Review Article

An Update on Treatment of Drug-Induced Liver Injury

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Abstract

Drug-induced liver injury (DILI) has been linked to more than 1,000 medications and remains the most common cause of acute liver failure in the United States. Here, we review the most current literature regarding treatment and make recommendations for the management of this relatively common disease. Since treatment of DILI remains largely elusive, recent studies have attempted to define new management strategies for these difficult patients. Early diagnosis and withdrawal of the suspected medication is the mainstay of treatment of DILI. For acetaminophen and Amanita mushroom poisoning, there are specific therapies in use. Finally, there are other possible management modalities for DILI, including corticosteroids and ursodeoxycholic acid.

Introduction

Drug-induced liver injury (DILI) is defined as a liver injury due to xenobiotics, herbs, or medications that leads to either liver dysfunction or abnormal liver serology, in the setting of no other identifiable cause. Unlike idiosyncratic drug induced liver injury (IDILI), DILI seems to be dose-dependent, predictable, and reproducible. DILI has been associated with more than 1,000 medications and is the most common cause of acute liver failure in the United States, accounting for approximately 50% of fulminant cases.[1–5,6] While retrospective studies have shown acetaminophen to be the most common cause of DILI, studies in liver transplant patients have demonstrated antibiotics and immunosuppressive agents, such as tacrolimus and azathioprine, as the top causes.[7,8] Bjornsson et al. performed a prospective study and found that amoxicillin-clavulanate was the most commonly implicated antibiotic. The incidence was approximately 19 cases per 100,000.[9] In addition to the typical suspects stated above, herbal and dietary supplements have been a rising cause of DILI, now accounting for up to 9% of all cases.[10] In fact, one study based in China, which spanned eight years, found that nearly half of all cases were secondary to medicinal herbs.[11] While DILI is most commonly due to only one drug, a prospective study demonstrated that nearly 10% of cases were attributable to more than one medication.[9]

DILI has several clinical manifestations ranging from asymptomatic elevations in liver enzymes to fulminant liver failure. Hepatic, or cytochrome P450, metabolism of a drug has been strongly linked to DILI, and one study demonstrated that those medications that rely on more than 50% hepatic metabolism have a greater risk for alanine transferase (ALT) elevation, liver failure, and mortality.[12] Other proposed mechanisms for DILI include autoimmunity and hypersensitivity.[2,13] Despite the possible mechanisms, treatment options all follow the same principles. The most important, and first, step is early diagnosis followed by discontinuation of the offending agent.[2]

Diagnosis

The most common presenting symptom in most cases of DILI is jaundice, although many cases are asymptomatic or have elevated enzymes incidentally detected.[11] However, DILI can present as cholestatic, hepatocellular, and mixed; and proper diagnosis will direct the treatment of a particular case. Cholestatic liver injury is defined by predominant elevations of alkaline phosphatase (ALP), whereas hepatocellular liver injury is defined as predominant elevations of aspartate transferase (AST) and ALT, and mixed has elevations in both ALP and transaminases.[14] It is important to note that ALT is liver-specific, whereas elevations in AST may be associated with damage to skeletal or cardiac muscle or in conditions such as myocardial infarction and rhabdomyolysis. Hepatocellular injury remains the most common presentation and is correlated with a worse outcome.[15,16] Table 1 provides specific definitions for both cholestatic and hepatocellular injury, which may aid in the identification of the patient's clinical diagnosis.

Once liver injury has been established, the next step is to determine the underlying cause. Risk factors for DILI have been difficult to determine with many studies because of conflicting results in regard to sex and age-related occurrences. However, a recent study found that older age and female sex was associated with a cholestatic type injury, while younger age and male sex was associated with hepatocellular type injury. Genetic polymorphisms have been consistently found to be a risk factor for DILI but are not typically tested for in patients prior to receiving a medication.[17,18] Finally, liver transplant patients where the reason for transplant was primary sclerosing cholangitis are at

Keywords: Drug-induced liver injury; Hepatotoxicity; Acetaminophen toxicity.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transferase; AST, aspartate transferase; CDS, clinical diagnostic scale; DDW-J, digestive disease week-Japan; DILI, drug-induced liver injury; IDILI, idiosyncratic drug induced liver injury; INR, international normalized ratio; IV, intravenous; NAC, *N*-acetylcysteine; PT, prothrombin; M&V, Maria and Victorino; PT, prothrombin time; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.
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Table 1. Definitions of DILI[20,23,24]

Cholestatic Liver Injury	Elevations of ALP $\geqslant$ 2X the upper limit of normal (ULN) OR ALT/ALP ratio of $<$ 2 with both ALT and ALP $>$ ULN
Hepatocellular Liver Injury	ALT $\geqslant$ 5X ULN AND Total bilirubin $\geqslant$ 2X ULN

greater risk for developing DILI.[8] Chronic liver disease is a risk factor but only for certain medications, including methotrexate, isoniazid, and HIV antiretroviral therapy.[2] When diagnosing DILI, several established criteria can be used, none of which is considered to be a gold standard. Hy's law is specific but not sensitive, whereas the Roussel Uclaf Causality Assessment Method (RUCAM) is more sensitive but more difficult to administer in its truest form as it is complicated and requires rechallenging patients once they have recovered.[19–21] One modification is the Digestive Disease Week-Japan (DDW-J) scale, which includes lymphocyte stimulation testing, although this test has not been validated.[22] Yet another modification is the Clinical Diagnostic Scale (CDS) or Maria and Victorino (M&V) scale, which is more simple to administer but less predictive in patients who have had a prolonged period of time between drug use and development of symptoms or in those patients who have developed chronic liver injury.[23–24] When examining these scales, common features, which make them specific and sensitive tests, include temporal relationship, exclusion of other causes, and prior reports of hepatoxicity of the suspected medication. While specific criteria may be used, at a minimum the above three commonalities should be investigated. For reference, Wang et al found in China that the majority of cases occurred between 5 and 90 days of the initiation of the drug.[11] As an aid for the clinician, Table 2 provides medications and their typical liver injury presentation.

Once a specific drug has been identified as the cause of DILI, it must be discontinued.[2] Following withdrawal of the suspected agent, therapy is largely supportive with a few notable exceptions for acetaminophen and Amanita mushroom poisoning. All patients' laboratory values, including AST, ALT, ALP, bilirubin, and international normalized ratio (INR) and mental statuses should be monitored for changes. It is important to note that measuring only AST and ALT is insufficient when monitoring liver function in DILI. Damage to hepatocytes causes elevation of AST and ALT levels, and once sufficient damage has occurred, there are less hepatocytes and AST and ALT levels begin to decrease.[14] Therefore, bilirubin and INR must also be monitored. With discontinuation of the drug, most cases resolve without further sequelae, with one prospective study reporting a median duration from diagnosis to normalization of laboratory values of 64 days.[9]

Lee et al. performed an eight year prospective, double-blind, placebo control trial of *N*-acetylcysteine (NAC) for patients with acute liver failure not secondary to acetaminophen overdose. While overall survival was similar in the populations (70% vs. 66%), transplant-free survival was significantly better for those who received NAC (40% vs. 27%).[25] At this time, NAC therapy can and should be considered for patients who are presenting with acute liver failure.

In addition, a small uncontrolled study performed by Wree et al. compared steroid pulse therapy with steroid step down therapy, both in combination with ursodeoxycholic acid, in the treatment of drug-induced liver injury, including patients with hepatocellular and/or cholestatic injury. Both therapies demonstrated a decrease in time to normalization of bilirubin, AST, and ALT values.[26] However, since this was an uncontrolled study, it is uncertain if the observed improvement in their patient population actually reflected the natural history of DILI.

Specific treatment

Treatment for acetaminophen toxicity largely consists of NAC therapy. Studies have conflicted between whether oral or intravenous (IV) therapy should be given. Yarema et al. compared IV to oral administration and found that hepatoxicity occurred less often in patients who received IV therapy within 12 hours of ingestion.[27] However, a recent study performed using a simulation system demonstrated that for those patients presenting within 24 hours of acetaminophen ingestion, the oral protocol is superior to the 21-hour intravenous protocol in persevering hepatocytes. These authors argued that Yarema's study contained two differing treatment groups.[28] Regardless, NAC therapy should be started if there is an elevation in AST, a detectable acetaminophen level, or if the level is above the treatment line on the Rumack-Matthew nomogram.[29] A computer simulation suggested that International Normalized Ratio (INR) did not undertreat patients but did lead to overtreatment, whereas treating until ALT peaked did not undertreat and rarely overtreated patients.[28] Current recommendations are to treat according to the protocol and to recheck AST and the acetaminophen level. At this point, AST should be less than 100 IU/L and acetaminophen level should be less than 10 mcg/mL. If not, therapy should be continued using the normalization of INR as a marker of resolution.[30]

Amanita mushroom ingestion can lead to liver injury via the amatoxin, which inhibits RNA polymerase II and leads to hepatocyte necrosis. Presentation consists of a gastrointestinal phase followed by a hepatic phase. The gastrointestinal phase is characterized by nausea, vomiting, and abdominal pain. This is followed by symptomatic improvement but an elevation in AST and ALT followed by the development of jaundice. Since the hepatic phase is preceded by a gastrointestinal phase where dehydration and metabolic derangements may have developed, it is important to treat any dehydration and electrolyte abnormalities.[31] While it has no proven efficacy for long-term survival, repeated activated charcoal administration is often recommended, which will prevent reabsorption of the amatoxin. While amatoxin may cause metabolic acidosis on its own, activated charcoal, which contains propylene glycol, can also cause a high anion gap metabolic acidosis. While clinicians should be aware of this potential complication, it should not preclude treatment with activated charcoal.[32] Silibinin is universally accepted as a treatment modality for amatoxin poisoning because it

Table 2. Common biochemical presentation in DILI and associated medications / environmental exposure

Biochemical presentation	Associated medications / exposure
Cholestatic *(ALP > 2 × ULN or ALP/ALT <2) with both ALP and ALT > 1 × ULN*	**Antimicrobials:** • Amoxicillin-clavulanate acid, Erythromycin, Trimethoprim-sulfamethoxazole **Cardiovascular:** • Clopidogrel, ACE inhibitors **Endocrine:** • Anabolic steroids **Immunosuppressive:** • Azathioprine **Gynecology:** • Oral contraceptives **Neuropsychiatric:** • Carbamazepine, Chlorpromazine, Tricyclic antidepressants **Anti-inflammatory:** • Sulindac
Hepatocellular *(ALT >5 × ULN and Bilirubin >2 × ULN)*	**Anti-inflammatory:** • Acetaminophen, Bromfenac, Diclofenac, Ibuprofen, Naproxen **Antimicrobials:** • Ciprofloxacin, Isoniazid, Ketoconazole, Nitrofurantoin, Protease inhibitors, Pyrazinamide, Rifampin, Tetracycline, Trimethoprim-sulfamethoxazole **Cardiovascular:** • Amiodarone, Lisinopril, Quinidine, Statins **Endocrine:** • Acarbose, Troglitazone **Gastrointestinal:** • Cimetidine, Omeprazole **Immunosuppressive:** • Allopurinol **Neuropsychiatric:** • Bupropion fluoxetine, Methyldopa, Nefazodone, Paroxetine, Risperidone, Sertraline, Trazodone, Valproic acid **Environmental exposures:** • Amatoxin **Other:** • Halothane
Mixed *(ALT >5 × ULN or Bilirubin >2 × ULN) and (ALP >2 × ULN or ALP/ALT <2 with both ALP and ALT >1 × ULN)*	**Antimicrobials:** • Clindamycin, Protease inhibitors, Reverse transcriptase inhibitors, Sulfonamides **Cardiovascular:** • ACE inhibitors, Statins **Immunosuppressive:** • Azathioprine **Neuropsychiatric:** • Amitriptyline, Phenytoin,
Steatohepatitis	**Antineoplastic:** • Tamoxifen **Cardiovascular:** • Amioderone
Veno-occlusive	**Antineoplastic:** • Busulfan, Cyclophosphamide **Environmental exposures:** • Arsenic, Thorium dioxide, Vinyl chloride, **Other:** • Vitamin A

inhibits the transfer of amanitin into hepatocytes. It should be administered within 48 hours of mushroom ingestion. The current recommended dose is 20 to 50 mg/kg/day IV, which should be continued for 48–96 hours. High dose penicillin G is also known to displace amatoxin and promote its excretion. The recommended dose is 1,000,000 IU/kg for first day and 500,000 IU/kg for next two days via continuous IV administration. Some studies suggest co-administration with NAC as

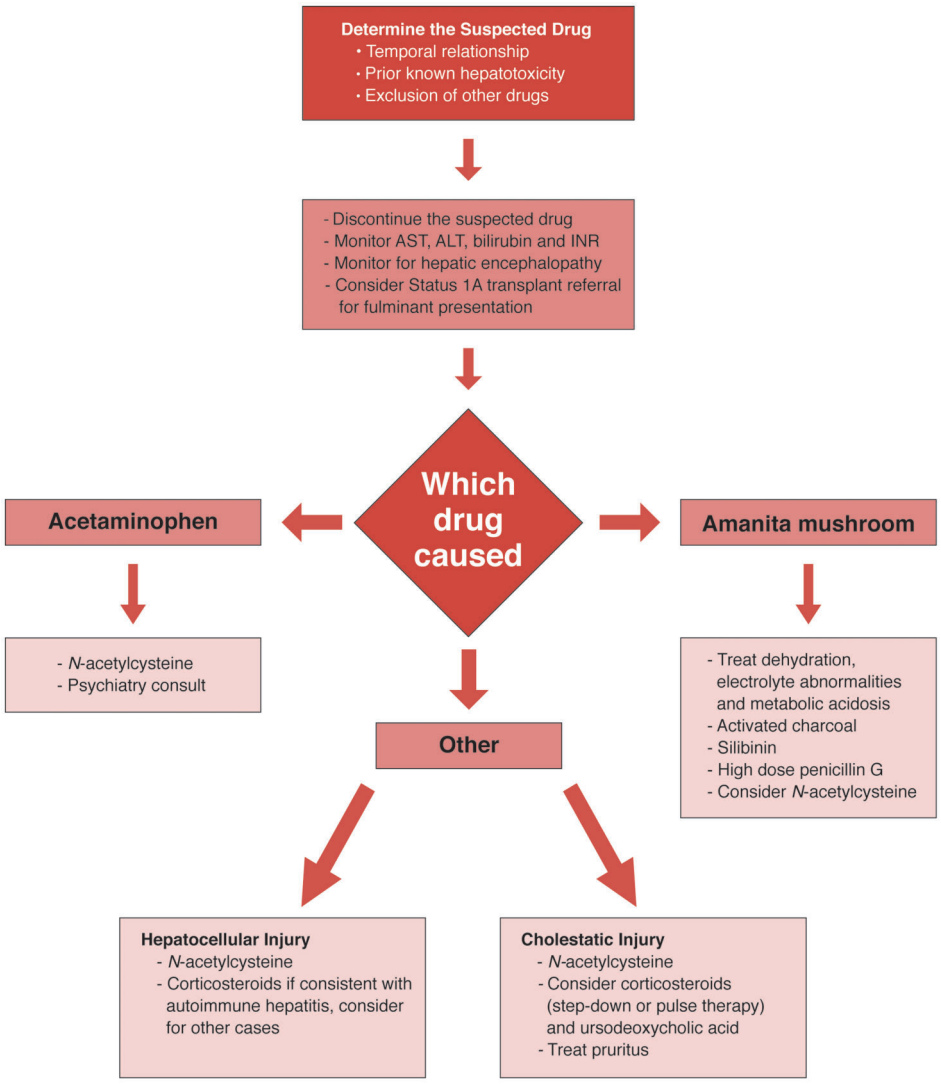

Fig. 1. Proposed treatment algorithm

well. Finally, if started early, the Molecular Adsorbent Recirculating System may be considered as it does improve liver function, although no specific studies have been done with Amanita mushroom poisoning.[31]

Patients who present with fever, rash, and eosinophilia should be considered for a diagnosis of drug-induced autoimmune hepatitis. If the DILI is severe, corticosteroid therapy should be considered as studies have demonstrated normalization of biochemical tests within six months.[33]

Finally, patients who present with a cholestatic picture may complain of intense pruritus. Treatment options for these patients include emollients, hydroxyzine, diphenhydramine, bile acid resins, and rifampicin.[34]

Potential role for liver assist devices

Extracorporeal systems have progressed through advances in genetically produced cell lines, stem cell-derived functional hepatocytes, immortalized human hepatocytes as well as improved techniques and methods for preserving the hepatocytes. Demetriou et al. conducted the first prospective randomized trial using the HepatAssist Liver Support System. The system, composed of a hollow-fiber cartridge lined with porcine hepatocytes, was used in a multi-center trial showing survival benefit to those treated.[35] Advances in bioartificial livers continue with current trials being conducted by Vital Therapies and Hepa Wash GmbH (clinicaltrials.gov). These devices provide the potential for significant benefit to patients with DILI, subacute fulminate failure, and fulminate failure; and we are encouraged for the use of this technology in the future treatment of these patients.

Liver transplant referral considerations

The King's College criteria have been developed for both paracetamol and non-paracetamol causes in order to determine when a patient should be initially referred for transplantation. The criteria include a prothrombin time (PT) over 100 seconds or at least three of the following: PT over 50 seconds, bilirubin> 300 micromol/Liter, age below 10 or

over 40, an interval between jaundice and encephalopathy greater than seven days, or drug toxicity.[37] Other criteria that may be used include Clinchy's criteria and Escudie's criteria.

Patients with fulminant liver failure, defined as the presentation of hepatic encephalopathy within eight weeks of the development of symptoms related to liver disease, should be referred for transplant. In the United States, according to United Network for Organ Sharing (UNOS), a status 1A listing may be obtained if the patient has a life expectancy of seven days or less, does not have a pre-existing liver disease, and is in the intensive care unit requiring either ventilator assistance or dialysis or with an INR greater than two.[38] However, it is important to keep in mind the contraindications for transplant, which include significant comorbidities and active malignancy. Each patient should be considered on a case-by-case basis, and the guidelines should be consulted when considering a patient for transplant.

Conclusions

DILI remains an important cause of liver disease. Although it has a varied presentation and multiple possible drug causes, treatment for all cases requires discontinuation of the offending agent. If a patient has ingested acetaminophen or Amanita mushrooms, appropriate therapy should be administered. All patients can now be considered for NAC therapy and should be monitored for normalization of biochemical tests. Finally, early referral for liver transplant may be life saving for some patients.

Conflict of interest

None

Author contributions

Writing the manuscript and creating figures and tables (CG), performing literature searches (CG, XZ), and editing and revising the manuscript (XZ).

References

[1] Zimmerman H. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd edition. Philadelphia: Lippincott, Williams &Wilkins; 1999.

[2] Dienstag J L, Isselbacher K J. Toxic and drug-induced hepatitis. Harrison's Principles of Internal Medicine 2001;2:1737–1741.

[3] Lee W, Senior J. Recognizing drug-induced liver injury: current problems, possible solutions. Toxicol Pathol 2005;33:155–164. doi: 10.1080/01926230590522356.

[4] Kaplowitz N. Drug-induced liver disorders: implications for drug development and regulation. Drug Saf 2001;24:483–490. doi: 10.2165/00002018-200124070-00001.

[5] Chang CY, Schiano TD. Review article: drug hepatoxicity. Aliment Pharmacol Ther 2007;25:1135–1151. doi: 10.1111/j.1365-2036.2007.03307.x.

[6] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, *et al*. 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. doi: 10.7326/0003-4819-137-12-200212170-00007.

[7] Vuppalanchi R, Liangpunsakul S, Chalasani N. Etiology of new-onset jaundice: how often is it caused by idiosyncratic drug-induced liver injury in the United States? Am J Gastroenterol 2007;102:558–562.

[8] Sembera S, Lammert C, Talwalkar J, Sanderson SO, Poterucha JJ, Hay JE, *et al*. Frequency, clinical presentation and outcomes of drug-induced liver injury after liver transplantation. Liver Transpl 2012;18:803–810. doi: 10.1002/lt.23424.

[9] Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, and Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013;144:1419–1425. doi: 10.1053/j.gastro.2013.02.006.

[10] Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, *et al*. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008;135:1924–1934. doi: 10.1053/j.gastro.2008.09.011.

[11] Wang YP, Shi B, Chen, YX, Xu J, Jiang CF, and Xie WF. Drug-induced liver disease: an 8-year study of patients from one gastroenterological department. J Dig Dis 2009;10:195–200.

[12] Lammert C, Bjornsson E, Niklasson A, Chalasani N. Oral medications with significant hepatic metabolism at higher risk for hepatic adverse events. Hepatology 2010;51:615–620. doi: 10.1002/hep.23317.

[13] Farrell GC. Liver disease caused by drugs, anesthetics, and toxins. In: Feldman M, Friedman LS, Sleisenger MH, editors. Gastrointenstinal and liver disease. 7th edition. Philadelphia: WB Saunders; 2002. p. 1403–1447.

[14] Aragon G, Younossi ZM. When and how to evaluate mildly elevated liver enzymes in apparently healthy patients. Cleve Clin J Med 2010;77:195–204. doi: 10.3949/ccjm.77a.09064.

[15] De Valle MB, Klinteberg V, Alem N, Olsson R, Björnsson E. Drug-induced liver injury in a Swedish university hospital out-patient hepatology clinic. Aliment Pharmacol Ther 2006;24:1187–1195. doi: 10.1111/j.1365-2036.2006.03117.x.

[16] Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, García-Ruiz E, *et al*. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512–521. doi: 10.1016/j.gastro.2005.05.006.

[17] Bell LN, Chalasani N. Epidemiology of idiosyncratic drug-induced liver injury. Semin Liver Dis 2009;29:337–347. doi: 10.1055/s-0029-1240002.

[18] Lucena MI, Andrade RJ, Kaplowitz N, García-Cortes M, Fernández MC, Romero-Gomez M, *et al*. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and gender. Hepatology 2009;49:2001–2009. doi: 10.1002/hep.22895.

[19] Schomaker S, Warner R, Bock J, Johnson K, Potter D, Van Winkle J, *et al*. Assessment of emerging biomarkers of liver injury in human subjects. Toxicol Sci 2013;132:276–283. doi: 10.1093/toxsci/kft009.

[20] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ UCM174090.pdf. Accessed December 20, 2013.

[21] Rochon J, Protiva P, Seef LB, Fontana RJ, Liangpunsakul S, Watkins PB, *et al*. Reliability of the Roussel Uclaf Causality Assessment Method for assessing causality in drug-induced liver injury. Hepatology 2008;48:1175–1183. doi: 10.1002/hep.22442.

[22] Takikawa H, Takamori Y, Kumagi T, Onji M, Watanabe M, Shibuya A, *et al*. Assessment of 287 Japanese cases of drug induced liver injury by the diagnostic scale of the International Consensus Meeting. Hepatol Res 2003;27:192–195. doi: 10.1016/S1386-6346(03)00232-8.

[23] Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatoxicity. Hepatology 2001;33:123–130. doi: 10.1053/jhep.2001.20645.

[24] Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology 1997;26:664–669. doi: 10.1002/hep.510260319.

[25] Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, *et al*. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856–864. doi: 10.1053/j.gastro.2009.06.006.

[26] Wree A, Dechene A, Herzer K, Hilgard, Syn WK, Gerken G, *et al*. Steroid and ursodesoxycholic acid combination therapy in severe drug-induced liver injury. Digestion 2011;84:54–59. doi: 10.1159/000322298.

[27] Yarema MC, Johnson DW, Berlin RJ, Sivilotti ML, Nettel-Aguirre A, Brant RF, *et al*. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med 2009;54:606–614. doi: 10.1016/j.annemergmed.2009.05.010.

[28] Woodhead JL, Howell BA, Yang Y, Harrill A, Clewell HJ, Andersen ME, *et al*. An analysis of N-acetylcysteine treatment for acetaminophen overdose using a systems model of drug-induced liver injury. J Pharmacol Exp Ther 2012;342:529–540. doi: 10.1124/jpet.112.192930.

[29] Wolf SJ, Heard K, Sloan EP, Jagoda AS. Clinical policy: critical issues in the management of patients presenting to the emergency department with acetaminophen overdose. Ann Emerg Med 2007;50:292–313. doi: 10.1016/j.annemergmed.2007.06.014.

[30] http://www.acep.org/content.aspx?id=26830, Accessed on December 28, 2013.

[31] Santi L, Maggioli C, Mastroroberto M, Tufoni M, Napoli L, Caraceni P. Acute liver failure cuased by Amanita phalloides poisoning. Int J Hepatol 2012;2012:487480

[32] Gatselis NK1, Liamis G, Makaritsis KP, Dalekos GN. Metabolic acidosis during treatment of mushroom poisoning: a diagnostic pitfall. Intern Med 2012;51:1077–1080.

[33] Czaja A. Drug-induced autoimmune-like hepatitis. Dig Dis Sci 2011;56:958–976. doi: 10.1007/s10620-011-1611-4.

[34] Patel T, Yosipovitch G. Therapy of pruritus. Expert Opin Pharmacother 2010; 11:1673–1682. doi: 10.1517/14656566.2010.484420.
[35] Demetrious AA, Brown RS, Busuttil RW, Fair J, McGuire BM, Rosenthal P, *et al*. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. Ann Surgery 2004;239:660–670. doi: 10.1097/01.sla.0000124298.74199.e5.
[36] http://clinicaltrials.gov/show/NCT01079091. Accessed on December 30, 2013.
[37] O'Grady JG1, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–445.
[38] http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf, Accessed on December 29, 2013.