Thursday, 28 June 2012

Review: Use of Hepatotoxic Drugs in Chronic Liver Disease

[1]Balthasar L. Hug, M.D., M.B.A., M.P.H.

[2]Christian Surber, Ph.D.

[3]David W. Bates, M.D., M.Sc.

Word count Abstract: 235
Word count text body: 3712

[1] Division of Internal Medicine, Basel University Hospital, Basel, Switzerland.

[2] Division of Pharmaceutical Service, Basel University Hospital, Basel, Switzerland.

[3] Division of General Internal Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Acknowledgements:
Conflicts of interest: none declared.
Ethical conflicts: none declared.
Funding: The authors did not receive any funding.

Corresponding author:
Balthasar L. Hug, M.D., M.B.A., M.P.H., Division of Internal Medicine, Basel University Hospital, Petersgraben 4, 4059 Basel, Switzerland., Tel. +41-61-328 68 28, Fax +41-61-265 47 22, E-Mail: bhug@uhbs.ch

Keywords: Liver, illness, chronic, cirrhosis, drug treatment, liver toxicity, dose adaptation, clinical decision support system, electronic prescription

Contents

Abstract

Cirrhosis and chronic liver disease are common illnesses that cause high mortality and require treatment. Medication use in these patients may be challenging because of idiosyncratic or dose dependent drug toxicity. Therefore, drug choice and drug dose adaptations play an important role. The objective of this clinical review is to discuss the literature about and challenges in drug use in patients with chronic liver disease.

To make good decisions regarding drug choice and dose adjustments in these patients, well defined clinical information about diagnoses and laboratory results (creatinine, International Normalized Ratio, bilirubin and serologies) as well as in some instances pathological findings like liver biopsies are needed. In a second step, these data should be organized in electronically supported clinical decision systems, which can then assist providers in making choices about medication selection and dosage.

In summary, while substantial research has been done in the field of drug use in patients with liver dysfunction, a great deal also remains to be learned. Although many of these patients can now be identified, it is still very difficult to assess their individual level of hepatic function. The degree of risk associated with drug use and how best to use medications in these patients represents an important area for further study. In the future, pharmacogenomics and electronic linking of clinical data may well prove helpful for making decisions about optimal drug choices in this complex group of patients.

1. Introduction

Cirrhosis and other chronic liver diseases (CLD) are common illnesses in the general population, which lead to additional hospitalizations, medical treatment and a high mortality in affected patients. According to the National Center for Health Statistics, the age-adjusted death rate in 2004 was 9.0/100,000 US inhabitants per year dying of CLD making it the twelfth leading cause of death(1). One recent study found that 1.7% of patients in a population in the greater Boston area suffered from CLD (2).

Serious drug-induced liver failure represents the leading identifiable cause of acute liver failure in the United States (3, 4). Drugs may be idiosyncratically hepatotoxic or have dose dependent hepatoxicity. In one cohort study with 461 cases of drug-induced liver injury, 53% of patients had to be hospitalised and 4% suffered severe liver failure; of these, 12 died and 6 received a liver transplant(5). In the mentioned study, 32% of the culprit substances were antibiotics, 17% neurotropic drugs, 17% musculoskeletal and 10% gastrointestinal active drugs. In the United Network for Organ Sharing (UNOS) database (1990-2002), acetaminophen alone or in combination accounted for 49% of liver transplantation cases (3).

Drugs are metabolized and excreted almost exclusively by the liver and the kidneys. Failure of one of these organ systems may have an important impact on patient safety and drug dose adjustment. In patients with chronic renal insufficiency, it has been well established that dosages of nephrotoxic and renally excreted drugs should be adjusted, and some drugs should probably be avoided altogether (6, 7). In these patients, rates of adverse drug events have recently been shown to reach 10% of admissions(8). Many drugs are hepatically metabolized, and it stands to reason that it might make sense to alter dosages and avoid certain medications in patients with CLD, although it has been much less clear how important this is relative to the situation in chronic renal insufficiency.

This review addresses issues of the diagnosis of chronic liver illness, estimating the hepatic functional status, mortality risk stratification and drug choice in CLD. We reviewed the literature on this topic of the last 10 years adding single older landmark papers as well.

2. Diagnosis of Chronic Liver Illness

Clinical judgment plays a key role in the diagnosis of the liver disease, but objective parameters such as laboratory values, liver biopsy and serologies are also important. Liver biopsy remains the gold standard for assessment and staging of liver inflammation and fibrosis before potential treatment(9, 10) but is no longer needed to establish the diagnoses of chronic hepatitis B or C(11). There are several biopsy scores for the stages of liver inflammation and fibrosis with no final consensus on which score to use; three of the most used are mentioned in the following. First, Knodell et al (1981) published a score involving both inflammation and fibrosis (12); the Scheuer system (1991) described for the first time inflammatory grading and fibrosis staging separately(13). Five years later the French METAVIR group consisting of several hepatology specialists published a score using grading of inflammation from A0 (no inflammatory activity) through A3 (severe inflammation) as well as fibrosis staging from F0 (no fibrosis through F4 (cirrhosis)(14).

Serology is used to screen for hepatitis B and C for more than a decade using enzyme immunoassay (EIA) also called enzyme-linked immunosorbent assay (ELISA)(15). These tests bind to antigenic proteins such as the recombinant C-100 protein from the hepatitis C virus(15). Third generation ELISA tests for hepatitis C show a sensitivity of 94-100% and a specificity of 97-98.8% compared to the reference of polymerase chain reaction (PCR) in a review of evidence for the U.S. Preventive Services Task Force(16). Hepatitis B (HBs) antigen is generally acknowledged to be the hallmark of chronic hepatitis B. Today, HBs antigen, HBe antigen and HBV DNA levels are analyzed in chronic hepatitis B(17). HBs

antigen titres correlate with HBV DNA levels in different stages of chronic hepatitis B except in HBe antigen negative hepatitis B(17).

The most commonly used diagnosis classification systems are the International Classification of Diseases (ICD)-9-CM and ICD-10. ICD-9-CM (clinical modification) is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States(18). In ICD-9-CM, chronic liver disease and cirrhosis are coded in 571 and chronic viral hepatitis is coded in 070.3 (chronic hepatitis B) and 070.54 for chronic hepatitis C. In ICD-10, diseases of the liver are coded K70-K77 and chronic viral hepatitis B18(19).

Sociodemographic factors may influence the prevalence of certain disease etiologies in CLD. As an example, of 20,158 patients with CLD in one recent study located in the urban area of Boston 30.1% of patients were diagnosed with chronic hepatitis C, 7.5% with chronic hepatitis B and 1.8% with biliary cirrhosis; the diagnoses associated with alcohol abuse made up for 8.4% of patients(2). In contrast, *Said et al* found in their in-patient university hospital setting of 2,859 patients in Wisconsin, that 29.9% of patients suffered from alcohol associated liver disease and 21.8% from hepatitis C(20). Therefore, comparing cohorts with chronic liver disease warrants diligent comparison of sociodemographic factors and comorbidities.

3. Estimating hepatic functional status and mortality risk stratification

Liver function assessment may be challenging because of lack of an endogenous marker such as creatinine in renal failure(21). Generally, laboratory parameters such as aminotransferases, bilirubin, alkaline phosphatase (AP), albumin and prothrombin time (International Normalized Ratio, INR) are used. Single laboratory parameters such as aminotransferase levels have been suggested to estimate liver functional status and patient outcome(22-24). However, the differential diagnoses of elevated liver aminotransferase levels are broad and include infections with hepatitis A, B and C, Ebstein-Barr (EBV) and

cytomegaly (CMV) viruses, chemotherapy, hepatic steatosis, hepatic fibrosis among many others. Furthermore, alanine aminotransferase (ALT) levels may show dependency on body mass index (BMI) and gender(25); even caffeine seems to have an impact on ALT levels(26). Therefore, causality and predictive power of single tests have been challenged and patterns of liver function tests with or without clinical parameters have been developed but are rarely diagnostic.

One of the earliest and most widely applied mortality prediction models, the Child-Turcotte-Pugh (CTP) classification, relies on clinical judgement (encephalopathy, ascites) and laboratory parameters (INR, bilirubin, albumin) with all parameters being measured on a three point scale(27-29). It was developed more than thirty years ago to assess preoperative risk before esophageal shunt operations in patients with liver dysfunction. However, several groups have challenged the CTP score in recent years. Above all, observer dependency with a low kappa coefficient regarding clinical patient characteristics and the iatrogenic influence on plasma albumin level have been criticized (30). Newer models such as the Model for End-Stage Liver Disease (MELD) have been successfully developed and use laboratory parameters only ($3.8 \times \log_e$ (bilirubin, mg/dL) + $11.2 \times \log_e$ (INR) + $9.6 \times \log_e$ (creatinine, mg/dL)+6.4) (30, 31). The MELD score has been used in many clinical settings, such as to predict patient outcome in liver transplantation, insertion of transjugular intrahepatic portosystemic shunts, alcoholic hepatitis, and to predict fulminant hepatic failure in patients admitted for acetaminophen toxicity (28, 30, 32-34). Its generalizability to patients with diverse etiologies of liver disease and over longer periods of time is not clear. Its predictive capacity regarding mortality in patients with alcohol-induced, postnecrotic or primary-biliary cirrhosis has been reported to reach 78% (95% CI 0.74-0.81) over a period of three months (31). The predictive power of the MELD score over the CTP score has been challenged; above all the CTP adapted with creatinine as one of its score factors seems to predict mortality with a similar c-statistic (35, 36). Nevertheless, CTP depends on clinical assessments such as encephalopathy

and ascites, which might not be readily documented and might vary among physicians of varying clinical experience. The advantage of the MELD score is its objectivity and independence regarding clinical skills and experience of the examining physician.

Both the CTP and the MELD scores allow stratification of patients with chronic liver disease with respect to risk of mortality(2, 37). Above all the MELD score has been well studied in this regard and is used for organ allocation in liver transplantation(30). *Wiesner at al* found a 3-months mortality of 1.9% in patients with CLD and a MELD score of </=9 and a 3-months mortality of 71.3% in patients with a MELD score of =/>40(30) while *Kamath et al* found respective 3-months mortality rates of 1-8% (MELD score </=9) and 100% (MELD score =/>40)(31). Modification of the CTP score has resulted in a similar predictive power regarding mortality compared to the MELD score(29).

4. Drug Properties and Choice

Drug properties like the extrarenally excreted fraction, plasma protein binding and metabolism pathways in the liver and kidneys also affect how much viable liver tissue is needed to properly metabolize and excrete a specific drug. To this day, there exists no exo- or endogenous substance to estimate the hepatic clearance of drugs comparable to creatinine clearance in renal failure although many substances have been evaluated(21). Another issue is direct liver toxicity of certain drugs. Methods to guide clinicians in drug choice and dose adjustments in chronic liver disease are badly needed. There is a wide array of literature on dose adjustment with respect to general principles of hepatic drug clearance and single drug dose adjustments in patients with cirrhosis (21, 38). However, many issues regarding liver drug metabolism in CLD remain.

Specifically, some of the main questions are: (1) What are key characteristics of drugs regarding liver metabolism? (2) Which drugs are directly hepatotoxic? What kind of liver injury do they inflict? (3) What are the kinetics of specific drugs in patients with liver

dysfunction? Secondary questions are: If little is known about the metabolism of a specific drug in chronic liver disease, should it be prescribed, and in situations when it is, on what grounds should the drug dose for an individual patient be selected?

4.1 Key characteristics of drugs regarding liver metabolism

There are many different ways to classify hepatic drug metabolism. However, the key drug class regarding hepatic metabolism in chronic liver illness are drugs with a high hepatic flow-limited extraction. High extraction drugs typically show a liver clearance that is > 60% flow dependent, and flow is diminished in cirrhosis. This implies that the first pass effect of these drugs is reduced in chronic liver disease and free serum levels are expected to be higher than normal. ClHep = Q x E where ClHep is the hepatic clearance of a drug, Q = blood flow through liver and E = hepatic extraction of drug(21). The following are examples of drugs with a high hepatic extraction rate of >60% (= first pass effect) in healthy humans; they therefore show a clinically relevant flow dependent hepatic metabolism requiring dose reduction in liver illness: cyclosporine, fluorouracil, idarubicin, lovastatin, morphine, pentazocine, quetiapine, tacrolimus, verapamil, vinblastine and vincristine(21, 38).

4.2 Direct hepatotoxicity: Drugs and types of inflicted liver injury

Directly hepatotoxic drugs represent another issue, and the toxicity they cause can be dangerous and costly. Some of them like antiepileptics and tuberculostatics are used quite commonly in patients with chronic liver disease. Different patterns of hepatotoxicity have been discussed and they may or may not be predictable(39-41); most commonly, the approach is either clinically, by means of laboratory values, histo-pathologically or a combination of these. The clinical approach may show features such as acute hepatitis (acetaminophen, isoniazid, nevirapine, ritonavir, troglitazone), chronic hepatitis (dantrolene, diclofenac, methyldopa, minocycline, nitrofurantoin), acute cholestasis (ACE-inhibitors, amoxicillin/clavulanic acid, chlorpromazine, erythromycine, sulindac) or a mixed pattern like phenytoin or sulfonamides(40, 42). The laboratory approach may show patterns of liver injury

including the hepatocellular pattern with an elevated alanine transferase (ALT; e.g. acetaminophen, allopurinol, amiodarone, NSAIDs, statins and valproic acid), the cholestatic pattern with elevated total bilirubin and alkaline phosphatase (ALP; e.g. amoxicillin-clavulanic acid, anabolic steroids, clopidogrel and oral contraceptives) as well as the mixed pattern with elevated ALP and ALT (e.g. azathioprine, carbamazepine, phenytoin and trimethrim-sulfomethoxazole)(39, 43). Histo-pathologically, the most common features are the microvascular steatosis with small fat droplets in the hepatocytes (valproic acid, tetracyclines, non-reverse transcriptase inhibitors), acute hepatitis with hepatocellular swelling, inflammatory changes with disarray of the portal triad (e.g. isoniazid), cholestatic injury with hepatocellular swelling and bile-stained hepatocytes (amoxicillin/clavulanic acid, chlorpromazine) and eosinophil-containing inflammation (e.g. phenytoin)(40, 43). Other histo-pathological features include non-alcoholic steatohepatitis after exposure to amiodarone and tamoxifen, cirrhosis after methothrexate and methyldopa as well as veno-occlusive disease after busulfan and cyclophosphamide(40, 41). Granulomatous hepatitis is known to occur after carbamazepine, allopurinol and halothane exposure among others(41, 44). In rare cases, submassive to massive hepatic necrosis has been observed (indomethacin, labetalol, nicotinic acid, valproic acid and trazodone)(41).

4.3 Pharmacokinetics in patients with liver dysfunction

Predictive pharmacokinetic models for patients with chronic liver disease are scarce because of the highly complex metabolic circumstances in each individual. Not only does the kind and degree of liver disease and the drug properties play an eminent role, but chronic liver disease and above all cirrhosis also affect other organ systems such as the intestine, the lungs and the kidneys. In chronic liver disease, the drug dose usually does not have to be adapted unless there is a cirrhosis of the liver(45).

In cirrhosis, all three pharmacokinetic phases are affected, namely absorption, distribution and elimination of the drug. Because of the high portosystemic pressure, drugs

won't be absorbed as readily in the gastrointestinal tract. The reduced presystemic metabolisation in the liver leads to a higher bioavailability of intermediate to high extraction drugs as outlined above(21, 38). Examples of intermediate to high extraction drugs and their increase in bioavailability in cirrhosis are +132% in flumazenil, +115% in morphine, +100% in midazolam, +91% in labetalol and +60% in verapamil (38). The distribution process into the body compartments depends on the unbound fraction of the drug. The distribution volume is getting larger for protein-bound drugs, since albumin and other plasma proteins are lowered. The same is true for water soluble drugs, because of the volume overload and ascites in patients with cirrhosis(38). Drug elimination is impaired in hepatic cirrhosis by a reduced cell mass of functional hepatocytes and their enzymes. Of the two main enzyme systems within the hepatocytes, the P450 family with its six known subunits seems to be more affected by liver disease than glucuronidation by the uridinediphosphate (UDP)-glucoronosyltransferase (GT) family(46); it has been suggested that UDP-GT is even up-regulated in cirrhosis(47). Intra- or extrahepatic biliary obstruction may block drug elimination and change pharmacokinetics. Intrahepatic cholestasis may be caused by drugs such as erythromycin, amoxicilline/clavulanic acid or ACE-inhibitors, primary sclerosing cholangitis, during pregnancy or the familial progressive form(48, 49). Diseases such as bile duct stones, cancer of the bile duct and pancreas may cause extrahepatic cholestasis.
Renal excretion is an important in two ways: 1) most drugs are excreted at least partially by the kidneys and 2) chronic liver disease is often accompanied by renal failure. Unfortunately, neither serum creatinine levels nor creatinine clearance seem to be fully reliable markers of the renal dysfunction commonly associated with liver disease since muscle mass often is diminished and the estimated glomerular filtration rate by Cockroft-Gault may therefore be too high (45).

4.4 Pharmacogenetics

The science of the influence of the individual genetic pattern on drug metabolism is developing fast. For example, it has been recognized that breast cancer is a genetically heterogeneous disease and that the presence of the HER2 oncogene has an influence on the treatment success with trastuzumab(50). Furthermore, it is well known that genetic patterns of the cytochrome P 450 in the liver have an influence on drug metabolism; e.g. the anti-estrogen tamoxifen is metabolized by the CYP 2D6 subfamily of the P 450 enzyme complex. A recent publication found that tamoxifen is metabolized more or less due to genetic variation in the CYP 2D6 enzyme influencing prognosis and recurrence of breast cancer (51). Therefore, knowledge of genetic patterns of liver metabolism may have a direct impact on patient life expectancy. Although powerful tests are already available commercial solutions are still lacking and warrant further research(52, 53).

4.5 Dose adjustment in single drugs

To our knowledge, there exists no systematic, clinically feasible way to adjust drug dosage in patients with chronic liver illness. As a rule of thumb, it has been suggested that there is no need for dose adjustment unless cirrhosis of the liver is present(45). As we may not know whether cirrhosis is present in an individual patient, data from observational studies are needed. There are certain drug classes that are associated with higher mortality in these patients and therefore may warrant dose reduction or even stopping of the drugs. A recent study found that the anti-cancer drugs docetaxel (hazard ratio (HR) 7.53, 95% CI 3.91-14.48) and oral etoposide (HR 3.55, 95% CI 2.15-5.87), oral morphine (HR 2.26, 95% CI 1.78-2.86) as well as the immunosuppressant sirolimus (HR 1.81, 95% CI 1.02-3.21) were associated with higher mortality in patients with chronic liver disease. This results remained even after adjustment for a cancer diagnosis, liver disease, age and laboratory values (bilirubin, creatinine and INR), although it cannot be concluded these associations were causal(2).

The anti-cancer drug docetaxel causes adherence of microtubuli to each other within the cell and therefore inhibits DNA, RNA and protein synthesis. It is used in breast cancer,

metastatic prostate cancer, non-small cell lung cancer and gastric adenocarcinoma. The Federal Drug and Food Administration (FDA) issued the following drug labelling because of its liver toxicity. Docetaxel should not be administered if the total bilirubin is greater than the upper limit of normal (ULN) or AST/ALT are higher than 1.5 times ULN and alkaline phosphatase (AP) is higher than 2.5 times ULN(54). If AST and/or ALT are elevated up to 1.5 times ULN with AP and bilirubin within normal limits, 100% of the normal dose should be applicable. With AST/ALT between 1.6 to 6.0 times ULN only 75% of the normal dose should be used(55). Treating physician should reconsider using docetaxel above this threshold.

The topoisomerase II inhibitor etoposide causes DNA strand breaks and is used against small cell cancer, lymphoma and refractory testicular cancer among others. Although generally not considered hepatotoxic in standard doses, there have been cases reports on severe hepatocellular injury(56). Suggestions are to reduce the dose to 50% if AST levels are >160 U/L or >3 times ULN and bilirubin levels between 1.5 – 3.0 mg/dL(55, 56).

In addition, the use of oral morphine was associated with a more than twofold higher mortality in patients with chronic liver illness even after adjustment for liver disease and cancer(2). This might be due to the high extraction (>60%) in the liver impaired by liver illness(21). Another potential reason for the association, though, is the use of this drug in end-of –life situations which may lead to a selection bias in epidemiologic studies(57). We suggest that caution is warranted using oral morphine in these patients because of its metabolism and patients need to be well monitored for alertness and respiratory rate.

The macrolide antibiotic and immunosuppressant sirolimus has also been shown to be associated with an almost twice as high a mortality in patients with persistent liver disease(2). Since the drug is used for solid organ transplantation such as the kidney, the higher mortality may reflect an intrinsic toxicity or the influence of the underlying disease. One study found significant differences to other immunosuppressants regimes after kidney transplants

suggesting intrinsic sirolimus toxicity, such as more biopsy proven transplant rejections and a lower glomerular filtration rate(58, 59). Serious adverse events were more common in the sirolimus group compared to the other immunosuppressants. Unlike other immunosuppressants e.g. cyclosporin, sirolimus does not seem to promote de novo cancer growth nor metastasizing by inhibiting angioneogenesis(60). Since sirolimus belongs to the group of high extraction drugs (>60%) and shows a potential for causing kidney damage that may facilitate hepato-renal syndrome, we suggest avoiding the drug in patients with persistent liver disease. If it is needed, we suggest using the minimum drug dose possible, and monitoring serum levels as well as checking regularly for side effects.

5. Potential models for drug dose adaptation and future research

Individual drug dose adaptation in chronic liver illness with potentially hepatotoxic drugs remains a challenge. Before marketing, kinetics of a drug are generally estimated from healthy individuals; in the post marketing phase there is little incentive for companies to evaluate kinetics in patients with disease let alone single diseases. One way to tackle the challenge next to kinetics is to combine objective patient and drug informations and to derive from there a prognostic stratification as well as the best possible choice of drug and its dosage.

Patient information should include sociodemographic parameters, information about the liver disease, comorbidities, laboratory parameters and in the future pharmacogenomic information. Data about the drug should include its intrinsic potential of liver toxicity, known kinetics in liver disease, usual dosage patterns, time span between applications and total amount applied. Smart IT-supported clinical decision support systems could provide the knowledge base and compute suggestions of drug use for the clinician combining the information.

6. Outlook

A great deal of additional research is needed in this area. Clearly, research in how pharmacogenomics affects hepatic metabolism is needed. In addition, we believe it will be helpful to integrate clinical data to predict outcome and support dosing recommendations, as well as sociodemographic informations, diagnosis, liver function tests, type of drugs applied and their expected liver metabolism. Work is also needed to help make recommendations about whether some drugs should be avoided altogether, and whether dosing should be altered. Eventually, electronic decision support systems should guide the clinician through the process of prescribing the correct drug in the correct dose in patients with liver disease, as has become possible in patients with renal insufficiency(7).

7. Conclusions

While substantial research has been done in this area, a great deal also remains to be learned. Many patients with chronic liver dysfunction can now be identified, although it is still a challenge to assess the level of metabolic function in patients with CLD. The degree of risk associated withto the use of medications that show a high hepatic extraction rate or that are directly hepatotoxic in this population represents an important area for further study. While single drug classes such as anticancer drugs or immunosuppressants show a well documented hepatotoxicity, the use of many other medications remains to be defined in patients with CLD.

Conflicts of interest: none declared.

Ethical conflicts: none declared.

References

1. **Minino AM Heron MP, Smith BL.** Deaths: preliminary data for 2004. *Natl Vital Stat Rep*. 2006;54(19):1-49.
2. **Hug BL, Lipsitz SR, Seger DL, Karson AS, Wright SC, Bates DW.** Mortality and drug exposure in a 5-year cohort of patients with chronic liver disease. *Swiss Med Wkly*. 2009;139(51-52):737-46.
3. **Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P.** Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl*. 2004;10(8):1018-23.
4. **Ostapowicz G, Fontana RJ, Schiodt FV, 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(12):947-54.
5. **Andrade RJ, Lucena MI, Fernandez MC, et al.** Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005;129(2):512-21.
6. **Bennett WM, Singer I, Coggins CJ.** A guide to drug therapy in renal failure. *Jama*. 1974;230(11):1544-53.
7. **Chertow GM, Lee J, Kuperman GJ, et al.** Guided medication dosing for inpatients with renal insufficiency. *Jama*. 2001;286(22):2839-44.
8. **Hug BL, Witkowski DJ, Sox CM, et al.** Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. *Kidney Int*. 2009;76(11):1192-8.
9. **Rosen HR.** Clinical practice. Chronic hepatitis C infection. *N Engl J Med*. 2011;364(25):2429-38.
10. **Lefkowitch JH.** Liver biopsy assessment in chronic hepatitis. *Arch Med Res*. 2007;38(6):634-43.
11. **Guido M, Mangia A, Faa G.** Chronic viral hepatitis: the histology report. *Dig Liver Dis*. 2011;43 Suppl 4:S331-43.
12. **Knodell RG, Ishak KG, Black WC, et al.** Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*. 1981;1(5):431-5.
13. **Scheuer PJ.** Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol*. 1991;13(3):372-4.
14. **Bedossa P, Poynard T.** An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology*. 1996;24(2):289-93.
15. **Gretch D, Lee W, Corey L.** Use of aminotransferase, hepatitis C antibody, and hepatitis C polymerase chain reaction RNA assays to establish the diagnosis of hepatitis C virus infection in a diagnostic virology laboratory. *J Clin Microbiol*. 1992;30(8):2145-9.
16. **Chou R, Clark EC, Helfand M.** Screening for hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2004;140(6):465-79.
17. **Kim YJ, Cho HC, Choi MS, et al.** The change of the quantitative HBsAg level during the natural course of chronic hepatitis B. *Liver Int*. 2011;31(6):817-23.
18. National Center of Health Statistics, www.cdc.gov/nchs. Accessed April 18th 2008.
19. International Classification of Diseases, www.who.int/classifications/icd/en/index.html. Accessed April 2nd, 2008.
20. **Said A, Williams J, Holden J, et al.** Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol*. 2004;40(6):897-903.

21. **Delco F, Tchambaz L, Schlienger R, Drewe J, Krahenbuhl S.** Dose adjustment in patients with liver disease. *Drug Saf*. 2005;28(6):529-45.
22. **Yokogawa K, Ido A, Kurihara T, et al.** Serum aminotransferase activity as a predictor for estimation of total clearance of hepatically metabolized drugs in rats with acute hepatic failure. *Biol Pharm Bull*. 2006;29(1):141-5.
23. **Lazo M, Selvin E, Clark JM.** Brief communication: clinical implications of short-term variability in liver function test results. *Ann Intern Med*. 2008;148(5):348-52.
24. **Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I.** Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. *Bmj*. 2004;328(7446):983.
25. **Piton A, Poynard T, Imbert-Bismut F, et al.** Factors associated with serum alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. MULTIVIRC Group. *Hepatology*. 1998;27(5):1213-9.
26. **Ruhl CE, Everhart JE.** Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. *Gastroenterology*. 2005;128(1):24-32.
27. **Child CG Turcotte JG.** Surgery and portal hypertension. In: Child CG, editor: *The liver and portal hypertension*. Philadelphia: Saunders; 1964:50-64.
28. **Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R.** Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646-9.
29. **Huo TI, Lin HC, Wu JC, et al.** Proposal of a modified Child-Turcotte-Pugh scoring system and comparison with the model for end-stage liver disease for outcome prediction in patients with cirrhosis. *Liver Transpl*. 2006;12(1):65-71.
30. **Wiesner R, Edwards E, Freeman R, et al.** Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003;124(1):91-6.
31. **Kamath PS, Wiesner RH, Malinchoc M, et al.** A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464-70.
32. **Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC.** A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864-71.
33. **Schmidt LE, Larsen FS.** MELD score as a predictor of liver failure and death in patients with acetaminophen-induced liver injury. *Hepatology*. 2007;45(3):789-96.
34. **Teh SH, Nagorney DM, Stevens SR, et al.** Risk factors for mortality after surgery in patients with cirrhosis. *Gastroenterology*. 2007;132(4):1261-9.
35. **Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK.** Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment Pharmacol Ther*. 2005;22(11-12):1079-89.
36. **Papatheodoridis GV, Cholongitas E, Dimitriadou E, Touloumi G, Sevastianos V, Archimandritis AJ.** MELD vs Child-Pugh and creatinine-modified Child-Pugh score for predicting survival in patients with decompensated cirrhosis. *World J Gastroenterol*. 2005;11(20):3099-104.
37. **Costa BP, Sousa FC, Serodio M, Carvalho C.** Value of MELD and MELD-based indices in surgical risk evaluation of cirrhotic patients: retrospective analysis of 190 cases. *World J Surg*. 2009;33(8):1711-9.
38. **Verbeeck RK, Horsmans Y.** Effect of hepatic insufficiency on pharmacokinetics and drug dosing. *Pharm World Sci*. 1998;20(5):183-92.
39. **Norris W, Paredes AH, Lewis JH.** Drug-induced liver injury in 2007. *Curr Opin Gastroenterol*. 2008;24(3):287-97.
40. **Kaplowitz N.** Drug-induced liver injury. *Clin Infect Dis*. 2004;38 Suppl 2:S44-8.

41. **Chitturi S, George J.** Hepatotoxicity of commonly used drugs: nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. *Semin Liver Dis*. 2002;22(2):169-83.
42. **Andrade RJ, Lucena MI, Kaplowitz N, et al.** Outcome of acute idiosyncratic drug-induced liver injury: Long-term follow-up in a hepatotoxicity registry. *Hepatology*. 2006;44(6):1581-8.
43. **Navarro VJ, Senior JR.** Drug-related hepatotoxicity. *N Engl J Med*. 2006;354(7):731-9.
44. **Stricker BH, Blok AP, Babany G, Benhamou JP.** Fibrin ring granulomas and allopurinol. *Gastroenterology*. 1989;96(4):1199-203.
45. **Morgan DJ, McLean AJ.** Clinical pharmacokinetic and pharmacodynamic considerations in patients with liver disease. An update. *Clin Pharmacokinet*. 1995;29(5):370-91.
46. **Hoyumpa AM, Schenker S.** Is glucuronidation truly preserved in patients with liver disease? *Hepatology*. 1991;13(4):786-95.
47. **Debinski HS, Lee CS, Danks JA, Mackenzie PI, Desmond PV.** Localization of uridine 5'-diphosphate-glucuronosyltransferase in human liver injury. *Gastroenterology*. 1995;108(5):1464-9.
48. **O'Leary JG, Pratt DS.** Cholestasis and cholestatic syndromes. *Curr Opin Gastroenterol*. 2007;23(3):232-6.
49. **Alissa FT, Jaffe R, Shneider BL.** Update on progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 2008;46(3):241-52.
50. **Regan MM, Gelber RD.** Using clinical trial data to tailor adjuvant treatments for individual patients. *Breast*. 2007;16 Suppl 2:S98-104.
51. **Goetz MP, Knox SK, Suman VJ, et al.** The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat*. 2007;101(1):113-21.
52. **Weinshilboum R.** Inheritance and drug response. *N Engl J Med*. 2003;348(6):529-37.
53. **Evans WE, McLeod HL.** Pharmacogenomics--drug disposition, drug targets, and side effects. *N Engl J Med*. 2003;348(6):538-49.
54. http://www.fda.gov/cder/foi/label/2007/020449s045lbl.pdf, accessed June 13th 2008. 2007.
55. **Floyd J, Mirza I, Sachs B, Perry MC.** Hepatotoxicity of chemotherapy. *Semin Oncol*. 2006;33(1):50-67.
56. **King PD, Perry MC.** Hepatotoxicity of chemotherapy. *Oncologist*. 2001;6(2):162-76.
57. **Glynn RJ, Knight EL, Levin R, Avorn J.** Paradoxical relations of drug treatment with mortality in older persons. *Epidemiology*. 2001;12(6):682-9.
58. **Ekberg H, Tedesco-Silva H, Demirbas A, et al.** Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med*. 2007;357(25):2562-75.
59. **Leichtman AB.** Balancing efficacy and toxicity in kidney-transplant immunosuppression. *N Engl J Med*. 2007;357(25):2625-7.
60. **Gutierrez-Dalmau A, Campistol JM.** Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. *Drugs*. 2007;67(8):1167-98.