The Weekly Probe

22nd April 2016 **Volume 13 Issue 11**

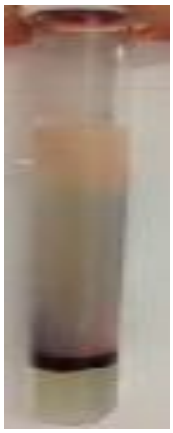
STEMI phone- there is a new mobile carried by the cardiology registrar "in hours" Mon-Fri 0800-1700. The flyer is near the comms clerk – 0401 879 960 if you want to put it in your phone contacts

Dabigatran Reversal – Couple of weeks ago we mentioned the new reversal agent for Pradaxa (dabigatran)- it's now available, Three steps – 1) speak to haem if immediate reversal for life-saving surgical or invasive procedures which cannot be performed whilst therapeutically anticoagulated or if life-threatening bleeding. 2) Two 2.5gm ampoules in 50ml saline over 5-10 min 3) Wait – continue other supportive measures, watch bleeding and repeat coags

THIS WEEK

Last weeks case – Pancreatitis secondary to hyperlipidaemia

A 45yo type 1 diabetic man presents with abdominal pain and vomiting. The lab reports problems with the sample yet reports a lipase of 983- the other results will "take time" What could be going on? Hint below is a picture of the white top tube (serum)



Triglycerides > 50 (normal upper limit 2) – cholesterol 25.2- bicarb 18 – BSL 13 – ketones 3.3.

He was diagnosed as pancreatitis secondary to his hyperlipidaemia and treated aggressively with insulin and dextrose (his normal baseline insulin requirement 100U/d ie 4U/hr – given double this 10U/hr) with glucose supplementation, hourly BSLs and 2nd hourly EUC watching for hypoK. The plan was for plasmaphoresis the next day if his triglycerides were > 100. As he was nil by mouth gemfibrozil, statins and fish oil tablets were not commenced. After 5 days in ICU his TG are now 10 and cholesterol 8.3

So this prompts a discussion on pancreatitis – aetiology and treatment. Thanks go to DR JO COLLINS the gastro fellow from Bankstown Hospital and PROF SHAN RAJENDRA for their updated information on pancreatitis which they presented at Fairfield Grand Rounds 2 weeks ago.

Aetiology: You may have a mnemonic to remember the different causes – here is one

A,B,C,D,E,F,G,H,I then jump to PSTV

A- Alcohol (25-35%)
B- Biliary (40-70%)– gallstones / sludge/ microlithiasis

These 2 cause the majority of pancreatitis cases we see. However remember the other causes including:

C – congenital (choledochal cysts, pancreatic divisum) – genetic mutations/
-Calcium (hyperCa)
D- drugs (valproate, azathioprine, ezetimibe, prednisone, olanzepine, simvastatin, erythromycin, HIV drugs) - The mechanisms include immunologic reactions (eg, 6-mercaptopurine, aminosalicylates, sulfonamides), direct toxic effect (eg, diuretics, sulfonamides), accumulation of a toxic metabolite (valproic acid, didanosine, pentamidine), ischemia (diuretics, azathioprine), intravascular thrombosis (oestrogen), and an increased viscosity of pancreatic juice (diuretics and steroids).
E – endocrine / electrolytes – HONK/ DKA, hyperparathyroidism/ hyperCa
F – fat – hyperlipidaemia- up-to-date reports this as the 3rd most common cause after alcohol and biliary disease- interestingly there were 2 very similar cases in the last week
G- gastric ulcers – penetrating peptic ulcers (gastric or duodenal)
H- haematological – lymphomas / leukaemias,
I – infection
– viral – mumps, EBV, CMV, HIV, hepatitis B
- bacterial – mycoplasma, legionella , salmonella, mening, strept
- parasitic – ascaris, toxoplasma, malaria
- Idiopathic
- Immunological – autoimmune Dx- primary or in association with other diseases of presumed autoimmune etiology including primary sclerosing cholangitis (PSC), primary biliary cirrhosis, retroperitoneal fibrosis, rheumatoid arthritis, sarcoidosis, and Sjögren's syndrome

P- pregnancy – Post ERCP (suspect if develops pain within 6hrs of procedure- esp younger pts, females, sphincter dysf'n, recurrent pancreatitis, prior post ERCP pancreatitis, ductal or sphincter intervention)
S- scorpions – common- in certain subsets of desert dwelling insect handlers that is
T – tumour – (pancreatic or periampullary leading to ductal obstruction) / Trauma
V –vascular - vasculitis, hypotension with ischaemia, atheroembolism

Mortality 1.5-4.2% depending on severity – up to 30% in infected pancreatic necrosis

Presentation – typically epigastric / LUQ with radiation to back, flanks or chest – note that the intensity and location of the pain does not correlate with the severity of the pancreatitis

Diagnosis

The diagnosis of AP is most often established by the presence of **2 of the 3** following criteria:
1.Abdominal pain consistent with the disease

2.Serum amylase and/or lipase greater than three times the upper limit of normal – see comments below re lipase and amylase - lipase is preferred due to limitations of amylase in sensitivity, specificity, and positive and negative predictive value.
3.Characteristic findings from abdominal imaging

Imaging

- Upper abdo US should be considered as an initial investigation in all patients to assess for stones esp CBD (>6 mm + 1 mm per decade >60 yo- >10 mm post-chole / dilated intrahepatic biliary tree) See radiopedia for other info imaging of choledocholithiasis
- Note that there are limitations with CT as a screen for cholelithiasis or choledocholithiasis
    - Routine contrast enhanced CT is moderately sensitive for detecting choledocholithiasis with sensitivity of 65-88%
- Contrast-enhanced CT and/or MRI (MRCP- MR cholangiopancreatogram) should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48 – 72 h after hospital admission or to evaluate complications. CT cholangiogram or

MRCP (or endoscopic ultrasound) help define biliary anatomy and need for ERCP and sphincterotomy – both have their "pros and cons"

- Routine early CT/MRI scanning does not improve clinical outcomes

Severity – not defined by lipase elevation- note these manifestations take time (24-48 hrs +)

Mild – absence of organ failure (CBP < 90, renal, pulmonary)/ absence of local complications (peripancreatic fluid collections, pancreatic necrosis, pseudocysts)

Moderate – local complications and / or transient organ failure (< 48 hrs)

Severe – persistent organ failure (> 48 hrs)

Consider components of Ranson's criteria (which include factors on admission and also at 48 hrs), in addition to SIRS criteria and common sense to assess prognosis and indications for admission to HDU / ICU. On the floor to access Ranson's criteria go to CIAP – TOOLS – Medcalc 3000

HYPERTRIGLYCERIDEMIA RELATED PANCREATITIS - the pathogenesis of inflammation in this setting is unclear. Can be a primary disorder or acquired (diabetes mellitus esp if poorly controlled (including DKA) , hypothyroidism, pregnancy (up to 56% of cases in pregnancy), oestrogen or tamoxifen therapy, glucocorticoid excess, nephrotic syndrome, and beta blockers).

CLINICAL FEATURES — The initial presentation is similar to that of pancreatitis of other causes; abdominal pain, nausea, and vomiting are the major complaints.
Other signs of hypertrigylceridaemia may lead to the formation of eruptive xanthomas over the extensor surfaces of the arms, legs, buttocks, and back; lipemia retinalis; and hepatosplenomegaly from fatty infiltration of the liver.

There is a progressive risk of pancreatitis with serum triglyceride levels over 5mmol/L with the risk increasing markedly with levels over 10mmol/L. However note that the severity of the hypertriglyceride related pancreatitis does not seem to correlate directly with the triglyceride level.

PANCREATITIS TREATMENT PRINCIPLES

– supportive management to treat or prevent complications

- **look for aetiology - treat or remove precipitating factors**

1) Supportive management

A/ B – pancreatitis may be complicated by atelectasis, effusions, ARDS - optimise tissue oxygenation + ventilation with supplemental O2+/- airway adjuncts – ANALGESIA – IV opiates – consider PCA
C – may have 3rd space losses +/- vomiting, haemorrhage - most important factor to optimise – crystalloid, colloids , blood products may be used – guide progress with combination of clinical exam, vital signs, urine output, CVP measures, lab results esp lactate and gases
D- other complications or associated illnesses may alter the neuro status – in particular watch BSL - ? alcohol withdrawal ? encephalopathy
E – watch temp (hypothermia / fever with sepsis) / correct electrolytes (BSL, K, Ca, Mg, PO4)
F- fluids – strict fluid balance
G – NBM – consider NG tube if gastric distension, vomiting, paralytic ileus or if tubed (See comment below under N)
H – optimise Hb with transfusion as necessary / WCC will often be raised – may be complicated by DIC in severe cases – prior liver disease may be associated with coagulation factor deficiencies – optimise with vit K or FFP
I – no role of routine antibiotics – consider if possible cholangitis or abscess formation, other infective complications or extrapancreatic infections
L – consider appropriate access for rapid IV fluid administration + monitoring of haemodynamics – may need art lines or central lines depending on severity
M- analgesics / DVT prophylaxis ? benefits of PPI / thiamine + diazepam for Etoh
N – nutrition - Multiple studies have shown that patients provided oral feeding early in the course of acute pancreatitis have a shorter hospital stay, decreased infectious complications, decreased morbidity, and decreased mortality
In mild episodes, oral feeding can be started immediately if there is no nausea and vomiting, *and the abdominal pain has resolved* - low-fat solid diet appears as safe as a clear liquid diet
In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided, unless the enteral route is not available, not tolerated, or not meeting caloric requirements. Nasogastric and nasojejunal delivery appear comparable in efficacy and safety. **Check with the admitting team re feeding**

2) Treat cause / complications

- **Operative** – ERCP + sphincterotomy for gallstones / Surgery – later for extensive necrosis / abscesses (or percutaneous drainage) -
- **Hypertriglyceridaemia –** aim to decreasing serum triglyceride levels to <5mmol/L. Multiple options including:
    - **Apharesis** – may be considered if patient does not have concurrent hyperglycaemia (yet can give concommittent glucose!) Will bring down the TG levels rapidly – patent may need retreatment.
    - **Insulin** — Insulin decreases serum triglyceride levels by enhancing lipoprotein lipase activity, an enzyme that accelerates chylomicron metabolism to glycerol and fatty free acids. Slower onset and may take days to work. Easiest modality for us to start –use IV infusion 0.1-0.3U/ kg/hr- in this case insulin treated his ketosis, hyperglycaemia and her hyperTG. As mentioned can add dextrose if BSL < 15 and TG still > 5mol/L. watch with hourly BSLs and q2-4hr EUC to watch K.
    - **Heparin** — The role of heparin is controversial. Heparin stimulates the release of endothelial lipoprotein lipase into the circulation and has been used +/- insulin to manage HTG. However only transient benefit
    - **Antihyperlipidaemic agents**
        - gemfibrozil – works on TG levels through reducing release of VLDL and helping clear lipoproteins from the circulation –can cause rhabdo esp if used with statin
        - Statin – HMG-COa inhibitor – reduced production of cholesterol + increased LDL metabolism onset of effect 3-5 days – max at 2 weeks
        - Fish oil - reduce levels of TGs through inhibition of the synthesis of VLDL-triglycerides and apolipoprotein B- In hypertriglyceridemic subjects, in a dose of 15 g/day, TG levels are lowered by ~ 50%.? Onset of effect?
- Withdraw ppt drugs / treat other causes
- Avoid falling asleep in deserts or hanging around with entymologists

LIPASE / AMYLASE in PANCREATITIS

52yo man presents with upper abdominal pain and vomiting. Drinker ~ 50gm/d – no Hx of pancreatitis O/E afebile - tender epigastrium with guarding – WCC 12 – normal CXR, lipase and amylase – CT c/ w pancreatitis ((stranding with fluid around pancreas) Can we rely on these markers to rule out or in with pancreatitis?

Normally we rely on lipase or amylase to diagnose acute pancreatitis, the more sensitive and specific being lipase, which will be a focus of this discussion. Like any diagnostic test these lab tests have their limitations and THE MAIN EMPHASIS IS TO TAKE A GOOD HISTORY AND EXAM – labs support these other aspects of your assessment, not replace it. Several non-pancreatic conditions can present with abnormal serum amylase and lipase levels. On the other hand, some patients with pancreatitis have normal serum amylase and lipase levels when a blood sample is examined.

Several factors can influence serum amylase and lipase levels.

- The levels depend upon the rate of production from different tissues and the rate of clearance. As an example, serum amylase and lipase levels may be elevated in patients with renal failure.
- Organs other than the pancreas can produce these enzymes. Alcoholics, for example, may have an elevated serum amylase of salivary origin. The most commonly used amylase assays cannot differentiate between salivary and pancreatic amylase.
- Certain serum factors influence amylase and lipase enzyme activity. As an example, patients with pancreatitis due to hypertriglyceridemia may appear to have normal amylase levels, most likely due to a circulating factor that inhibits the enzyme's activity.
- The aetiology may influence the degree of elevation - Patients with gallstone pancreatitis tend to have higher amylase and lipase levels than patients with pancreatitis of other aetiology. Note also that amylase and lipase levels do not correlate with the severity of pancreatitis and therefore are not included in any of the several prognostic scores.

LIPASE — There are several lipases in the human body, including lingual, pancreatic, lipoprotein, intestinal, and hepatic lipase. The main function of the pancreatic lipase is to hydrolyze triglycerides into glycerol and free fatty acids. Like amylase, lipase is a relatively small molecule that can be filtrated by the kidney. Unlike amylase, lipase can be reabsorbed in the renal tubules, which increases its half-life (6.9 to 13.7 hours). During acute pancreatitis, serum lipase increases within four to eight hours, peaks at 24 hours, and remains elevated for one to two weeks, with a half−life between 7 and 14 hours. It is excreted by the ductal system and kidneys. Thus, impaired renal function leads to an increased level of lipase. It can also be elevated in several other conditions other than pancreatitis. These include : cholecystitis, bowel obstruction or infarction, DU, pancreatic calculi or tumours, DKA,

HIV disease, pancreatic trauma, idiopathic. However the higher the level of lipase, the more likely that this is pancreatitis, figures of > 3-5 times normal being quoted by some as a “cutoff”

A review by Al-Bahrani showed looked at studies of the value of lipase, and you can look at these individually if you wish but one message is the sensitivity and the negative predictive values ie can a normal value rule it out and the answer is no

Value of serum lipase in the diagnosis of acute pancreatitis

	No of patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Kylanpaa−Back, et al, 2002	237	55	99	88	94
Treacy, et al, 2001	328	67	97	80	94
Gumaste, et al, 1993	170	100	99	99	100
Panteghini and Pagani, 1989	54	100	81	93	100
Hemingway, et al, 1988	20	100	96	95	100
Steinberg, et al, 1985	216	87	99	95	97

Also note that the lipase level has not been found to be related to severity, suggesting that severe pancreatitis could be associated with initial lipase above normal range and below the usual threefold threshold.

AMYLASE — The main sources of amylase is the pancreas and salivary glands, but it can be found in other tissues in small quantities. It is excreted by the reticuloendothelial system (75 percent) and the kidneys (25 percent). The serum amylase level rises within 2 to 12 hours of the onset of symptoms and returns to normal over the next 3 to 5 days in patients with acute pancreatitis. Peak amylase levels are typically seen within the first 48 hours of the attack. It has a shorter half life than lipase. It subsequently can be elevated in a number of other conditions such as:

1) Pancreatic Dx – pancreatitis or complication, trauma, surgery, ERCP, CA, CF
2) Salivary Dx – infection, trauma, radiation, ductal obstruction
3) GI disease – perf or penetrating PU, perf or obstructed bowel, isch gut, appendicitis, cholecystitis, gastroenteritis, liver dx, coeliac dx
4) Gynae dx – ruptured ectopic, ovarian or fallopian cysts, PID
5) Neoplasms - Solid tumours of the ovary, prostate, lung, oesophagus, breast and thymus, myeloma, phaeo
6) Other – renal failure, alcoholism, burns, DKA, AIDS, pregnancy, AAA, cerebral trauma, anorexia nervosa, post-op, acute liver failure

Thus lipase is more specific. It is also recognized that patients with severe pancreatitis commonly have normal serum amylase levels, particularly in patients with pancreatitis related to hypertriglyceridemia and alcohol.

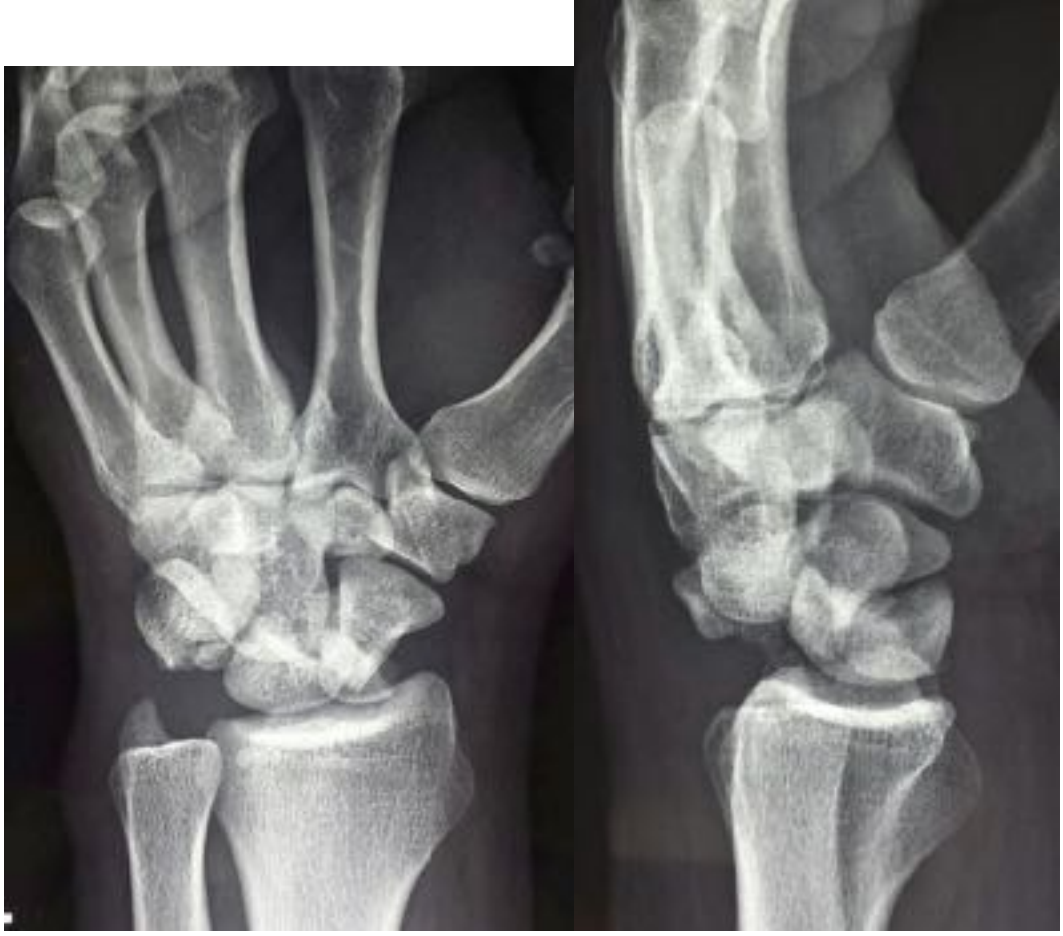
So if the patient is in pain and the history is c/w pancreatitis yet normal lipase or amylase then consider a CT scan abdo with thin cuts through the pancreas. This may also be helpful in the setting of a high amylase or lipase level when the diagnosis is uncertain.

Refs – Up to date / Al-Bahrani A Z, Ammori B J. Clinical laboratory assessment of acute pancreatitis. Clin Chim Acta 2005. 36226–48./ Normal lipase serum level in acute pancreatitis: a case report T Cartier Emerg Med J. 2006 September; 23(9): 701–702 / Miller FH, Hwang CM, Gabriel H et-al. Contrast-enhanced helical CT of choledocholithiasis. AJR Am J Roentgenol. 2003;181 (1): 125-30

NEXT WEEK’S CASE

A 35yo man presents with left wrist pain after falling off the back of a ute. On examination he has diffuse volar and dorsal swelling and tenderness over his carpal bones and evidence of a median nerve sensory deficit.. His X-rays are shown below. What is going on?

Editor: Peter Wyllie



JOKE / QUOTE OF THE WEEK

Adeel has pointed out this cost saving measure Sutho style ?

A customer asked, "In what aisle could I find the Irish sausages?"
The assistant asks, "Are you Irish?"

The guy, clearly offended, says, "Yes I am, but let me ask you something...
If I had asked for Italian sausage, would you ask me if I was Italian?

Editor: Peter Wyllie

Or if I had asked for German Bratwurst, would you ask me if I was German?
Or if I asked for a kosher hot dog would you ask me if I was Jewish?
Or if I had asked for a Taco, would you ask if I was Mexican?
Or if I asked for Polish sausage, would you ask if I was Polish?"

The assistant says, "No, I probably wouldn't."
The guy says, "Well then, just because I asked for Irish sausage,why did you ask me if I'm Irish?"

The assistant replied, "Because you're in Bunnings."

Please forward any funny and litigious quotes you may hear on the floor (happy to publish names if you want)

THE WEEK AHEAD
Tuesdays - 12:00 – 13:45 Intern teaching -Thomas & Rachel Moore
Wednesday 0800-0900 Critical Care Journal Club. ICU Conf Room / 12.00-1.15 Resident MO in Thomas & Rachel Moore
Thursday 0730-0800 Trauma Audit. Education Centre / 0800-0830 MET Review Education centre / 1300-1400 Medical Grand Rounds. Auditorium.