European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 37-45

Liver transplantation for drug-induced acute liver failure

M. BIOLATO, C. ARANEO, G. MARRONE, A. LIGUORI, L. MIELE, F.R. PONZIANI, A. GASBARRINI, A. GRIECO

Liver Transplant Medicine, Gastroenterological Area, Gastroenterological and Endocrino-Metabolic Sciences Department, Fondazione Policlinico Universitario Gemelli, Catholic University of the Sacred Heart, Rome, Italy

Abstract. – OBJECTIVES: To summarize the different clinical features of drug-induced acute liver failure, the diagnostic work-up, conservative management and the prognostic scores currently used to list patients for liver transplantation.

EVIDENCE AND INFORMATION SOURCES: The current review is based on an analysis of the current literature and the caseload experience of the Authors on this topic.

STATE OF THE ART: Drug-induced liver injury is the leading cause of acute liver failure in the adult population in Western countries, with a transplant-free survival rate of less than 50%. Main subtypes include paracetamol and idiosyncratic drug-induced injury, which differ in epidemiology, clinical course, prognosis and conservative management. In cases of a high likelihood of death, urgent hepatic transplantation is indicated, but the decision whether and when to put a patient with drug-induced acute liver failure on the list for urgent liver transplant is extremely difficult and requires constant interdisciplinary exchange and continuous updating of the clinical picture.

CONCLUSIONS: Intensive management should be done in a clinical tertiary referral center which has a specialized team of hepatologists and a liver transplant center.

Key Words

Paracetamol, Acetaminophen, Drug list, Fulminant hepatitis.

Introduction

Acute liver failure (ALF) is severe and rapid liver function deterioration in a patient with a previously normal liver, with the development of progressive hepatic encephalopathy, coagulopathy and jaundice, and the potential to rapidly progress to multiorgan failure[1]. ALF is rare, with an incidence between one and five cases per million people every year in developed countries[2-4], but occurs mostly in young adults and is associated with high mortality and healthcare costs. Among patients hospitalized with ALF at tertiary care centers, the transplant-free survival rate is less than 50%[5]. Death is mainly due to systemic infection or cerebral oedema[6]. The most prominent cause of ALF in the United States and Western Europe is drug-induced liver injury (DILI), accounting for about 50% of cases[7]. In this review, we summarize the different clinical features of drug-induced ALF, the diagnostic work-up, conservative management and the prognostic scores currently used to list patients for liver transplantation.

Paracetamol

It is usually considered that daily therapeutic doses of paracetamol (acetaminophen) are primarily metabolized by glucuronidation and sulfation. With higher doses, the conjugation pathways become saturated, and the metabolism of paracetamol is shunted to the cytochrome P450 system; this generates the highly reactive toxic metabolite N-acetyl-p-benzoquinone-imine[8,9]. Glutathione stores can inactivate this toxic metabolite to a certain extent, beyond which N-acetyl-p-benzoquinone-imine binds to hepatocellular proteins and leads to hepatocellular necrosis[10].

Because of its widespread use and characteristics of sale in many countries (it can be purchased without a medical prescription and outside pharmacies), paracetamol-induced hepatotoxicity is the most common cause of ALF in the United States, Australia, United Kingdom and other countries in Western Europe[11-16]. Patterns of intoxication include single time point overdose (usually with intent for deliberate self-harm) or staggered overdose (unintentional repeated consumption of one or more paracetamol-containing products for analgesic effect)[17]. A staggered

Corresponding Author: Antonio Grieco, MD; e-mail: antonio.grieco@unicatt.it

overdose pattern is associated with late presentation to medical attention and an increased risk of death despite lower total ingested paracetamol doses[18]. Paracetamol is also a potential cofactor for hepatic injury in patients taking the drug for the relief of symptoms from hepatic illness of other causes[19,20]. Pharmacodynamic studies have shown a dose-response relationship between the amount of paracetamol ingested and the extent of the elevation of transaminases; the same studies have shown that hepatotoxicity is greater if associated with fasting or with alcohol consumption[21-23]. According to the package insert[24], 4 g of paracetamol represents the maximum recommended daily dosage, but due to different individual susceptibility and multiple co-factors (fasting, nutritional impairment, alcohol, weight, pregnancy, oral contraceptives) that amplify liver injury, in clinical practice, it is difficult to estimate the minimum toxic dose of paracetamol in the individual patient[25,26]. In the European SALT study, about half of the cases of paracetamol-induced ALF were due to exposure at therapeutic doses of paracetamol[15]. Furthermore, in cases of exposure to other hepatotoxic drugs, non-overdose paracetamol might also play a direct or indirect causal role, maybe through depletion of glutathione, reducing liver detoxification capabilities[27]. Measurement of serum acetaminophen–protein adducts, a specific biomarker of drug-related toxic effects, may help to reveal unknown paracetamol exposure in cases of ALF of indeterminate aetiology[11,20].

Paracetamol-induced ALF (Table I) presents a characteristic hyperacute form: very high aminotransferase levels (> 3000 UI/L), low bilirubin levels, severe coagulopathy and high risk of intracranial hypertension[28]. The clinical course is often rapidly progressive multiorgan failure, with a greater severity of illness than that seen in liver failure from other causes[29]. Paradoxically, in patients who do not meet the criteria for transplantation, outcomes with medical management alone are better than for patients with ALF of other causes, because of an increased potential for hepatic regeneration and recovery[4].

Idiosyncratic drug-induced liver injury

Overall, non-paracetamol drug-induced ALF is less frequent than paracetamol-induced ALF; in the United States, Australia, United Kingdom and many countries in Western Europe, non-paracetamol drug-induced ALF accounts for 10-15% of cases of ALF, compared to 35-40% of cases of paracetamol-induced ALF[11-14]. Contrary to this trend are the data reported for Spain (17% non-paracetamol, 2% paracetamol) and Germany (14% non-paracetamol, 15% paracetamol), probably as a result of different patterns of drug use[3,30]. Non-paracetamol drug-induced ALF is caused by idiosyncratic hepatotoxicity and is, therefore, individual, dose-unrelated and unpredictable[31]. Most examples of idiosyncratic drug hepatotoxicity occur within the first 3 months after drug initiation, but cases of ALF after months of uneventful treatment before presentation are described and, rarely, chronic toxic liver injury develops before presentation[6].

Drugs commonly associated with ALF include antibiotics, antituberculotics, anticonvulsants and anti-inflammatory drugs, but virtually any drug, albeit rarely, can lead to ALF[6]. In the United States Drug-Induced Liver Injury Network, which collects cases of ALF admitted to tertiary centers (either transplanted or not), antimicrobials were the most represented therapeutic class, and amoxicillin-clavulanate was the most frequent individual agent[32]. In the European SALT study, which collects only cases of ALF listed for transplantation,

Table I. Subtypes of drug-induced acute liver failure.

	Paracetamol	Idiosyncratic DILI
Exposure-response relationship	Dose-dependent	Dose-independent
Clinical course	Hyperacute	Subacute
Conservative management	Activated charcoal (< 4 hrs) N-acetylcysteine	Steroids (?)*
Survival rate without liver transplantation	Good	Poor
Suggested criteria for listing	King's College criteria	Hepatic encephalopathy ± MELD worsening

*Consider steroid therapy if idiosyncratic DILI is associated with immunoallergic reaction (rash, eosinophilia or autoantibody positivity).

nonsteroidal anti-inflammatory drugs were the most represented therapeutic class, and ibuprofen was the most frequent individual agent[15]. Over-the-counter medications, herbal preparations, weight loss agents, other nutritional supplements and even illicit drugs can also cause idiosyncratic drug-induced ALF[33].

There might be a genetic predisposition to idiosyncratic DILI. An increased incidence of DILI has been seen with glutathione S-transferase and manganese superoxide dismutase gene polymorphisms, specific HLA genotypes and polymorphic variations of enzymes involved in the metabolism of drugs[34-36]. Today, the characterization of genetic predisposition to DILI is confined to the research field.

The clinical course of idiosyncratic drug-induced ALF is usually subacute, with slow progression to hepatic failure in weeks, in some cases despite drug discontinuation (Table I)[37-39]. Signs and symptoms of immunoallergic reaction (rash, eosinophilia or autoantibody positivity) are seen in less than a third of patients[41,42]. Some cases present a cholestatic or mixed pattern of liver biochemistry, which can be classified according to R-ratio score (R = (ALT value/ALT upper normal limit)/(ALP value/ALP upper normal limit); briefly, R-ratios of > 5 define a hepatocellular pattern of liver injury, < 2 a cholestatic pattern of liver injury and between 2 and 5 a mixed pattern of liver injury[43]. Factors associated with reduced survival in drug-induced ALF include pre-existing liver disease, a hepatocellular pattern of liver injury, bilirubin levels and coagulopathy[30,38,40]. Transplant-free survival is generally poor in idiosyncratic drug-induced ALF[39,40].

Diagnostic work-up

A diagnosis of ALF is made in the presence of an International Normalized Ratio (INR) elongation ≥ 1.5 and any degree of mental alteration (encephalopathy) in a patient without pre-existing cirrhosis and with an illness of < 26 weeks' duration[1,44]. Because the prognosis of these patients is expressed by a transplant-free survival rate of less than 50%[5], early discussion with specialists at a liver unit connected to a transplant center is warranted, and suitable patients should be transferred as quickly as possible. In the liver unit, diagnostic work-up, conservative therapy, and repeated re-evaluation to determine the proper timing for listing are carried out in parallel.

Clinicians should obtain a detailed medical history from the patient and/or family, including the first onset of symptoms. A careful drug history should include a list of all agents taken over the last 6 months, the dose ingested and the timing of drug exposure compared with the onset of liver disease. Inquiry about over-the-counter medications, herbal preparations, weight loss agents, nutritional supplements and illicit drugs should be included in a complete medication history. The possible concurrent intake of alcohol and attitude to alcohol must be investigated, and intake of some potentially toxic foods such as wild mushrooms or seafood should be determined. A detailed history of current and prior substance use, current or prior depression (including assessment of suicidality), anxiety, psychosis or other mental illness, prodromal viral infection and recent travel should also be obtained[45].

A complete physical examination should be performed. Particular attention should be paid to the assessment of mental status and neurologic examination in patients with hepatic encephalopathy of stage 2 or higher. Physical examination should include a search for signs suggesting underlying chronic liver disease that have different management implications. Diagnostic work-up for drug-induced ALF is summarized in Table II[1].

It is clinically important to assess all main organs in order to identify both early signs of multiorganic progression of ALF and the presence of comorbidities that would contraindicate transplantation. Multiorgan failure induced by ALF includes renal failure, lactic acidosis, high output cardiac state (sometimes with subclinical myocardial injury), acute lung injury, pancreatitis, bone marrow suppression, relative adrenal insufficiency and cerebral oedema with intracranial hypertension[31]. Absolute contraindications to emergency liver transplantation include active extrahepatic tumours, HIV infection (outside of specific programs), active bacterial infections, dependence on illicit drugs, serious psychiatric/neurological diseases and co-existing advanced cardiovascular or lung disease[1,31]. Active alcohol abuse should no longer be considered an absolute contraindication for liver transplantation: when medical urgency does not allow a 6-month waiting time, the liver transplantation evaluation may proceed in selected patients, incorporating expert assessment by a mental health professional who may include a contract for addiction treatment before or after transplantation, depending on clinical circumstances[46].

Table II. Diagnostic work-up for drug-induced acute liver failure.

Initial assessment	Complete blood count International Normalized Ratio (INR) Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, transaminases, alkaline phosphatase, gamma-glutamyl-transferase, bilirubin, albumin creatinine Arterial blood gas with arterial lactate Ammonia Amylase and lipase
Minimum requirements for listing patient for liver transplantation	Serological testing for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) Blood group
Suggested diagnostic tests in every patient with ALF	Serological testing for herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), hepatitis E virus (HEV) Anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-liver kidney microsomal antibody (LKM), immunoglobulin levels Toxicology screen
Diagnostic tests to be considered according to clinical suspicion	Serological testing for parvovirus B19, adenovirus, leptospirosis, brucellosis, typhoid, rickettsial infection Thick blood film Ceruloplasmin level Ferritin Alpha-1 antitrypsin

Liver biopsy is not performed routinely. It can be considered when the real cause is uncertain or a differential diagnosis is considered necessary such as for autoimmune hepatitis, lymphoma, metastatic infiltration, herpes simplex infection or unknown cause. In cases of severe coagulopathy, it can be performed by the transjugular route[47].

The diagnosis of ALF secondary to a particular drug or xenobiotic is a diagnosis of exclusion[48]. For this purpose some tools have been developed for causality assessment, such as the Roussel UCLAF Causality Assessment Method (RUCAM), which depends on R-ratio value and assigns a score to factors such as time to onset, course, risk factors, concomitant drugs, non-drug causes of liver injury, previous information on the hepatotoxicity of the drug and response to rechallenge; briefly, RUCAM indicates that a drug is a possible (3-5), probable (6-8) or highly probable (> 8) to cause liver injury[49].

Conservative management

General management issues include correction of volume depletion with active fluid management, avoiding nephrotoxic agents, giving glucose infusion to normalize hypoglycaemia, administering proton pump inhibitors for prophylaxis of stress ulceration, performing periodic surveillance cultures and antibiotic prophylaxis[1,50-52]. It is not recommended to administer plasma, coagulation factors and platelets (except in cases of active bleeding or for invasive procedures), to avoid distorting INR monitoring[53]. Conventional treatments for hepatic encephalopathy in chronic liver disease (lactulose and rifaximin) are not recommended in ALF, because of clinical concern for the ileus and overdistention of the bowel[31]. If a reduced level of consciousness develops, an early tracheal intubation for airway control is required, and the patient needs admission to an intensive care unit.

Specific treatments for paracetamol-induced ALF include administration of activated charcoal and N-acetylcysteine[1]. Activated charcoal (standard dose 1 g/kg orally) may be useful for gastrointestinal decontamination within 3 to 4 hours after ingestion[54,55]. N-acetylcysteine behaves as a replenisher of glutathione stores and represents the specific antidote for paracetamol poisoning; when given within 24 hours of ingestion it can prevent or reduce liver damage even after large overdoses[56-58]. Probably, N-acetylcysteine is effective even if administered within 36 hours of ingestion[59]. The loading dose of intravenous N-acetylcysteine is 150 mg/kg in 5% dextrose over 15 minutes; the maintenance dose is 50 mg/kg given over 4 hours followed by 100 mg/kg administered over

16 hours or 6 mg/kg/hour[60]. Controversy exists over when to stop the use of N-acetylcysteine, whether a standard 72-hour period or continuation until liver chemistry values have improved is optimal. Beneficial effects of N-acetylcysteine administration have also been observed in non-paracetamol-induced ALF[61].

There are no specific antidotes for idiosyncratic drug reactions; corticosteroids are not indicated unless an immunoallergic reaction (rash, eosinophilia or autoantibody positivity) is associated[62]. Any presumed or possible offending agent should be stopped immediately where possible.

Decision to list for liver transplantation

Urgent hepatic transplantation is indicated in ALF in cases of high likelihood of death. Current United Network for Organ Sharing criteria for Status 1A listing (urgent liver transplant) include: (1) age 18 years or older without pre-existing liver disease and currently in an intensive care unit, (2) life expectancy without liver transplantation of less than 7 days, (3) onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease, (4) the patient must also meet one of the following criteria: ventilator dependence, requirement for renal replacement therapy or INR above 2.0[1].

In the previously mentioned multicentre prospective US study, overall, 44% of patients with ALF hospitalized at tertiary care centers were eventually listed for liver transplantation[11]. According to European Registry 1998-2012, ALF is the primary indication for liver transplantation in 8% of cases, with a 5-year survival rate of 64% and an improving trend during the last 5 years[63,64]. Overall, the 1-year survival rate following liver transplant is lower than that seen in patients who have been transplanted for chronic liver failure; however, following the first year, this trend is reversed and ALF patients have a better chance of long-term survival[11,65-67]. The majority of deaths are usually secondary to neurologic complications or sepsis. Outcomes after liver transplantation for drug-induced ALF are comparable to other causes of ALF; however, survival seems lower in the antiepileptic group[64,68]. Attention should be paid to patients transplanted for paracetamol-induced ALF because of a higher risk of post-transplant suicide and non-adherence to immunosuppressive medications[64].

As previously mentioned, among patients hospitalized with ALF at tertiary care centers, the transplant-free 1-year survival is less than 50%, but exceeds 80% when liver transplantation is an option[5]. Nevertheless, 25% of patients with ALF listed for liver transplantation in the largest US study died while on the waiting list[11]. At the same time, approximately 35% of patients listed for transplantation for ALF underwent delisting for spontaneous recovery[69]. For these reasons, the decision whether and when to put a patient with ALF on the list for an urgent liver transplant is extremely difficult, as it is extremely difficult to explain the clinical decisions to the patient's family. On the one hand, we should try to prevent listing a patient with ALF for liver transplantation who subsequently dies ('*too late*'); on the other hand, we should avoid transplant in a patient who would likely have survived with his native liver ('*too soon*')[70].

Candidacy for transplantation must be determined very quickly and discussed in a multidisciplinary team (hepatologists, anaesthesiologists, surgeons and, in some cases, social workers and psychiatrists). When the decision to list the patient has been taken, re-evaluation of suitability for transplantation when an organ becomes available is warranted, especially to exclude irreversible brain injury and sepsis.

In the literature, several prognostic scoring systems have been proposed, aiming to help clinicians better assess eligibility for liver transplantation, but currently none are recommended by current guidelines[1]. For paracetamol-induced ALF, the most widely applied is the King's College Hospital criteria, based on experience among nearly 600 patients (Table III)[71]. In a meta-analysis of studies using the King's College criteria, the pooled sensitivity and specificity was 69% and 92%, respectively[72]. For non-paracetamol drug-induced ALF, many scoring systems have been proposed (non-paracetamol King's College criteria, Clichy criteria, Japanese criteria, Acute Liver Failure Study Group Index, Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, Model for End-Stage Liver Disease, etc.) but none of these are optimal, so there remains an urgent need for more accurate prognostic scoring systems in non-paracetamol ALF[73]. In clinical practice, it's reasonable to list the patient when grade II or greater hepatic encephalopathy develops according to the West Haven criteria[74], or any grade of hepatic encephalopathy together with worsening over time in the Model for End-Stage Liver Disease.

Table III. King's College criteria for paracetamol-induced ALF[68].

Arterial pH < 7.30 OR All of the following: • PT > 100 sec (INR > 6.5) • Creatinine level > 3.4 mg/dL • Grade 3/4 encephalopathy

Conclusions

DILI is the leading cause of ALF in the adult population in the USA and the Europe. Drug-induced ALF requires complex management, constant interdisciplinary exchange and continuous updating of the clinical picture to re-evaluate the prognosis and decide whether to proceed to liver transplantation. It follows that such intensive management should be done in a clinical tertiary referral center which has a specialized team of hepatologists and a liver transplant center.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology 2012; 55: 965-967.
2) Bower WA, Johns M, Margolis HS, Williams IT, Bell BP. Population-based surveillance for acute liver failure. Am J Gastroenterol 2007; 102: 2459-2463.
3) Escorsell A, Mas A, de la Mata M; Spanish Group for the Study of Acute Liver Failure. Acute liver failure in Spain: analysis of 267 cases. Liver Transpl 2007; 13: 1389-1395.
4) Brandsaeter B, Höckerstedt K, Friman S, Ericzon BG, Kirkegaard P, Isoniemi H, Olausson M, Broome U, Schmidt L, Foss A, Bjøro K. Fulminant hepatic failure: outcome after listing for highly urgent liver transplantation-12 years experience in the nordic countries. Liver Transpl 2002; 8: 1055-1062.
5) Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a model to predict transplant-free survival of patients with acute liver failure. Clin Gastroenterol Hepatol 2016; 14: 1199-1206.
6) Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010; 376: 190-201.
7) Goldberg DS, Forde KA, Carbonari DM, Lewis JD, Leidl KB, Reddy KR, Haynes K, Roy J, Sha D, Marks AR, Schneider JL, Strom BL, Corley DA, Lo Re V 3rd. Population-representative incidence of drug-induced acute liver failure based on an analysis of an integrated health care system. Gastroenterology 2015; 148: 1353-1361.
8) Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975; 55: 871-876.
9) Mattia C, Coluzzi F. A look inside the association codeine-paracetamol: clinical pharmacology supports analgesic efficacy. Eur Rev Med Pharmacol Sci 2015; 19: 507-516.
10) Davern TJ 2nd, James LP, Hinson JA, Polson J, Larson AM, Fontana RJ, Lalani E, Munoz S, Shakil AO, Lee WM; Acute Liver Failure Study Group. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. Gastroenterology 2006; 130: 687-694.
11) Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM; 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: 947-954.
12) Wei G, Bergquist A, Broomé U, Lindgren S, Wallerstedt S, Almer S, Sangfelt P, Danielsson A, Sandberg-Gertzén H, Lööf L, Prytz H, Björnsson E. Acute liver failure in Sweden: etiology and outcome. J Intern Med 2007; 262: 393-401.
13) Bernal W, Auzinger G, Wendon J. Prognostic utility of the bilirubin lactate and etiology score. Clin Gastroenterol Hepatol 2009; 7: 249.
14) Gow PJ, Jones RM, Dobson JL, Angus PW. Etiology and outcome of fulminant hepatic failure managed at an Australian liver transplant unit. J Gastroenterol Hepatol 2004; 19: 154-159.
15) Gulmez SE, Larrey D, Pageaux GP, Lignot S, Lassalle R, Jové J, Gatta A, McCormick PA, Metselaar HJ, Monteiro E, Thorburn D, Bernal W, Zouboulis-Vafiadis I, de Vries C, Perez-Gutthann S, Sturkenboom M, Bénichou J, Montastruc JL, Horsmans Y, Salvo F, Hamoud F, Micon S, Droz-Perroteau C, Blin P, Moore N. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. Drug Saf 2013; 36: 135-144.
16) Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz G, Shakil AO, Lee WM; Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005; 42: 1364-1372.
17) Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. Br J Clin Pharmacol 2011; 71: 273-282.
18) Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. Br J Clin Pharmacol 2012; 73: 285-294.
19) Rezende G, Roque-Afonso AM, Samuel D, Gigou M, Nicand E, Ferre V, Dussaix E, Bismuth H, Féray C. Viral and clinical factors associated with the fulminant course of hepatitis A infection. Hepatology 2003; 38: 613-618.
20) Khandelwal N, James LP, Sanders C, Larson AM, Lee WM. Unrecognized acetaminophen toxicity as a cause of indeterminate acute liver failure. Hepatology 2011; 53: 567-576.

21) Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, Harris SC. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA 2006; 296: 87-93.
22) Temple AR, Lynch JM, Vena J, Auiler JF, Gelotte CK. Aminotransferase activities in healthy subjects receiving three-day dosing of 4, 6, or 8 grams per day of acetaminophen. Clin Toxicol (Phila) 2007; 45: 36-44.
23) Heard K, Green JL, Bailey JE, Bogdan GM, Dart RC. A randomized trial to determine the change in alanine aminotransferase during 10 days of paracetamol (acetaminophen) administration in subjects who consume moderate amounts of alcohol. Aliment Pharmacol Ther 2007; 26: 283-290.
24) http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm165107.htm
25) Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, Guarner C, Forné M, Solà R, Castellote J, Rigau J, Laporte JR. Paracetamol in therapeutic dosages and acute liver injury: causality assessment in a prospective case series. BMC Gastroenterol 2011; 11: 80.
26) Kulo A, Van Calsteren K, van de Velde M, Mulabegovic N, Verbesselt R, de Hoon JN, Verhaeghe J, Allegaert K. Weight, pregnancy and oral contraceptives affect intravenous paracetamol clearance in young women. Eur Rev Med Pharmacol Sci 2014; 18: 599-604.
27) Jalan R, Williams R, Bernuau J. Paracetamol: are therapeutic doses entirely safe? Lancet 2006; 368: 2195-2196.
28) Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 1995; 22: 767-773.
29) Bernal W, Cross TJ, Auzinger G, Sizer E, Heneghan MA, Bowles M, Muiesan P, Rela M, Heaton N, Wendon J, O'Grady JG. Outcome after wait-listing for emergency liver transplantation in acute liver failure: a single centre experience. J Hepatol 2009; 50: 306-313.
30) Hadem J, Stiefel P, Bahr MJ, Tillmann HL, Rifai K, Klempnauer J, Wedemeyer H, Manns MP, Schneider AS. Prognostic implications of lactate, bilirubin, and etiology in German patients with acute liver failure. Clin Gastroenterol Hepatol 2008; 6: 339-345.
31) Bernal W, Wendon J. Acute liver failure. N Engl J Med 2013; 369: 2525-2534.
32) Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, Watkins PB, Navarro V, Barnhart H, Gu J, Serrano J; United States DILIN. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015; 148: 1340-1352. e1347.
33) Beaune S, Juvin P, Beauchet A, Casalino E, Megarbane B. Deliberate drug poisonings admitted to an emergency department in Paris area – a descriptive study and assessment of risk factors for intensive care admission. Eur Rev Med Pharmacol Sci 2016; 20: 1174-1179.
34) Lucena MI, Andrade RJ, Martínez C, Ulzurrun E, García-Martín E, Borraz Y, Fernández MC, Romero-Gomez M, Castiella A, Planas R, Costa J, Anzola S, Agúndez JA; Spanish Group for the Study of Drug-Induced Liver Disease. Glutathione S-transferase m1 and t1 null genotypes increase susceptibility to idiosyncratic drug-induced liver injury. Hepatology 2008; 48: 588-596.
35) Huang YS, Su WJ, Huang YH, Chen CY, Chang FY, Lin HC, Lee SD. Genetic polymorphisms of manganese superoxide dismutase, NAD(P)H: quinone oxidoreductase, glutathione S-transferase M1 and T1, and the susceptibility to drug-induced liver injury. J Hepatol 2007; 47: 128-134.
36) Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, Daly MJ, Goldstein DB, John S, Nelson MR, Graham J, Park BK, Dillon JF, Bernal W, Cordell HJ, Pirmohamed M, Aithal GP, Day CP; DILIGEN Study; International SAE Consortium. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet 2009; 41: 816-819.
37) Daly AK, Aithal GP, Leathart JB, Swainsbury RA, Dang TS, Day CP. Genetic susceptibility to diclofenac-induced hepatotoxicity: contribution of UGT2B7, CYP2C8, and ABCC2 genotypes. Gastroenterology 2007; 132: 272-281.
38) Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology 2005; 42: 481-489.
39) Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, González-Grande R, Pizarro A, Durán JA, Jiménez M, Rodrigo L, Romero-Gomez M, Navarro JM, Planas R, Costa J, Borras A, Soler A, Salmerón J, Martin-Vivaldi R; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005; 129: 512-521.
40) Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-2076.
41) Björnsson E, Kalaitzakis E, Olsson R. The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury. Aliment Pharmacol Ther 2007; 25: 1411-1421.
42) Takikawa H, Murata Y, Horiike N, Fukui H, Onji M. Drug-induced liver injury in Japan: an analysis of 1676 cases between 1997 and 2006. Hepatol Res 2009; 39: 427-431.
43) Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014; 109: 950-966.
44) Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure - one disease, more than 40 definitions. Aliment Pharmacol Ther 2012; 35: 1245-1256.
45) Patton H, Misel M, Gish RG. Acute liver failure in adults: an evidence-based management protocol for clinicians. Gastroenterol Hepatol (N Y) 2012; 8: 161-212.

46) Addolorato G, Bataller R, Burra P, DiMartini A, Graziadei I, Lucey MR, Mathurin P, O'Grady J, Pageaux G, Berenguer M. Liver transplantation for alcoholic liver disease. Transplantation 2016; 100: 981-987.
47) Lee WM. Recent developments in acute liver failure. Best Pract Res Clin Gastroenterol 2012; 26: 3-16.
48) Hayashi PH, Fontana RJ. Clinical features, diagnosis, and natural history of drug-induced liver injury. Semin Liver Dis 2014; 34: 134-144.
49) Rockey DC, Seeff LB, Rochon J, Freston J, Chalasani N, Bonacini M, Fontana RJ, Hayashi PH; US Drug-Induced Liver Injury Network. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. Hepatology 2010; 51: 2117-2126.
50) Stravitz RT, Kramer AH, Davern T, Shaikh AO, Caldwell SH, Mehta RL, Blei AT, Fontana RJ, McGuire BM, Rossaro L, Smith AD, Lee WM; Acute Liver Failure Study Group. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. Crit Care Med 2007; 35: 2498-2508.
51) Eefsen M, Dethloff T, Frederiksen HJ, Hauerberg J, Hansen BA, Larsen FS. Comparison of terlipressin and noradrenalin on cerebral perfusion, intracranial pressure and cerebral extracellular concentrations of lactate and pyruvate in patients with acute liver failure in need of inotropic support. J Hepatol 2007; 47: 381-386.
52) Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology 2004; 39: 464-470.
53) Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, Williams R. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol 2013; 59: 74-80.
54) Green R, Grierson R, Sitar DS, Tenenbein M. How long after drug ingestion is activated charcoal still effective? J Toxicol Clin Toxicol 2001; 39: 601-605.
55) Sato RL, Wong JJ, Sumida SM, Marn RY, Enoki NR, Yamamoto LG. Efficacy of superactivated charcoal administration late (3 hours) after acetaminophen overdose. Am J Emerg Med 2003; 21: 189-191.
56) Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. N Engl J Med 1988; 319: 1557-1562.
57) Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991; 324: 1852-1857.
58) Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R. A prospective controlled trial of intravenous N-acetylcysteine in paracetamol-induced fulminant hepatic failure. BMJ 1991; 303: 1024-1029.
59) Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. Lancet 1990; 335: 1572-1573.
60) Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? J Toxicol Clin Toxicol 1999; 37: 759-767.
61) Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TJ 2nd, Murray NG, McCashland T, Reisch JS, Robuck PR; Acute Liver Failure Study Group. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009; 137: 856-864.
62) Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin Exp Dermatol 2011; 36: 6-11.
63) European Association for the Study of the Liver. EASL Clinical Practice Guidelines: liver transplantation. J Hepatol 2016; 64: 433-485.
64) Germani G, Theocharidou E, Adam R, Karam V, Wendon J, O'Grady J, Burra P, Senzolo M, Mirza D, Castaing D, Klempnauer J, Pollard S, Paul A, Belghiti J, Tsochatzis E, Burroughs AK. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol 2012; 57: 288-296.
65) Farmer DG, Anselmo DM, Ghobrial RM, Yersiz H, McDiarmid SV, Cao C, Weaver M, Figueroa J, Khan K, Vargas J, Saab S, Han S, Durazo F, Goldstein L, Holt C, Busuttil RW. Liver transplantation for fulminant hepatic failure: experience with more than 200 patients over a 17-year period. Ann Surg 2003; 237: 666-675.
66) Barshes NR, Lee TC, Balkrishnan R, Karpen SJ, Carter BA, Goss JA. Risk stratification of adult patients undergoing orthotopic liver transplantation for fulminant hepatic failure. Transplantation 2006; 81: 195-201.
67) Freeman RB Jr, Steffick DE, Guidinger MK, Farmer DG, Berg CL, Merion RM. Liver and intestine transplantation in the United States, 1997-2006. Am J Transplant 2008; 8: 958-976.
68) Mindikoglu AL, Magder LS, Regev A. Outcome of liver transplantation for drug-induced acute liver failure in the United States: analysis of the United Network for Organ Sharing database. Liver Transpl 2009; 15: 719-729.
69) Lake JR, Sussman NL. Determining prognosis in patients with fulminant hepatic failure: when you absolutely, positively have to know the answer. Hepatology 1995; 21: 879-882.
70) O'Grady J. Liver transplantation for acute liver failure. Best Pract Res Clin Gastroenterol 2012; 26: 27-33.
71) O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97: 439-455.
72) Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. Crit Care Med 2003; 31: 299-305.

73) McPhail MJ, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College criteria and Model for End-Stage Liver Disease scores to predict mortality of patients with acute liver failure: a meta-analysis. Clin Gastroenterol Hepatol 2016; 14: 516-525.

74) Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy–definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35: 716-721.