Module 3 Self-directed Questions

Answers

1. **What is the typical picture (in the context of lab values) of cholestatic hepatitis and toxic hepatitis ?**

   The main differences: in cholestasis there is a blockage of the bile duct and if severe the person is likely to be jaundiced due to conjugated hyperbilirubinaemia (this may not always be as apparent in toxic hepatitis). In cholestasis there is usually raised ALP and GGT but increases in AST and ALT may be quite mild. In toxic hepatitis there are usually marked increases in AST and ALT, especially if the toxicity is acute. ALP, GGT may also be increased in toxic hepatitis but may not be as marked in cholestasis. Ultrasound of the bile duct will show abnormalities in cholestasis which will not be seen in toxic hepatitis where the toxicity is on the hepatic cells in general rather than focused on the bile duct area.

2. **What is fatty liver? What are the causes and what laboratory value results may indicate fatty liver? (NB consider alcoholic and non-alcoholic).**

   Fatty liver is basically infiltration of fat into the hepatocytes. In some cases this is relatively harmless but in other cases it can progress to serious disease e.g. fibrosis and cirrhosis.

   Nonalcoholic fatty liver disease (NAFLD) is very common. It consists of two stages – a fatty liver and NASH (nonalcoholic steatohepatitis). The only way to distinguish between these two stages is by biopsy of liver tissue.
   A fatty liver is considered a benign condition characterized by fat deposits in liver cells (hepatocytes). This is a reversible condition, and does not have the potential to lead to cirrhosis, liver failure or liver cancer. NASH is when a fatty liver has progressed to inflammation (steatohepatitis) and scarring (steatonecrosis) of the liver. Unlike a fatty liver, NASH is not considered harmless and can progress with the potential to cause cirrhosis, liver failure, and liver cancer.
   Causes of NAFLD include; obesity, diabetes, metabolic syndrome.
   In the early stages fatty liver would be associated with relatively mild increases in AST and ALT. If it progresses to NASH and cirrhosis other markers of liver toxicity would be present.
   Alcoholic fatty liver is very hard to distinguish from NAFLD and differential diagnosis would usually be made on the basis of history of alcohol intake. There may be other markers of alcohol intake such as increased GGT and macrocytosis.

3. **A middle aged man (BMI 35) has a routine screen of LFTs. He has no symptoms, but AST and ALT are both about 1.5 times the ULN. All other LFTs are normal. FBC is normal and he is taking no hepatotoxic drugs. Nil alcohol intake. Comment on the results. Do you think further investigations are required?**

This might be asymptomatic increases in transaminases and this could be due to his obesity. For this man, these slight increases may not be harmful or associated with any disease process. Alcoholic hepatitis appears to be ruled out. Weight loss may normalize the transaminases and should be advised for general health reasons anyway. The AST and ALT should be checked again after a few months and if they have increased, further investigations are necessary to evaluate the possibility of progression to more serious disease. These investigations would include INR, albumin (for chronic liver disease), hepatitis markers (to exclude hepatitis) and perhaps iron chemistry markers (ferritin, serum iron etc), and possibly liver ultrasound/biopsy depending on the magnitude of the increase in transaminases. If the AST and ALT are unchanged (i.e. still slightly raised) it will be down to clinical judgment as to whether further tests are necessary. If there is no other indication of pathology, it may be that transaminases slightly above the ULN are the "normal" values for this man.

4. **In the context of hepatobiliary dysfunction, what could be the cause of dark urine and pale stools? What are some common causes of hyperbilirubinemia and jaundice?**

   If there is bile duct obstruction there is an increase in conjugated bilirubin in the blood stream. As this is water soluble it is excreted in the urine and leads to the dark coloration. As there is a decrease in the excretion of conjugated bilirubin in the bile, less will be present in the faeces, which explains the lighter colour.
   There are many causes of hyperbilirubinemia and jaundice. These include drug–induced, hepatobiliary diseases e.g. biliary cirrhosis, malignancy, infection to name but a few.

5. **A 67 yr old man is to be started on simvastatin for hyperlipidemia. Baseline ALT was 65 IU/mL. Is it OK to go ahead with the statin? If so, would any monitoring be required? Is monitoring of LFTs for people on statins routinely indicated?**

   This man's ALT is only slightly above the ULN and statin use is not contraindicated. Most guidelines and datasheets advise that statin treatment should not be routinely withheld unless the transaminase levels are more than three times the ULN. However, if there were other indications of liver disease, further checks might be indicated.
   Monitoring: it is now widely recognised that routine monitoring of LFTs is not necessary for people taking statins as liver toxicity is rare. However, there is some variance in recommendations and some guidelines still advise a check of LFTs at 3 and 12 months, and after dose increases. My advice would not to monitor routinely. However, if baseline LFTs were raised (especially close to 3 x ULN) I think a precautionary check at 2- 3 months is justified.

6. **Consider various liver diseases such as toxic injury, cirrhosis, acute viral hepatitis, chronic hepatitis, alcoholic liver disease and fatty liver. What is the relative magnitude of the increase in transaminases usually observed?**

   A general order would be:
   Toxic injury > Acute viral hepatitis > Alcoholic liver disease> Chronic Hepatitis > Fatty liver (mild).

7. **Select three drugs that can cause liver toxicity and describe the typical presentation and prognosis.**

   Flucloxacillin; Predominantly cholestatic hepatitis with jaundice, hyperbilirubinaemia, raised GGT and ALP and moderately raised transaminases. Reaction can be delayed for several weeks after stopping the drug. Complete recovery usually occurs but this may take weeks or months.
   Paracetamol; In an overdose, acute toxic liver injury associated with very large increases in transaminases.
   The toxicity is caused by a metabolite of paracetamol which is usually neutralized by glutathione. In an overdose, the stores of glutathione are exhausted and the metabolite can then cause direct injury to liver cells. This can progress to fulminant, fatal toxic hepatitis if the antidote (acetylcysteine) is not given in time.
   Isoniazid;
   This is a non dose-related, idiosyncratic reaction which can range from very mild elevations in AST and ALT which resolve on continued treatment to severe and potentially fatal hepatitis. There are several pre-disposing factors e.g. race, age, gender, acetylator status and concurrent intake of other hepatotoxic agents such as alcohol. For more information see;
   http://emedicine.medscape.com/article/180554-overview

8. **Practice using the Cockcroft and Gault (CG) equation to estimate renal function on some patients. There will be some calculation problems in the module quiz and in the final assessment.**

   I am sure you will all have tried your own examples. Some calculation "problems" will be posted on the site for you to try before the final assessment. The following is useful background to the CG equation.

   The typical adult reference ranges for serum creatinine are 60 – 120 µmol/L for men, and 50-110 µmol/L for women. These ranges vary slightly depending on the laboratory and the reference source used. Some laboratories report using mg/dL or mmol/L, so it can quite confusing. It is important to check that your version of the CG equation uses the units that you input, otherwise you will have to make a conversion. To convert from mg/dL to µmol/L a conversion factor of 88.4 is used. E.g. a serum creatinine of 0.8 mg/dL is equivalent to

about 70 µmol/L (which is equivalent to 0.07 mmol/L). NB serum creatinine alone is not an accurate marker of renal function. A baseline serum creatinine of 2.0 mg/dL (177 µmol/L) may indicate normal kidney function in a young, male rugby player (because of large muscle mass) but a serum creatinine of 1.2 mg/dL (106 µmol/L) can indicate significant renal impairment in an elderly female. This is why the CG equation includes the variables of weight, gender and age.

Cockcroft-Gault Equation

This seems to be the most commonly used version.

$$\text{CrCL (mL/min)} = \frac{(140 - \text{age}) \times \text{*Weight (kg)}}{\text{SCr (µmol/L)}} \times F \qquad F = 1.23 \text{ Males; } 1.04 \text{ Females}$$

*Ideal Body Weight

Example; 54 year old male with a SCr of 109 µmol/L. Weight is 79 kg (not obese so close to IBW) CrCl = 77 mL/min

You may find these on-line calculators useful for CG, eGFR, BSA and IBW calculations.

http://www.medcalc.com/body.html

http://kidney.net.nz/egfr-calculator.html

9. **How is renal function estimated in children? Can the CG equation be used?**
This is quite a specialized area and it is important to realise that the CG is not generally applicable in children. The Schwartz formula is the most widely used but this has recently been updated; see http://jasn.asnjournals.org/cgi/content/abstract/ASN.2008030287v1

Other references to consult include the BNF and specialised pediatric texts.

10. **What is eGFR and how does it differ from CrCl estimation using the CG equation?**
Can eGFR be used to guide adjustment of doses in renal impairment?
(hint check latest BNF on dose adjustment in renal impairment)

I think this is covered well in the BPAC article; here is the link to the on-line version
http://www.bpac.org.nz/magazine/2007/june/renal.asp?page=3
NB this was written before eGFR was being used to guide dose adjustment.

In summary, eGFR (from the MDRD) is an estimate of GFR which is normalized to 1.73m^2. It was derived from a population of African and white Americans with renal disease. It has not been validated in many other populations/ethnic groups. It is a very useful screening tool for the early detection of Chronic Kidney Disease and only requires the persons SCr and age for its calculation. NB, as the MDRD equation was derived in people with renal disease it is not accurate above 60

mL/min/1.73m^2

The CG is an estimate of CrCl which in turn is an estimate of actual GFR as it does take in to account body size. So, CG will give a clearer indication of the person's actual renal function. For values of 60 mL/min/1.73m^2 and less the eGFR will be very close to the CG value in people of normal body size. So, in these situations eGFR is being used increasingly to guide dose adjustment. However, at extremes of body size, obesity and for very toxic drugs the CG equation is still recommended to guide dose adjustment (See BNF).

11. How can an eGFR value be converted to an estimate of actual CrCl ?

The usual way to estimate actual CrCl is to use the CG equation. The estimated CrCL is also an estimate of the persons actual GFR. The CG equation corrects for body size whereas the eGFR is normalized to 1.73m^2

If someone is very tall and very muscular their actual GFR will be greater than the eGFR because GFR is related to body mass – larger bodies have larger kidneys and therefore a higher GFR.

So, let's say we have an eGFR value of 30 mL/min/1.73m^2 for a man who is very athletic, muscular and has a body surface area (BSA) of 2.1 m^2
From this we can estimate the actual GFR from eGFR x 2.1/1.173 = 36 mL/min (see BNF for more information).

If we had the relevant information (Age, IBW, SCr) we could calculate CrCl directly. For some drug dose adjustments it is fine to use eGFR (see BNF). However, for people at extremes of body size and highly toxic drugs it is recommended to use CrCl from CG or actual (sometimes called absolute) GFR as above.