.

The unit and its work on ALF will continue in the same vein, and is certain to improve. Its current members (Javier Fernández, Director, Àngels Escorsell who has been working on ALF for years, and Enric Reverter, the latest member of the team) have the training, interest and enthusiasm required to guarantee future success.

Conflicts of interest

None declared.

References

1. Mas A. The intensive care unit for digestive diseases at Barcelona Hospital Clínic. History, organization, structure and functions. In: Romaozinho JM, editor. Intensive care in gastroenterology. Coimbra, Portugal: Clairtimagem Lda.; 2007. p. 19–26.
2. Trey C, Davidson CS. The management of fulminant hepatic failure. In: Popper H, Schaffner F, editors. Progress in liver diseases. New York: Grune & Stratton; 1970. p. 282–98.
3. Navasa M, Panés J, Terés J, Bruguera M, Rodés J. Insuficiencia hepática aguda grave: análisis de 51 casos. Gastroenterol Hepatol. 1986;9:221–7.
4. O'Grady JG. Acute liver failure. Postgrad Med J. 2005;82:148–54.
5. Saiz JC, Sans M, Mas A, Olmedo E, Forns X, López-Labrador FX, et al. Hepatitis G virus infection in fulminant hepatic failure. Gut. 1997;41:696–9.
6. Giménez-Barcons M, Forns X, Ampurdanés S, Guilera M, Soler M, Soguero C, et al. Infection with a novel human DNA virus (TTV) has no pathogenic significance in patients with liver diseases. J Hepatol. 1999;30:1028–34.
7. Bruguera M, Sánchez Tapias JM. ¿Qué son las enfermedades hepáticas criptogenéticas? Med Clin (Barc). 2000;114:31–6.
8. Moitinho E, Salmerón JM, Mas A, Bruguera M, Rodés J. Hepatotoxicidad grave por tuberculostáticos: aumento de su incidencia. Gastroenterol Hepatol. 1996;19:448–51.
9. Elizalde JL, Salmerón JM, Mas A, Bruguera M. Hepatitis grave por VHA. Med Clin (Barc). 1994;102:479.
10. Crespo G, Mas A, Bruguera M. Hepatitis fulminante por virus A y vacunación en grupos de riesgo. Med Clin (Barc). 2007;129:438–9.
11. Mas A, Sánchez Tapias JM, Costa J. Infección por el virus de la hepatitis delta (VHD) en la hepatitis fulminante. Gastroenterol Hepatol. 1986;9:156–9.
12. Forns X, Caballería J, Bruguera M, Salmerón JM, Vilella A, Mas A, et al. Disulfiram-induced hepatitis. Report of four cases and review of the literature. J Hepatol. 1994;21:853–7.
13. Gómez-Gil E, Salmerón JM, Mas A. Phenelzine-induced fulminant hepatic failure. Ann Intern Med. 1996;124:692–3.
14. Andreu V, Mas A, Bruguera M, Salmerón JM, Moreno V, Nogué S, et al. Ecstasy: a common cause of severe acute toxicity. J Hepatol. 1998;29:394–7.
15. Carrión JA, Escorsell A, Nogué S, Mas A. Insuficiencia hepática aguda grave por 'éxtasis' y trasplante hepático urgente. Med Clin (Barc). 2003;121:118–9.
16. Balaguer F, Fernández J, Lozano M, Miquel R, Mas A. Cocaine-induced acute hepatitis and thrombotic microangiopathy. JAMA. 2005;293:793–8.
17. Sort P, Mas A, Salmerón JM, Bruguera M, Rodés J. Recurrent liver involvement in heatstroke. Liver. 1996;16:335–7.
18. Bernuau JR, Ichai P, Das A, Mas A, Cazals-Hatem D, Bruguera M, et al. Post-aspirin Reye's syndrome in young adults: frequent aggravation of encephalopathy by neurotropic drugs and spontaneous recovery. J Hepatol. 2007;46(Supp 1):S63.
19. Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther. 2007;25:1401–9.
20. Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, et al. Paracetamol in therapeutic dosages and acute liver injury: causality assessment in a prospective case series. BMC Gastroenterol. 2011;11, http://dx.doi.org/10.1186/1471-230X-11-80.
21. Mas A, Buti M, Esteban R, Sánchez-Tapias JM, Costa J, Jardí R, et al. Hepatitis B virus and hepatitis D virus replication in HBsAg-positive fulminant hepatitis. Hepatology. 1990;11:1062–5.
22. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with hepatitis B surface antigen. N Engl J Med. 1993;329:1842–7.
23. Titó L, Sánchez-Tapias JM, Mas A, Costa J, Bruguera M, Rodés J. Severe acute hepatitis an initial manifestation of chronic hepatitis B virus infection. Med Clin (Barc). 1989;93:702–4.
24. Palenzuela L, Mas A, Montaner J, Cordoba J. Matrix metalloproteinase-9 in fulminant hepatic failure. Hepatology. 2010;51:1475–6.
25. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, et al., U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947–54.
26. Escorsell A, Mas A, de la Mata M, The Spanish Group for the study of acute liver failure. Acute Liver Failure in Spain: analysis of 267 cases. Liver Transpl. 2007;13:1389–95.
27. Mas A, Uchima H, Escorsell A, Fernández J. Impact of epidemiological changes over the last 10 years in the characteristics of acute liver failure in Spain. Hepatology. 2011;54 Suppl:502A-3.
28. Mas A, Escorsell A. Medición de la presión intracraneal. Valor en el tratamiento de la hepatitis fulminante. GH Continuada. 2004;3:125–7.
29. Mas A, Bosch J, Rodés J, Bruguera J, Terés J, Bordas JM, et al. Insuficiencia renal en la hepatitis fulminante. Rev Clin Esp. 1974;133:423–8.
30. Navasa M, García-Pagán JC, Bosch J, Riera JR, Bañares R, Mas A, et al. Portal hypertension in acute liver failure. Gut. 1992;33:965–8.
31. Salmerón JM, Titó LL, Rimola A, Mas A, Castells A, Saló J, et al. Spontaneous bacterial peritonitis (SBP) in acute liver failure (ALF): incidence and characteristics. J Hepatol. 1991;13 Suppl 2:S68.
32. Sánchez-Tapias JM, Mas A, Costa J, Bruguera M, Mayor A, Ballesta AM, et al. Recombinant alpha-2c interferon therapy in fulminant viral hepatitis. J Hepatol. 1987;5:205–10.
33. Salmerón JM, Titó L, Rimola A, Mas A, Navasa MA, Llach J, et al. Selective intestinal decontamination in the prevention of bacterial infection in patients with acute liver failure. J Hepatol. 1992;14:280–5.
34. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcisteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009;137:656–64.
35. Mas A, Nogué S. N-acetilcisteína en la intoxicación por *Amanita phalloides*. Med Clin (Barc). 2009;133:486.
36. LLach J, Rimola A, Arroyo V, Garcia-Valdecasas JC, Grande L, Visa J, et al. Trasplante hepático: selección de candidatos y resultados obtenidos en un programa para pacientes adultos. Med Clin (Barc). 1991;96:41–6.
37. Taurà P, Martínez-Palli G, Martínez-Ocon J, Bertran J, Sánchez-Etayo G, Balust J, et al. Hyperlactatemia in patients with non-acetaminophen-related acute liver failure. World J Gastroenterol. 2006;12:1949–53.
38. Castells A, Salmerón JM, Navasa M, Rimola A, Saló J, Andreu, et al. Liver transplantation for acute liver failure: analysis of applicability. Gastroenterology. 1993;105:532–8.
39. Mas A, Escorsell A, Fernández J. Liver transplantation for acute liver failure: a Spanish perspective. Transpl Proc. 2010;42:619–21.
40. Prieto M, Clemente G, Casafont F, Cuende N, Cuervas-Mons V, Figueras J, et al. Documento de consenso de indicaciones de trasplante hepático. Gastroenterol Hepatol. 2003;26:355–75.
41. Salmerón JM, Lozano M, Agustí E, Mas A, Mazzara R, Marín P, et al. Soporte hepático bioartificial en la insuficiencia hepática

aguda grave. Primer caso tratado en España. Med Clin (Barc). 2001;117:781–4.
42. Demetriou AA, Brown RS Jr, Busuttil RW, Fairm J, Brendan M, McGuire BM, et al. Prospective, randomized, multicenter controlled trial of a bioartificial liver in treating acute liver failure. Ann Surg. 2004;232:660–70.
43. Saliba F, Camus C, Durand F, Mathurin P, Letierce A, Delafosse B, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med. 2013;159:522–31.
44. Escorsell A, Mas A, Sanz M, Herrera D, Fernández J, López E. MARS improves survival in acute liver failure with contraindications to emergency transplantation. Crit Care Med. 2013;41 Suppl:895.
45. Saliba F, Dahlqvist G, Lettierce A, Ichai P, Ruiz L, Boudon D, et al. Factors predicting outcome of patients with acute liver failure meeting the criteria of liver transplantation: impact of albumin dialysis with MARS. J Hepatol. 2014;60:S362-S3.
46. Mas A, Rodés J. Fulminant hepatic failure. Lancet. 1997;349:1081–5.
47. Mas A. Mushrooms, amatoxins and the liver. J Hepatol. 2005;42:166–9.
48. Mas A. Insuficiencia hepática aguda grave. In: Vilardell F, et al., editors. Enfermedades digestivas. Madrid: Ediciones CEM, SA; 1990. p. 1873–85.
49. Mas A. Complicaciones extrahepáticas en la insuficiencia hepática aguda grave. In: Rodés J, Arroyo V, Piqué JM, editors. Controversias en gastroenterología. Barcelona: Doyma SA; 1992. p. 361–5.
50. Mas A, Salmerón JM, Tost J. Applicability of liver transplantation in fulminant hepatic failure. In: Rodés J, Bosch J, Bruix J, Ginés P, Navasa M, Rodés J, editors. Therapy in hepatology. Barcelona: Ars Medica; 2001. p. 159–65.
51. Mas A, Salmerón JM. Insuficiencia hepática aguda grave (fallo hepático fulminante). In: Berenguer J, Bruguera M, García-Bengoechea M, Rodrigo L, editors. Tratamiento de las enfermedades hepáticas y biliares, AEEH. Madrid: Elba SA; 2001. p. 199–209.
52. Mas A, Salmerón JM. Urgencias en hepatología ii: hepatitis fulminante. In: Montoro M, et al., editors. Principios básicos de gastroenterología para médicos de familia. Jarpyo editores; 2002. p. 963–78.
53. Mas A, Escorsell A, Fernández J. Insuficiencia hepática aguda grave. In: Net A, Betbesé AJ, editors. Update en medicina intensiva. Barcelona: Ars Médica; 2005. p. 343–56.
54. Mas A. Insuficiencia hepática aguda grave (hepatitis fulminante). In: Montoro M, et al., editors. Problemas comunes en la práctica clínica. Gastroenterología y hepatología. Madrid: Jarpyo editores; 2006. p. 561–70.
55. Mas A. Insuficiencia hepática aguda grave (hepatitis fulminante). In: Montoro MA, García-Pagan JC, editors. Gastroenterología y hepatología, problemas comunes en la práctica clínica. 2nd ed. Madrid: Jarpyo Editores; 2012. p. 759–68.
56. Mas A, Escorsell A, Fernández J. Hepatitis fulminante. In: Montoro M, García Pagán JC, editors. Manual de emergencias en gastroenterología y hepatología. 2nd ed. Madrid: Jarpyo Editores; 2013. p. 397–404.
57. Escorsell Mañosa A, Mas Ordeig A, Fernández Gómez J. Insuficiencia hepática aguda. En Farreras-Rozman Medicina Interna, XVIII edición. Barcelona: Elsevier España; 2016. p. 286–91.
58. Jiménez Rivera DF, Mas Ordeig A, Osio LF. Falla hepática aguda-insuficiencia hepática aguda grave. In: Ordóñez CA, Ferrada R, Buitrago R, editors. Cuidado intensivo y trauma. 2nd ed. Bogotá: Distribuna Editorial Medica; 2009. p. 1121–41.
59. Mas A, Escorsell A. Insuficiencia hepática. In: Suárez J, Bruguera M, editors. Hepatología, de las ciencias básicas a la clínica, de los problemas a los síndromes, de la docencia a la práctica médica. Quito, Ecuador; 2016. p. 273–91.