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From My Keyboard

Dedicated healthcare workers save lives.

Unless you have been in a situation when you needed a dedicated healthcare worker this will truly be hard for you to appreciate. With my daughter turning one, God bless her, I could not help but reflect on what an eventful year I have had since her birth. A child is the greatest miracle anybody can ever have but when they get sick, you make all sorts of concessions with God if only they can get better. In such situations the best thing that can happen to you is to come into contact with dedicated health workers be it at the hospital, clinic, and pharmacy or at the medical laboratory.

All the times my daughter has needed medical assistance in any form, I have come into contact will all sorts of healthcare workers, some who have left me in awe as a result of their passion for the practice of medicine and others who have made me wish I had the power to revoke practice licences.

Understanding how your own job as a healthcare professional affects the overall quality of healthcare provided to a patient is something that really needs to be taken seriously by all healthcare professionals. To

Continued on Page 3

Inside this Issue

Recent Events @ DML	1
Gastroenteritis in Children	2-3
Laboratory Diagnosis & Assesment of Rheumatoid Arthritis	4-5
Relevance of Renal Impairment as a Risk Factor for Cadiovascular Disease	6
Use of Cadiac Enzymes	7
Diagnofirm in Pictures	8-9
Laboratory Medicine & Alcohol Abuse	10-11
Microbio-Alert: Cryptospodian & Immuno Compromised Patients	12
eGFR	13
World Laboratory Medicine Forum	14-15
Endothelial Dysfunction & Cardiovascular Disease	16
Jokes Corner	16

Tiger Design and Graphics

Diagnofirm QA Manager, Munyaradzi Mangwendeza with Dr. Klauss Stinshoff, Chairperson of ISO/TC 212 International Organisation of Standardisation (ISO) at the World Lab forum, Baltimore Maryland USA, August 2006

DIAGNOFIRM MEDICAL LABORATORIES

by Newton Tawanda Runyowa

Recent Events @ Diagnofirm

NEW DML DEPOT @ THE VILLAGE MEDICAL CENTRE

Diagnofirm Medical Laboratories in its commitment to continuously provide timely and quality medical laboratory services to all its clients opened a new depot at the Village Medical Centre. This move is intended to improve the turn around times (TATs) for laboratory investigations at point of care (POC) facilities in turn expediting the use of clinically significant results in patient treatment and management.

This takes the total number of depots to nine (9) including the main and viral laboratories here in Gaborone and the one in Selebi Phikwe. This last quarter saw our Selebi Phikwe branch launching partial HIV monitoring (using the cluster designation 4 and 8 counts) CD4+/CD8+ enumeration using an Epic Flow Cytometer by Beckman and Coulter. This has seen results being available to clients on a same day basis (no longer being sent to Gaborone except for viral load determinations).

This is sure expression of our commitment to provide comprehensive diagnostic and monitoring services to all our clients throughout the network and support for the attainment of the millennium development goals (MDGs), National Development Plan 9 (NDP9) and Vision 2016 targets. We wish our Village and Selebi Phikwe branches all the best!

Continued on Page 5

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by Munyaradzi Mangwendeza

GASTROENTERITIS IN CHILDREN

The stomach, small intestines and large intestines are collectively known as the gastrointestinal tract. Gastroenteritis is thus an inflammation of the stomach and intestines. It is a very common illness in infants and young children and is caused by bacteria, parasites and most commonly viruses. Viruses are the major causes of gastroenteritis since they account for 8 out of 10 of the cases of gastroenteritis. Most of the outbreaks of gastroenteritis are experienced during the winter months. The viruses mainly associated with gastroenteritis are:

- Rotaviruses
- Adenoviruses
- Caliciviruses
- Astroviruses
- Norwalk viruses
- Noroviruses

Bacteria like E.coli are also associated with bouts of bacterial gastroenteritis especially in food poisoning and children are particularly vulnerable. Parasites rarely cause gastroenteritis but in those cases encountered, *Giardia lamblia* parasites are the most common cause of parasitic cases of gastroenteritis. Cow's milk intolerance in infants or food allergies are also associated with cases of gastroenteritis. In infants diarrhea may be caused by other infections such as a chest infection or urinary tract infection. If the child has recently traveled to an area where malaria is present, this could also be a potential cause.

Since cases of viral gastroenteritis are more commonly encountered, we will dwell more on viral gastroenteritis of which Rotaviruses are mainly associated with winter outbreaks of gastroenteritis and Adenovirus infections which are encountered throughout the year. Rotaviruses account for 600 000 children deaths due to gastroenteritis annually worldwide. Infants are more prone to Rotavirus infection and younger children are affected by Adenoviruses with the Norwalk and Nooviruses affecting older children and adults. Outbreaks are more common in institutional settings for example schools, child daycare centers and nursing homes.

Transmission: Viral gastroenteritis is very contagious. The main mode of transmission is the fecal-oral route. This happens after an infected person goes to the toilet and does not wash hands properly afterwards before handling food or touching other people. Less commonly, it can be spread when someone infected coughs or sneezes and the next person breathes in the virus. It can also be spread via eating shellfish which are harvested in polluted waters. Drinking contaminated water is the major mode of transmission in developing countries where water is contaminated by sewage and levels of hygiene are very low. Since it is highly contagious, it is important to keep affected children away from those without gastroenteritis. Most children will however get gastroenteritis at some time in their life, no matter how high the standards of hygiene are at home.

To prevent transmission, if your child has gastroenteritis, wash hands after changing the nappy, hygienically disposing of, or properly cleaning all soiled items such as nappies, cleaning the toilet with disinfectants and by not sharing bathing towels. Hand washing with soap and water after using the toilet as well as before and after food preparation is very important to stop the spread of the virus. This also helps reduce reinfection. Ideally to reduce transmission there is need for frequent hand washing, prompt disinfection of contaminated surfaces with household chlorine bleach based cleaners like jik, prompt washing of soiled articles of clothing and the avoidance of contaminated food or water.

Symptoms: Viral gastroenteritis is characterized by very frequent watery diarrhea and vomiting. The victim also experiences headaches, fever and abdominal cramps. Symptoms appear 1-2 days following infection with the virus and may last up to 10 days depending on the virus which caused the illness. Serious illnesses are observed in infants and young children and people unable to care for themselves e.g. disabled or the very elderly. Immuno-compromised people are also at risk for more serious infection with more severe symptoms. Other symptoms include excessive thirst, dry mouth, little or no urine, low tears when crying and severe weakness and lethargy. A runny nose and sore throat are also common. More prolonged fevers, more severe pain and blood and mucus with the diarrhea may suggest that the gastroenteritis is caused by a bacteria usually associated with food poisoning.

The major risk posed by viral gastroenteritis is dehydration. The frequent watery diarrhea and vomiting cause the patient to lose a lot of fluid. This becomes a major concern in children because they do not need to lose a lot of fluid to lose a significant percentage of their total body fluid. Symptoms of mild to moderate dehydration are:

- lethargy or sleepiness
- Loss of elasticity of the skin so that when it is pinched gently between the fingers it does not immediately spring back into its normal position.
- In young babies, the fontanelle(soft spot on the scalp) may be sunken.
- Dry lips and mouth
- Sunken eyes
- Decreased tears when crying
- Less wet nappies than usual due to less urine being made by the baby's kidneys

More severe dehydration is characterized by:

- Pale or mottled skin
- Very few wet nappies
- Significant drowsiness
- Fast heart rate
- Cold fingers and toes, when gently squeezed, blood takes a long time to return.

Diagnosis: Diagnosis of viral gastroenteritis requires identification of the causative agent. Routine diagnosis is based on the identification of the virus in feces or suspensions of rectal swabs. A sample of the child's feces should be taken to the laboratory for testing.- For the detection of rotavirus this is routinely done by enzyme linked immunosorbent assay (ELISA) test for rotavirus specific antigen. ELISA can be used to detect antigen late in the course of illness.

For rapid diagnosis, latex agglutination is used as well as rapid detection strips. Polyacrylamide gel electrophoresis with silver stain may also be used to diagnose rotavirus infection without false positives and can be used to differentiate non-group A from group A rotavirus. Adenovirus infections can also be diagnosed in the same manner. If you

are in doubt about the causes of the gastroenteritis affecting your child, Diagnofirm medical laboratories have various diagnostic tests which can confirm the presence of viral, bacterial or parasitic gastroenteritis. Other laboratory tests can also be done. These include:

- Routine laboratory tests : Full blood count, electrolytes, renal function tests. These tests may be useful as indicators of severity of disease, especially in elderly or very young patients,
- Electrolytes and urea and creatinine tests are indicated in patients with severe diarrhea or dehydration to rule out hyponatremia or hypernatremia. Decreased serum bicarbonate suggests severe dehydration, especially in children. Acidosis secondary to bicarbonate loss in the stools and/or from hypovolemia-induced lactic acidosis may be present. Hypokalemia may also occur.
- A full blood count may be indicated with a prolonged course, severe diarrhea, or toxicity. The White blood cell count is usually increased in *Salmonella* infections but normal or low with significant left shift in *Shigella* infections. The White Blood Cell count is otherwise variable. Eosinophilia may be present in parasitic infections

This can help to have the appropriate action taken for your child as treatment differs depending on the causative agent.

Treatment: No treatment is currently available for viral gastroenteritis. Two vaccines against Rotavirus infection were shown to be safe and effective in children: Rotarix by GlaxoSmithKline and RotaTeq by Merck. Both are taken orally and contain disabled live virus. Immunity after infection is incomplete but repeat infections tend to be less severe than the original infection. Hence treatment is by way of controlling dehydration. Severe dehydration can result in persons unable to drink enough fluids to replace what they lose through vomiting or diarrhea. Most children recover quickly, however if the child does not recover, the major concern becomes dehydration due to loss of fluid in vomit and diarrhea. Hence it is imperative to encourage the affected child to drink fluids.

Please consult your doctor or hospital as soon as possible especially if your child:

- Is less than 6 months old
- Has other health problems
- Is unable to take the right amount of fluids.
- Keeps vomiting
- Is very tired and drowsy
- Has blood or mucus in the faeces
- Has ongoing abdominal pain
- Does not seem to be getting better.

Acute vomiting and diarrhea can rapidly lead to dehydration in infants and young children; seek medical attention promptly if you are concerned. Lost fluid must be replaced, initially with suitable fluids or breast milk. Give oral rehydration solution and clear fluids such as apple juice which must be diluted, otherwise they may make the diarrhea worse. Be patient with the child and give small but frequent amounts of fluid. Aim for at least 5ml of fluid per kg of body weight each hour, for example to a 6kg infant offer 30ml every hour and a 12 kg toddler offer 60ml every hour.

APPROXIMATE REPLACEMENT VOLUMES

1.	<6 months old	see your doctor
2.	6-23 months old	40-60ml/hr
3.	2-5years old	60 100ml/hr
4.	6-10 years old	100-120ml/hr
5.	11-16 years old	120- 160ml/hr

It is vital to start offering easily digested foods as soon as the vomiting stops and no later than 24 hours even if the stools are still lose. Continue breast feeding on demand or every 2 hours and in between breast feeds, offer water or oral rehaydration solution. Do not give solids if the child is vomiting. For bottle fed babies, replace formula milk with oral rehydration solution or a suitable fluid. Give enough fluid to cover normal requirements and to replace what is lost through vomiting and diarrhea. The objective is to get the child to normal strength within 24 hours. If this does not happen and the child has a high temperature of over 38 degrees Celsius, seek medical advice.

Disclaimer: this information is for educational purposes only. Please consult your doctor or other health professionals to make sure that this information is right for your child.

Continued from Page 1

From My Keyboard

all healthcare professionals, form nurses, to doctors, to pharmacists, to physiotherapists, to radiographers to medical laboratory medicine practitioners and everybody else in the healthcare industry I ask you to pause for a moment and ask yourself these questions, "Why am I here. What is my purpose on earth, what do I want to do with my life as a healthcare professional"?

Whatever answers you have to these questions, I leave you with a quote from George Bernard Shaw, **"I am of the opinion that my life belongs to the whole community and as long as I live, it is my privilege to do for it whatever I can. I want to be thoroughly used up when I die, for the harder I work the more I live."**

Early in August I had the pleasure of attending the world laboratory medicine symposium held in Baltimore, Maryland USA. This symposium brought together some of the great thinkers in laboratory medicine from all over the world and really awakened my mind to the importance of laboratory medicine and quality healthcare.

For more information on this important and educative forum, log on to *www.worldlabforum.org* . Till the next issue may you provide quality healthcare by being a dedicated healthcare professional or if you are not a healthcare industry may you experience the joy of being attended to by a dedicated healthcare professional.

Lets all work together for excellence in healthcare!

Stay informed!!!

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Interlude

Emergency Call

Dad's pager went off, summoning him to the hospital, where he is an anesthetist. As he raced toward the hospital, a patrol car sped up behind him--lights flashing. Dad hung his stethoscope out the window to signal that he was on an emergency call. Within seconds, came the police officer's hand in response, dangling a pair of handcuffs out the window.

by Tapiwa P. Makunde

LABORATORY DIAGNOSIS AND ASSESSMENT OF RHEUMATOID ARTHRITIS

Rheumatoid Arthritis

It is an auto immune disease that causes chronic inflammation of the joints. It can also cause inflammation of the tissue around the joints. Auto immune diseases are illnesses which occur when the body tissues are mistakenly attacked by is own immune system. It is a progressive illness that has the potential to cause joint destruction and functional disability.

SYMPTOMS

Morning Stiffness in the Joints: The hallmark symptom of rheumatoid arthritis is morning stiffness that lasts for at least an hour. (Stiffness from osteoarthritis, for instance, usually clears up within half an hour.) Even after remaining motionless for a few moments, the body can stiffen. Movement becomes easier again after loosening up.

Swelling and Pain: Swelling and pain in the joints must occur for at least six weeks before a diagnosis of rheumatoid arthritis is considered. The inflamed joints are usually swollen and often feel warm and "boggy" when touched. The pain often occurs symmetrically but may be more severe on one side of the body, depending on which hand the person uses more often.

Specific Joints Affected: Although rheumatoid arthritis almost always develops in the wrists and knuckles, the knees and joints of the ball of the foot are often affected as well. Indeed, many joints may be involved, even causing the spine to become misaligned. It does not usually show up in the fingertips, where osteoarthritis is common, but joints at the base of the fingers are often painful.

Nodules: In about 20% of people with RA, inflammation of small blood vessels can cause nodules, or lumps, under the skin. They are about the size of a pea or slightly larger, and are often located near the elbow, although they can show up anywhere. Nodules can occur throughout the course of the disease. Rarely, nodules may become sore and infected, particularly if they are in locations where stress occurs, such as the ankles. On rare occasions, nodules can reflect the presence of rheumatoid vasculitis, a condition that can affect blood vessels in the lungs, kidneys, or other organs.

Fluid Build-up: Fluid may accumulate, particularly in the ankles. In rare cases, the joint sac behind the knee accumulates fluid and forms what is known as a Baker cyst. This cyst feels like a tumor and sometimes extends down the back of the calf causing pain.

Flu-Like Symptoms: Symptoms such as fatigue, weight loss, and fever may accompany early rheumatoid arthritis. Some people describe them as being similar to those of a cold or flu, except, of course, RA symptoms can last for years.

Symptoms in Children: In children, juvenile rheumatoid arthritis, also known as Still's disease, is usually preceded by high fever and shaking chills along with pain and swelling in many joints. A pink skin rash may be present.

LABORATORY DIAGNOSIS

GENETIC MARKERS

RA has a genetic association implying that some individuals with certain genetic material are more susceptible to the disease. The availability of serological typing showed a genetic association of RA with the major histocompatibility complex class 1 HLA-DR4 (DR1) antigen (Stastny 1974 &1978). The HLA DR1 subtypes associated with an increased prevalence of RA have a common amino acid sequence in the peptide binding area of the HLA molecule i.e. shared epitope (Wordsworth &Bell 1990). There is evidence of difference in prevalence of the share epitope from race to race (Emery1997).

IMMUNOLOGIC MARKERS

Rheumatoid Factor (RF): Rheumatoid Factor is a circulating antibody against multiple antigenic determinants on the Fc fragment of the IgG molecule. Conventional agglutination and immunoturbimetric techniques measure predominantly the IgM class RF. However, radio immunoassay or enzyme-linked immunosorbent assays (ELISA) allow measurement of RF of all the major immunoglobulin classes namely IgM, IgG and IgD (Harris 1997).

In clinical settings, RF can be detected in most cases of RA but only occasionally in the sera of healthy subjects. Only up to about a third of individuals (random) exhibiting positive RF reactions show clinical and/or radiological evidence of RA (Kellgren 1966). In addition, subjects with RA have on average higher titer levels of RF than those with false positive RF reactions. The proportions of RA cases among RF positives are dependent on the sensitivity of the techniques used (Aho et al 1994). It is also important to note that RF precedes the onset of RA by years therefore its not good to dismiss positive RF results at a glance. Healthy subjects with positive sensitized sheep red cell agglutination test results have an approximately 40 fold risk of developing RF positive RA compared to subjects with negative results during a 10 year period (Aho et al 1994). One third of patients initially presenting with signs and symptoms compatible with RA are seronegative according to the conventional RF tests (Masi et al 1976, Heliovaara et al 1993). These RF negative patients have a more favourable disease course than those with positive RF reactions and many of them end up in complete remission (Isonaki 1987). Cases of seroconversion of RF positives due therapy are also a common occurrence (Smolen and Steimer 1998).

OTHER MARKER ANTIBODIES

Seropositive RA may represent a single disease whereas seronegative RA is likely to be a combination of different clinical and immunogenetic entities. The seropositive RA patients have associated antibody markers defining the disease. These antibodies include the antibody against the perinuclear factor in human buccal mucosa cells (ANF); the antibody against the keratin associated component in the stratum corneum of rat esophagus and the anti-RA33 (Aho and Kurki 1994). Anti- keratin is highly specific although not very sensitive markers for RA, 40-50% of sera from patients with established RA have been found to be positive. The anti-nuclear factor (ANF) test is more sensitive

but less specific than the anti-kerratin antibody test; the frequency of positive reactions in RA patients being about 60-80%. The absence of the above marker antibodies implies absence of humoral evidence of the rheumatoid immuno-logical process i.e. the disease is seronegative.

ACUTE PHASE REACTANTS

Measurement of acute phase reactants in plasma provides clinically valuable indication of inflammation and its extent. The most commonly used measurements of acute phase response are erythrocyte sedimen-tation rate (ESR), plasma viscosity, C - reactive protein (CRP), arosomucoid, haptoglobin and alpha 1- antitrypsin. Inducers for the production of acute phase proteins (APPs) are the cytokines inter-leukin 1 (IL 1), IL 6, and tumour necrosis factor (TNF). The different APPs respond differently to different cytokine combi-nations, which explain the occurrence of different patterns of acute phase responses in RA or any other inflammatory process.

ESR: ESR has been found to be the best single measure in the assessment of the effects on treatment of RA .It has achieved a 75 % success rate in predicting the absence or presence of radiological damage by means of the baseline ESR value and HLA DR4 status over a follow up of two years (Blackburn 1994 , Vander Heijde 1991).

CRP: The prognostic value of CRP measurement has mostly been evaluated for the short term outcome of RA. In these evaluations CRP levels correlate with clinical disease activity, radiologic pro-gression and response to therapy (Ebehardt etal 1990).

CONCLUSION

No single laboratory diagnostic method should be used to diagnose, monitor disease progression and assess therapy as seen from the above. Thus a battery of laboratory tests is to be undertaken for us to be in a position to have a clear picture of the RA disease state.

References available upon request.

Continued from Page 1

Recent Events @ Diagnofirm

Staffing and Training

Also during the last three months and in response to growth (real and anticipated) of our branch networks and intended move to our new headquarters DML is pleased to announce the appointment of six (6) new members of staff, 2 medical laboratory scientific officers and four nurse phlebotomists (Newton Tawanda Runyowa, Kennedy Mokgethi, Maria Kachuta, Maureen Nguni, Nokuthula Ndlovu and Ivah G Makuni).

We warmly welcome you all to the DML family and hope that you settle down well and contribute to the DML team objectives, aspirations and quality accreditation project.

Between the months of May and July DML played teaching host to four (4) third year Medical Laboratory Sciences students from the Institute of Health Sciences (IHS) and these are Ketumetse Brendah Modisane and Felicia Malebogo Maase here in Gaborone and Naledi Jane and Tshepiso Tielo in Selebi Phikwe.

The students worked in rotation in all departments under supervision and were assessed using the DML departmental secondment checklists. We would like to thank them and wish them well in their academic and professional endeavors.

Diagnostics in the Community

DML was in the communities once again as part of our corporate social responsibility and in the month of June we participated in the Old Naledi Health Fair organized by Tebelopele VCT and graced by most stakeholders involved in the HIV/AIDS campaign. Information booths and onsite testing and counseling services were offered.

In July we conducted in partnership with The Cardiac Clinic a health awareness campaign in Molepolole where also health awareness lectures and free onsite testing services were offered. We are grateful to our management for facilitating continuous community awareness in line with the Vision 2016 targets of an informed and healthy nation.

Again in July, Diagnofirm helped in sending Obakeng Kgosi to Pakistan for his kidney transplant. We sincerely hope the transplant will be a success and he will be able to live a normal life like any other young man.

Continuous Professional and Quality Improvement!

Everyone at Diagnostic Update would like to congratulate our Laboratories Manager Mr. D Mhlabi for passing with distinction in his Business Administration and Management studies, well done makhosi!!!

Last but not least our Quality Manager Mr. M Mangwendeza was in the United States of America recently where he attended a scientific conference on laboratory quality improvement and presented a paper on your award winning DML quality activities and plans putting us on the global map!

Cervical Cancer Facts

- Half of the women diagnosed with cervical cancer are between 35 and 55 years of age. The disease rarely affects women under the age of 20
- Approximately 20 percent of women diagnosed with cervical cancer are over age 65. For this reason, it is important for women to have annual Pap tests until at least the age of 70.
- Human papillomavirus (HPV) is the main risk factor for cervical cancer. This virus can be spread through sexual contact and can lead to genital warts, cancer and other problems.
- A Pap test is the most effective screening method for cervical cancer. The test detects precancerous changes and allows for early treatment.
- Women who have many sexual partners have a higher-than-average risk of developing cervical cancer. Women with HIV infection also have a higher risk.
- Finding and treating abnormal cells can prevent most cervical cancers. Regular pelvic examinations with a Pap test are very important for the prevention of this disease.

by: Professor Kiran Bhagat, Cardiac Clinic

RELEVANCE OF RENAL IMPAIRMENT AS A RISK FACTOR FOR CARDIOVASCULAR DISEASE

The presence of renal damage is associated with an increased risk of a future development of cardiovascular events and death. There is a continuous relation between cardiovascular risk and renal function. Chronic kidney disease and cardiovascular disease can then develop in parallel as a consequence of similar risk factors. This fact explains the need for an early integral approach for these patients in an attempt to control cardiovascular risk.

Renal damage and CV risk: The presence of renal damage is associated with an increased risk of future development of cardiovascular (CV) events and death. The enhanced risk is already present when microalbuminuria is detected in the presence of a totally preserved glomerular filtration rate (GFR). Since then and until the development of end-stage renal disease (ESRD), CV risk rises continuously to attain a maximum level 20 to 30 times above that of the general population (1)

The evolution of Chronic Kidney Disease (CKD): Four stages have been defined before the development of ESRD (stage 5) in the evolution of Chronic Kidney Disease (CKD) as defined in the Kidney Disease Outcomes Quality Initiative (K-DOQI)(2).

They are based on the level of estimated glomerular filtration rate (eGFR), obtained using the MDRD formula (3), or of estimated creatinine clearance using the Cockroft-Gault formula (4), and on the presence of albuminuria either micro (30-300 mg/g of creatinine) or macro (> 300 mg/g). The presence of albuminuria is more frequent with diminished values of eGFR and their simultaneous finding is accompanied by an additive effect on risk prediction.

CKD and the level of renal function in the Prevention of CV disease : The relevance of CKD for the prediction of CV disease has been demonstrated in the general (5) and hypertensive populations (6), as well as in patients with established cardiac disease in particular coronary artery disease (7), post-MI patients (8), and heart failure (9). The level of renal function has also been shown to be a good predictor of outcome after coronary interventions (10) and cardiac catheterisation (11).

The development of CKD is associated with the presence of classical CV risk factors in particular age, arterial hypertension, and hyperlipidemia (12) and recently it has been shown to be associated with the presence of metabolic syndrome (13).

In hypertensive patients longitudinal data have shown that the progressive decay of eGFR from normal or mildly diminished levels to values below 60 ml/min/m2 is accompanied by a significant increase in CV events and death during that evolution (14). CKD and CV disease can then develop in parallel being the consequence of the activity of similar risk factors (15) and both contribute independently to increase the risk prediction (16). Once CKD has progressed and eGFR are below the figure of 60 ml/min/m2, other factors specifically dependent on the level of renal insufficiency appear and contribute to enhance the level of CV risk. These are the presence of changes in calcium/phosphate homeostasis and the ulterior development of secondary hyperparathyroidism (17) and anaemia due to a diminished renal production of erythropoietin (18).

In patients presenting with heart failure, it has been shown that renal function is independently associated with a heightened risk for death, CV death and hospitalisation from heart failure in patients with both preserved and reduced left ventricular ejection fraction (9).

Interestingly, in heart failure the finding of a diminished level of eGFR could be, not the consequence of established renal disease but a direct reflection of an impaired haemodynamic status related to the severity of the underlying cardiac disease causing a functional derangement in renal function (19). Data from the CHARM study have shown that eGFR and cardiac function had effects that were independent in terms of predicting the primary end-point of the study (9).

The factors explaining the increased risk of CV events and death in the presence of any manifestation of CKD are the presence of advanced atherosclerosis and very frequently hypertensive vascular disease. This fact contributes to explain the frequent association of renal insufficiency and established CV disease and explains the need for an early integral CV intervention in an attempt to control all the different CV risk factors usually present in these patients (20)(Table 1). It also must be stressed that patients with renal insufficiency are less likely to be prescribed efficacious therapies in particular when situations like heart failure or established coronary artery disease are present (21). The prescription of the adequate medications is accompanied by better survival rates across the full spectrum of renal function (21).

TABLE: THERAPEUTIC ATTITUDES IN PATIENTS WITH RENAL DAMAGE AND HIGH CARDIOVASCULAR RISK.

Life-style Changes	▸ Salt intake, body weight, and smoking
Strict Blood Pressure Control	▸ Goal BP control <130/80 mmHg, (<125/75 mmHg if Proteinuria>1g/d). ▸ Combination therapy required in most cases ▸ Blockade of angiotensin II effects is required
Control Of Associated Risk Factors	▸ Lipids: Statins, fibrates ▸ Insulin resistance: Insulin sensitizers (Metformin, glitazones) ▸ Platelet aggregation: Aspirin,others

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by Dr. D. Gangopadhyay, Physician, Cardiac Clinic

USE OF CARDIAC ENZYMES IN THE DIAGNOSIS OF ACUTE CORONARY SYNDROMES

Acute coronary artery syndromes (ACS): Individuals who present with ACS represent a spectrum of patients, from those with unstable angina to those with non-ST segment elevation myocardial infraction (NSTEMI)

These patients can be difficult to distinguish from one another solely on the basis of clinical symptoms and ECG findings. Approximately three fourths of patients with ACS have an abnormal ECG, more often seen as labile ST segment depression or T wave inversions, or less frequently transient ST segment elevations. NSTEMI is defined by an elevation of cardiac isoenzymes (CK-MB or Troponin) and the absence of persistent ST segment elevations In patients with ACS, approximately 60% have unstable angina and 40% are diagnosed with MI. Of the patients with MI, two-thirds have NSTEMI and the remainder one-third present with acute ST-segment elevation MI.

In patients with ACS, the risk of subsequent cardiac death is directly proportional to the increase in cardiac specific troponin, even if CPK-MB levels are not elevated. Troponin T or I levels increase 3-12 hours after onset of MI and peak at 24-48 hours, then return to baseline over 5-14 days.

Cardiac enzyme elevations are useful for diagnosing myocardial necrosis and have been used to differentiate non-ST segment elevation myocardial infarction (NSTEMI) from unstable angina. In addition, the ECG may be non-diagnostic in up to 50% of patients with suspected acute myocardial infarction, so cardiac enzymes have proved useful adjuvants for diagnostic purposes. Traditionally, the rather nonspecific CK and the more cardiac-specific CK-MB fraction have been used for diagnostic purposes, but more recently use of the highly specific troponin I and T is increasing.

CK and CK-MB Fraction: Creatine kinase is an enzyme that stimulates transfer of high-energy phosphate groups. It is found in abundance in skeletal muscle, and also in heart muscle and the brain. Values for CK vary depending on muscle mass and are influenced by trauma, surgery, exercise, and other factors. During acute myocardial infarction, CK concentrations rise 6-8 hours after the onset, and reach maximal concentrations within 24hours. Serial CK measurements are sensitive (98%) but not specific (67%) for myocardial infarction. Creatinine kinase-MB is more sensitive (100%) and specific (98%) to myocardial injury than is CK, and the initial rise in CK-MB and CK-MB sub forms 1 and 2 may be in 2-8 hours. As such, CK no longer is indicated for diagnosis and risk stratification in chest pain syndromes. Elevations in CK-MB may be influenced by myocardial surgery, hypo- and hyperthermia, hypothyroidism, renal failure, and other causes. Creatinine kinase-MB elevations are associated with adverse outcome, but the degree of elevation necessary to increase risk has been controversial. Recently, a separate retrospective analysis (8250 patients) of the PURSUIT trial evaluated mortality at 30 days and 6 months. The authors sought to determine the significance of the peak CK-MB as a prognostic indicator. Peak CK-MB were categorized as 0-1, above 1-2, above 2-3, above 3-5, above 5-10, or above 10 times the upper limit of normal. Mortality at 6 months was 6.2%, 8.2%, 7.5%, 10%, and 11% respectively, at 6 months. These data indicated that even small degrees of CK-MB elevation help select patients at high risk for mortality. The underlying mechanism of this CK-MB elevation may be a greater degree of atherosclerotic plaque burden and calcification versus that in patients without elevations.

Troponin T:

Troponin mediates the interaction of actin and myosin. Troponin T is found in skeletal and cardiac muscle, but not normally in the serum. Results of prospective clinical studies, retrospective analyses of large trials and angiographic studies indicated that the quantification of troponin T is useful in diagnosis of acute coronary syndrome.

Further, Troponin T was compared with CK-MB and was demonstrated to be superior in terms of diagnostic and prognostic capability, in most, studies. It appears to be especially beneficial in differentiating risk among patients with unstable angina.

Troponin T may be elevated in patients with pulmonary embolism, and this should be taken into consideration when evaluating patients. The presence of renal failure (generally considered to be serum creatinine level > 2.5 mg/dl) may cause false positive troponin T.

Troponin I : Troponin I is also found in cardiac muscle but is not present in skeletal muscle. Troponin I also appears to be affected by renal failure and may be elevated with pulmonary embolism. Like troponin T, troponin I is available in rapid (qualitative) and quantitative forms.

Troponin I can accurately predict adverse cardiovascular events like death and myocardial infarction during follow up. In addition, one study demonstrated a trend toward more vessel occlusions in the patients with positive troponin I ($p=0.07$) compared with those with negative troponin I. In that study, positive troponin I was associated with higher mortality than in those with negative troponin I among patients with a baseline negative CK-MB. The prognostic value of troponin I was higher in patients who presented more than 6 hours after the outset of chest pain than in those who presented earlier, probably due to distribution kinetics of the troponin.

C- Reactive Protein and other Markers: Atherosclerosis is an inflammatory disease with a complex pathogenesis. C-reactive protein (CRP) is an acute-phase reactant, thought to be stimulated into hepatic production by the release of circulating inflammatory mediators (cytokines). An elevated CRP may directly interact with atherosclerotic and/or ischaemic vessels to promote inflammation and thrombosis. In addition to the extent of ischaemia, necrosis, and atherosclerosis, CRP also reflects inflammation by infectious agents and the amount of circulating pro-inflammatory cytokines. Combined CRP levels and lipoprotein assessment have additive usefulness in the evaluation of apparently healthy individuals.

The authors of one study prospectively identified that CRP and serum amyloid A, another acute phase reactant protein, predicted coronary ischaemic episodes during hospitalization in patients with unstable angina. At hospital admission, patients without a positive troponin T or

Continued on Page 12

Diagn
In Pic

World Lab Forum attendees at the COLA Head Office, August 2006

Ms Tebelelo Seretse, former MP for Serowe South giving her keynote speech during the donation ceremony by Diagnofirm in Mogorosi

Diagnofirm Quality Manager Munyaradzi Mangwendeza with Christine Head of Clinical Chemistry Department John Hopkins University Hospitality Department of Pathology

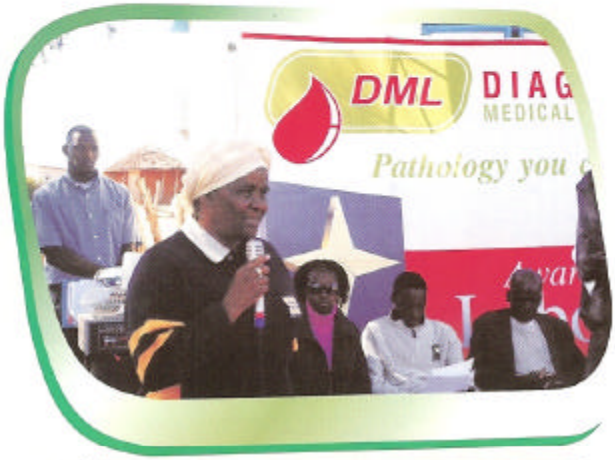
Mogorosi Chief Pherethego Segoea thanking Diagnofirm for the donations

(Left to right) Dr. Thuppil Venkatesh, Jennifer Phelps QA Manager Haematology Department John Hopkins University Hospital Department of Pathology, Diagnofirm QA Manager Munyaradzi Mangwendeza

Hon. MPs F. Venson-Moitoi and T. Masisi pose with Mr. I. Chand, Obakeng Kgosi, Mr. Kgosi and Mrs. Masisi on the day Obakeng left for his kidney transplant in Pakistan

ofirm tures

Mr. I. Chand and Mrs W. Chand hand over Diagnofirm folders to invited guests



Hon. MP P Venson-Moitoi MP for Serowe South giving a vote of thanks after Diagnofirm donation in Mogorosi Village

Hon. MP T. Masisi, MP for Francistown West and Mrs Masisi together with Mr. I. Chand bid farewell to Obakeng Kgosi and his father at the SSK Airport as the two were on their way to Pakistan

Mr. I. Chand hands over a Diagnofirm folder to Molepolole Kgosi Baaisane Kgari

Mr. Chand Donating glucometers to the Kweneng Clinic Matron.

Kennedy from DML getting ready to do glucose testing in Molepolole

LABORATORY MEDICINE AND ALCOHOL ABUSE

Alcohol abuse is a common causative factor to health problems and affects many people without them being aware of it. Thus at times it becomes vital for the doctor to investigate the absence or presence of alcohol abuse. Many conditions can results from alcohol abuse. These include:

- Liver disease, gastritis and pancreatitis
- Hypertension, cardiomyopathy, cardiac arrhythmias
- Strokes, brain damage
- Cancer of mouth, larynx, esophagus
- Contribution to breast and colon cancer
- Nutritional deficiencies, obesity
- Diabetes, gout
- Myopathy, neuropathy
- Sexual dysfunction, infertility
- Foetal alcohol effects
- Hemopoetic toxicity
- Reactions with other drugs
- Intoxication-related problems acute alcohol poisoning, accident and trauma.

Some physical signs that may be apparent on assessment of someone abusing alcohol include:

- Obesity
- nicotine staining on fingers from smoking which is often associated with heavy drinking
- Scars which may indicate trauma
- Facial erythema which is sometimes present as a result of chronic heavy drinking.

Many heavy drinkers are in excellent health, with no obvious ill-effects from their extreme drinking and are unlikely to seek medical advice and can expertly hide their addiction but when medical advice is at last sought it is often too late to reverse either the organ damage or the reliance on alcohol. On the average a unit of alcohol contains 8g of absolute alcohol and a can of beer or lager contains about 1.5 units of alcohol. Using the above details, the definitions of the different kinds of drinkers are as follows:

a. Social drinkers- usually drink about 2-3 units of alcohol a day and do not get intoxicated.
b. Heavy drinkers regularly drink more than 6 units a day but without immediate harm
c. Problem drinkers experience physical, psychological, social, family, occupational, financial or legal problems attributable to drinking. For men the values are > 50 units a week and for women > 35 units.
d. Alcohol dependence people with a compulsion to drink , who take roughly the same amount of alcohol each day , have increased tolerance in the early stages and reduced tolerance later, suffer withdrawal symptoms if alcohol is stopped and in whom drinking takes precedence over other activities.

CLINICAL FEATURES AND EFFECTS OF VARIOUS ALCOHOL CONCENTRATIONS

Blood alcohol concentration in mg/100ml	Clinical effects
20	Excitement
30	Increased likelihood of having an accident
40	Disinhibited
80	Impaired coordination
150	Loss of self control, slurred speech, sleepiness and forgetfulness
300	Stupor, coma
500	Coma, death possible
600	Death certain

Laboratory medicine plays a vital role in the diagnosis of alcohol abuse and should be used principally in cases where this is suspected to help identify alcohol related illnesses.

Ideally any marker used should reflect on individuals consuming alcohol both constantly (screen marker) and acutely (relapse marker). A screening marker should show high sensitivity and specificity and differentiate between safe social drinking and heavy hazardous drinking. The marker should not be elevated by non-alcohol induced organ tissue damage. A marker used to detect relapse should be sensitive to any consumption above safe levels. Unfortunately no such marker exists at present. In this article we will examine the common tests used in the diagnosis of alcohol abuse and determine their usefulness in the different examples of alcohol abuse.

COMMON LABORATORY MARKERS

Blood/urine/breath ethanol: The test has a low sensitivity and provides no information as to the severity of drinking but when it is positive it gives objective evidence of recent drinking and identifies increased tolerance.

SerumGamma- glutamyltransferase (GGT): This is a membrane bound enzyme found in the sinusoidal membranes of the cell wall. It cannot reliably identify heavy drinkers but when elevated in drinkers in the absence of other known causes it is likely to be alcohol related. Increased GGT in drinkers can be attributed to (a) enzyme induction possibly as a protective effect on the liver or (b) liver cell death associated with chronic consumption may result in release of GGT enzyme into the blood stream. Its use as a marker of liver damage is supported by the fact that GGT is predictive of increased alcohol morbidity as well as the association of high GGT with increased mortality in middle aged men. It is nevertheless elevated in individuals who are alcohol dependent but infrequently in subjects under 30 years of age and is less sensitive in women. It is used chiefly as an indicator of chronic consumption of large amount of alcohol and is not increased by binge drinking in non-alcohol abusers unless there is associated liver disease. Despite its poor specificity, 50-72 % of elevated GGT levels can be explained by excess alcohol consumption. It is quite useful in confirming a clinical suspicion of alcoholism and in monitoring abstinence in the recovering alcoholic.

Serum transaminases: AST and ALT are often raised in alcoholics but usually not more than 2-4 times the upper normal range. Acute alcohol intakes of 3-4g/kg body weight can lead to transient increase in AST within 24-48 hours. These two are however non specific markers but useful in the absence of other causes of liver damage. The use of the AST: ALT ratio is considered more specific than the use of

the individual test values. A ratio of >1.5 strongly suggests alcohol abuse and >2.0 is almost indicative of alcohol induced damage to the liver.

Mean Cell Volume (MCV) : Values >98 fl are reported in up to a 3rd of heavy drinkers and 5% of normal drinkers have elevated MCV values in the absence of known causes. This is so because alcohol and its derivative metabolite acetaldehyde exert toxic effects on bone marrow affecting erythropoiesis. The elevated MCV values in heavy drinkers are not related to B12 or folate deficiency. The main weakness of the MCV is low sensitivity both in hospital environments and in primary health care with an overall sensitivity of 40-50%. However the specificity is quite good and is between 80-90 %.

Lipids, Uric acid and serum IgA: Although increased high density lipoproteins and triglycerides can raise suspicion of excessive alcohol consumption, neither has adequate sensitivity and specificity to be of use in diagnosis and monitoring alcohol abuse. Serum IgA is raised in patients with alcohol induced liver disease. Uric acid is also raised in 20-40% of alcoholics but only helpful in supporting the diagnosis of gout and use as a marker which may improve with reduction in alcohol use. However no direct relationship exists between alcohol consumption and uric acid levels. None of these markers is useful in the screening of alcoholism or monitoring abstinence and all display inadequate sensitivity and specificity.

Serum carbohydrate-deficient transferrin (CDT): Is a more sensitive and specific marker of recent heavy alcohol consumption than most other tests. Alcoholic subjects consuming 50-80g of alcohol per day for at least a week will show increased serum levels. It is better at detecting alcoholics than hazardous drinkers but shows less sensitivity in less extreme populations for example women and healthy volunteers. It is also good for discriminating between alcohol induced hepatopathy and liver diseases of other origin and for detecting relapse. Patients with alcoholic liver disease have significantly higher values of CDT than alcoholics with no liver pathology. Diagnostic performance of CDT correlates positively with alcohol consumption. CDT is mostly increased in cases with an early stage of alcoholic liver disease, so that there is a weak negative correlation between CDT and disease severity which is of diagnostic value. It is of no use in screening for heavy alcohol consumption in the general population particularly in women and will not identify binge drinkers.

Serum/urine 5-hydroxytryptophol (5-HTOL): Serotonin is normally metabolized to 5-hydroxytryptophol-3-acetic acid (5-HIAA) and 5-HTOL, with 5-HIAA being the major metabolite. Alcohol dependently shifts serotonin metabolites towards 5-HTOL. The increase in 5-HTOL and a decrease in 5-HIAA can be measured in blood and urine. The 5-HTOL: 5-HIAA ratio can reveal alcohol intake in the past 24 hours and remains elevated for 6-15 hours after blood alcohol levels have returned to normal. This test has a high sensitivity because as little as 20g/day of alcohol consumption can be detected. It also has a high specificity for detecting very recent alcohol consumption and maybe very useful if employed in Traffic Medicine. It also has great use where frequent follow-up of a patient is feasible and necessary.

Serum mitochondrial AST: Serum AST consists of 2 isoenzymes: mitochondrial AST (mAST) and cytosolic AST (cAST). In the serum samples from healthy adults, cAST makes up >90% of the total activity but when excessive alcohol consumption selectively injures mitochondria in the liver, mAST is preferentially released. The test is 90% sensitive in alcoholic patients although it is not very specific. Using the ratio of mAST: totalAST improves the specificity of the test.

Serum Beta- Hexosaminidase (B-HEX): B-HEX is an acid lysosomal glycosidase. Increased serum and urine levels are present in alcoholic patients as well as healthy individual volunteers after consumption of >60g/day of alcohol for at least 10 days. It has a high sensitivity of 70-90% which is better than of most tests and falls rapidly to normal within 7-10 days following abstinence. Main advantage of B-HEX is that it is a sensitive test, easily measured in the laboratory and inexpensive test for excessive alcohol consumption.

Serum acetaldehyde and acetaldehyde adducts: Acetaldehyde is the first metabolite of ethanol and is not a good marker of alcohol use since it is metabolized within a few hours of consumption. Acetaldehyde-protein adducts are formed in the body after excessive ethanol intake and their formation triggers antibody production which may account for the tissue damage seen in alcohol abusers. Anti-adduct IgA, IgG and IgM titres in alcoholic liver disease (ALD) patients correlate well with the severity of liver disease. They find their convenience in the differential diagnosis of alcohol induced liver disease.

Other potential markers: Other markers include fatty acid ethyl esters, phosphatidylethanol, sialic acid, urinary salsolinol and urinary dolichols. The disadvantage of these tests is that they require complex measurement techniques outside the scope of the routine laboratory hence can not be used except in research institutions.

CONCLUSION

No laboratory test is dependable enough on its own to support a diagnosis of alcoholism. Laboratory test have to be part of a diagnostic process that includes a detailed clinical history as well as examination. Laboratory tests are valuable in both raising the suspicion and confirming the diagnosis of alcohol abuse. They are also good for following up patients undergoing treatment and in the monitoring of abstinence.

GGT continues to be the best test combining best convenience and sensitivity. Its diagnostic accuracy can be improved by combination with other tests such as ALT, AST and MCV. Most of the newer more complicated tests do not offer significant advantages over the use of GGT; however CDT seems to be better at monitoring patients for increased alcohol consumption or progress towards abstinence and also in distinguishing between alcoholic liver disease from non-alcoholic liver disease.

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Continued from Page 7

Use of Cardiac Enzymes in the Diagnosis of Acute Coronary Syndromes

CK who had chronic stable angina (32 patients), unstable angina (31), or acute myocardial infarction (29) had a 13%, 65%, and 76% incidence of elevated CRP and serum amyloid A (> 0.3 mg/dl), respectively. The 20 patients with unstable angina and elevated CRP and serum amyloid A had a higher incidence of ischaemic episodes (Holter monitoring) in the hospital than of patients without.

At 6 months, in patients with unstable angina, six patients with a positive CRP experienced death due to myocardial infarction, compared with zero patients with a negative CRP. In the unstable angina and myocardial infarction groups, the serum amyloid A and CRP correlated well.

Although CRP may predict early ischaemic episodes, studies indicate that it does not predict early in-hospital end points like death and myocardial infarction. In contrast, CRP does predict adverse outcome at 14 days and beyond. As addressed previously, troponin T can predict early events, and CRP and troponin T can be used in combination for effective risk stratification.

Creatine kinase-MB, troponin I and T, and CRP are the most well studied markers for risk stratification, and they represent the degree of myocardial necrosis and plaque rupture. Troponins are the preferred markers for myocardial injury, but CK-MB by mass assay and CRP are also recommended. Another marker for myocardial necrosis is myoglobin.

This marker is a low-molecular-weight heme protein that peaks rapidly (< 2 hrs), but it loses its sensitivity due to rapid clearance and is not cardiac specific. Myoglobin or CK-MB subforms are recommended for patients presenting within 6 hours of chest pain onset. Lactate dehydrogenase isoenzymes, CK, and aspartate aminotransferase, also markers of cell damage, are rather noncardiac specific and no longer are recommended.

References available upon request.

MICROBIO-ALERT : CRYPTOSPOSIDIA AND IMMUNO-COMPROMISED PATIENTS

Gastrointestinal infections can be of bacterial, viral or parasitic origin. Cryptosporidia, girdia lamblia, isospora and amoeba mainly cause parasitic infections of the gastrointestinal tract. During the period 01-05-2006 to 31-07-2006 at Diagnofirm a total of 136 stool samples were processed. Three (3) were positive for Salmonella and one (1) positive for Shigella. The rest of the samples were negative for any bacterial pathogens meaning that some of the gastroenteritis was probably due to other pathogens other than bacterial pathogens. This is an indication that doctors need to request more of the special tests used to detect parasitic infections such as those caused by cryptosporidia as well as those for viral gastroenteritis.

Stool specimens are normally processed according to the clinical information provided. Those specimens from patients with gastroenteritis or diarrhoea need to be tested for other pathogens such as viruses and parasites. Currently all stool specimens from children under 2 years of age are tested for rotaviruses and adenoviruses. This came up as a result of the fact that statistics at Diagnofirm showed a very high prevalence of these pathogens in children and hence this processing protocol became part of the standard operating procedures.

Likewise the current statistics that we have, although few, warrant us to suggest that for all HIV positive patients with gastroenteritis or diarrhea, there is a need to make the testing for cryptosporidia mandatory. This could also be extended to all immuno-compromised patients such as those on chemotherapy and diabetic patients.

Cryptosporidia and cyclospora are the human pathogens likely to be encountered in stool samples stained by the modified Ziehl-Neelsen method. These are some of the gastrointestinal pathogens that need to be paid particular attention to since they still cause a lot of problems in the developing countries and the method used for their identification is cheap and widely available.

From a quality assurance point of view, the submission of relevant clinical date is also quite important as it guides the laboratory scientists on the best procedures to use for each individual case based on the data provided. Hence we call upon all physicians to include the clinical data whenever they request laboratory tests more so for stool samples since most of the testing will depend on that information.

Most statistics used currently are from other countries and in light of the recent diarrhoea out-break in Botswana where the causative organism was identified as cryptosporidia, it becomes essential that Botswana adopt the idea of routinely screening for cryptosporidia and collecting statistics for our own health system planning. At Diagnofirm from 01-01-2006 to 18-08-2006, 76 patients were screened for cryptosporidium prevalence of which 30 were positive representing 39.47% of the referred cases. Predicting disease outbreak can be made much easier if the correct statistics are available and this can only be done if routine testing is done for the risk groups as indicated by the current statistics.

Alcohol Abuse Facts

- Lack of parental support, monitoring, and communication have been significantly related to frequency of drinking, heavy drinking, and drunkenness among adolescents. Harsh, inconsistent discipline and hostility or rejection toward children have also been found to significantly predict adolescent drinking and alcohol-related problems.
- Parents' drinking behavior and favorable attitudes about drinking have been positively associated with adolescents' initiating and continuing drinking. Children who are warned about alcohol by their parents and children who report being closer to their parents are less likely to start drinking.
- The three leading causes of death for 15- to 24-year-olds are automobile crashes, homicides and suicides -- alcohol is a leading factor in all three.

by Desire B. Mhlabi.

REPORTING OF EGFR (ESTIMATED GLOMERULAR FILTRATION RATE) WITH ALL SERUM CREATININE REQUESTS.

Please be informed that latest pathology recommendations require that we routinely report eGFR levels with all serum creatinine requests. You will therefore find this parameter on all our reports. Below is an extract of the background information for your perusal.

INTRODUCTION

The Glomerular Filtration Rate (GFR) is the best overall measure of renal function. The most accurate measurement of GFR requires complex technology, which is not routinely available. Alternate estimates of the GFR (eGFR) can be made by the following methods:

- **Estimate of GFR (eGFR) by MDRD formula (which requires age, sex and serum creatinine only). The MDRD formula for estimation of GFR is recommended for routine use and is reported with all requests for serum creatinine from Diagnofirm.**
- **Estimate of GFR by the Cockcroft and Gault equation** (which requires patient age, sex, weight or height, and serum creatinine). This estimate is recommended for drug dosing decisions.
- **Measurement of Creatinine Clearance** (which requires a serum creatinine measurement and a 24 hour urine collection). This is the least reliable method for routine use but is valuable in extremes of body composition where the estimation formulae above are not reliable.

eGFR using MDRD Formula

$$eGFR\ (mL/min/1.73m^2) = 186 \times [SerumCreatinine(umol/L) \times 0.0113]^{-1.154} \times Age\ (years)^{-0.203}\ (\times 0.742\ if\ female)$$

NOTES

- eGFR using the MDRD equation will be reported with all requests for serum creatinine.
- This is a recommendation of the peak renal and pathology bodies in Australia (Chronic Kidney Disease and Automatic reporting of glomerular filtration rate: a position statement. MJA 2005; 183 (3): 138-141. Www.mja.com.au)
- The formula is named after the Modification of Diet in Renal Disease study in the USA.
- The results are expressed relative to a standard body surface area of 1.73 m^2 to allow for different body sizes. The units are mL/min/1.73m^2.
- The equation is only valid in persons 18 years of age or older and not reported in younger patients.
- Results >60 mL/min/1.73m2 are likely to deviate from the true value and are not routinely reported.
- The use of the eGFR in patients on dialysis is inappropriate and will give misleading results.The formula has not been validated for drug dosing and alternate estimates of GFR such as the Cockcroft and Gault methods should be used.
- Results may deviate from true values in patients with exceptional dietary intake (eg vegetarian diet, high protein diet, creatine supplements); extremes of body composition (eg lean, obese, paraplegia), or severe liver disease.
- Drug Dosing information in Australia (eg MIMS, Australian Medicines Handbook, Therapeutic Guidelines) is based on Cockcroft and Gault estimates of creatinine clearance. Cockcroft and Gault is recommended for drug dosing decisions.

INTERPRETATION

The MDRD estimate of GFR can be used for identification of moderate to severe decrease in renal function and as a staging tool for Chronic Kidney Disease (CKD)

- eGFR >59 mL/min/1.73m^2 - Normal GFR or mild decrease in GFR
- eGFR 30 - 59 mL/min/1.73m2 - Moderate decrease in GFR (Stage 3 CKD)
- eGFR 15 - 29 mL/min/1.73m2 - Severe decrease in GFR (Stage 4 CKD)
- eGFR <16 mL/min/1.73m2 - End-stage kidney failure (Stage 5 CKD)

Please Note that:

- The MDRD eGFR is NOT a sensitive test for renal failure and cannot be used to detect mild renal impairment (GFR 60 - 90 mL/min/1.73m2).
- Results >60 mL/min/1.73m2 do NOT necessarily indicate normal renal function.
- The most sensitive routine test for small reductions in GFR is a comparison of a serum creatinine concentration with a previous result from the same patient. An increase of 15% or more in serum creatinine indicates a significant fall in GFR.

We hope that this extra information will help improve early diagnosis, treatment and management of chronic kidney disease.

Interlude

MY FATHER

Those three boys are in the schoolyard bragging of how great their fathers are.

The first one says: "Well, my father runs the fastest. He can fire an arrow, and start to run, I tell you, he gets there before the arrow".

The second one says: "Ha! You think that's fast! My father is a hunter. He can shoot his gun and be there before the bullet".

The third one listens to the other two and shakes his head. He then says: "You two know nothing about fast. My father is a civil servant. He stops working at 4:30 and he is home by 3:45"!!

by Munyaradzi Mangwendeza

WORLD LABORATORY MEDICINE FORUM

COLA, a leader in accreditation, education and consultation services, convened its first International Symposium July 30-August 1, 2006 and brought together key thought leaders who share a passion for improving the quality of laboratory medicine. The three-day symposium explored a global vision for creating quality in medical laboratory testing through cafe-style discussions and presen-tations. Several speakers gave presentations which included:

- **The Role of Laboratory Medicine in a World at Risk - Leslie Mancuso, Ph.D., JHPIEGO and Susan Berger, Ph.D., from Pfizer.**
- **Looking Forward: Our Vision for Laboratory Quality Worldwide - Klaus Stinshoff, Chair, ISO/TC 212 and Rosa Sierra Amor, Ph.D., from the Mexican Association of Biochemistry.**
- **Closing the Gap: What Must be Done to Achieve our Future Vision - John C. Nelson, M.D., Past President, American Medical Association.**
- **Building a Community of Action Dr. Thuppil Venkatesh, Ph.D., Professor and Head of the Department of Biochemistry and Biophysics, St. John's Medical College, Bangalore, India**

COLA also articulated its commitment to ISO initiatives and standards scaleability and how they are critical to safe and effective laboratory environ-ments. Dr. John G. Bartlett, M.D., Chief of Infectious Diseases at Johns Hopkins University School of Medicine keynoted the symposium at a reception held Sunday evening. Dr. Bartlett discussed avian flu crisis management and other public health risks such as HIV.

Additional participants of the International Symposium included public health leaders from Diagnofirm Medical Laboratories (Botswana), the Centers for Disease Control (CDC) and the U.S. Department of Health and Human Services (HHS); industry leaders from the World Medical Association and World Health Organization (WHO); and government and industry leaders from Egypt, Southern Africa, India, Singapore, Mexico, Thailand, the Caribbean, Europe, Asia, and the U.S.

The common thought was that there is an extreme need for high-quality, accurate, trusted diagnostic information to aid in the treatment of patients. Medical laboratories are at a critical spot to support and respond to these global health crises.

Left to right: Dr. Herm Abromowitz, MD, M. Mangwendeza and Eddie Ang. World Lab Forum 2006

The International Symposium was an opportunity for COLA and the attendees to meet and learn from one another to gain a collective awareness and understanding of the unique and varying needs of different countries and regions and prepare laboratories for the challenges ahead

Numerous questions guided the way the symposium was conducted and these were:

a) The Current State of Laboratory Medicine in a World at Risk

1. What is the current state of laboratory quality, standards, capacity and Infrastructure?
2. How did we come by the current state of laboratory medicine? Why do some countries/regions have standards and others not? Is it important?
3. What have we learned to date about setting laboratory standards?
4. Where do our world standards fall short in addressing the current world health concerns?

b) Looking Forward: Future State of Worldwide Laboratory Medicine

1. What are the characteristics of effective world laboratory medicine standards?
2. How can the different interested parties(Governments accreditors professional laboratory societies patient organizations standardization bodies) work together, perhaps even be coordinated?
3. What can medical devices manufacturers and the commercial laboratory industry contribute to Laboratory Standards?
4. How could countries/regions keep decision making local (to enhance flexibility) while at the same time participate in world quality standards?
5. What will laboratory medicine look

World Lab forum 2006 attendees from left to right:
Dr. Cecil Wilson, MD, Dr. Klauss Stinshoff, Dr. Leslie Mancuso and Dr. John Ridderhoff

like in 10 years? In 25 years?

6. What will be the nature of relationships between Governments, pharmaceuticals, laboratories, medical societies and quality organizations?

b) Closing the Gap: What Must Be Done to Realize our Future Vision?

1. What are some immediate actions that can be taken to move efficiently toward world standards build laboratory capacity and build infrastructure? 2. How do we seize upon the current best approaches to laboratory medicine?
3. What can be done to tap into both governmental interests and private interests to move laboratory medicine forward?
4. What is currently being done to move laboratory medicine toward high, collective standards?

c) Building a Community of Action

1. How can this body of concerned people move the agenda ahead, quickly and effectively?
2. What can we do as individuals to make a world difference in laboratory medicine?
3. What resources are we not tapping?
4. Moving from a community of interest to a community of action, what are our concerns/barriers? And how can we turn these concerns/barriers into advantages?

After the 3 days symposium, what came out were a lot of ideas and probable solutions to the current state of laboratory medicine worldwide. Of major interest was the state of laboratory medicine worldwide with the following issue taking centre stage:

The current state of laboratory medicine worldwide is:

- Those regions with the greatest need have the least capacity
- **Quality laboratory medicine is under valued**
- Lack awareness of the role of laboratory medicine in our world at risk
- We lack complete planning and we fail to recognize secondary risks
- There is a growing demand for laboratory testing
- There is too much of a western view in policy making related to healthcare and lab medicine, lack an appreciation for the reality "on the ground"
- Our financial and business models overly dictate what we should do and, as such, the solutions we develop are not applicable in others parts of the world
- **There does exist a "nucleus" of essential quality system standards that could be applied to all laboratories**
- Dumping "old generation" or graveyard laboratory equipment on other nations/regions is not helpful "poisonous gifts"
- We lack global view of the regional needs in terms of laboratory testing, testing environments, personnel qualifications and cultural/social norms leads to short term solutions or no solutions at all
- **Lack quality training that is relevant, science-based and hands-on in many regions of the world. Training is didactic, outdated and not practical.**
- Laboratory standards and training needs to be relevant to laboratory personnel and the region
- **"Compliance training" is insufficient...we need to tap the internal passion and commitment of people to improve laboratory quality**
- Poor quality reagents are being used in some parts of the world
- We overly focus on programs and funding on diseases, rather than the whole systems. While it is great to fund and plan for specific diseases, this does create the secondary problem of a disconnected system of healthcare
- Standards development is not the lagging system rather, the systems that are lagging include: 1. resources, 2. capacity; and 3. tools for the application/transferability of base standards to different testing applications and environments
- **Not all countries mandate laboratory quality**

At the end of it all, it was clearly noted that we all shared global visions which are:

- "One World Laboratory" database shared worldwide while protecting patient confidentiality
- More partnerships among stakeholders, working together, **holding a patient-centered focus**
- Standards and a system that is centered on the patients (individual and collective/public health)
- Lab is viewed as integral to the whole healthcare system
- Appropriate testing of high quality reflective of the reality in resource-stressed countries/regions
- The lab of the future will handle well the political landscape
- International database that allow us to make better predictions of disease

For a full report on this historic world laboratory medicine forum log on to *www.worldlabforum.org*

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ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR DISEASE

In atherogenesis, Endothelial Dysfunction (ED) is the earliest measurable functional abnormality of the vessel wall. ED is closely related to the risk factors of atherosclerosis, to their intensity and duration. The involvement of ED in cardiovascular disease is also supported by its relation to cardiovascular events.

A healthy endothelium plays a central role in cardiovascular control. Therefore, (ED) may have a particularly significant role in the pathogenesis of atherosclerosis (1).

ED is a consequence of the harmful effects of the risk factors of atherosclerosis on the vessel wall and is more or less important depending upon the number of risk factors, their intensity and their duration. ED has been demonstrated in subjects with hypercholesterolemia, diabetes, hypertension, and in patients who smoke, and patients with atherosclerotic disease (coronary, peripheral arterial) (2, 3). It was also shown that ED is an early event in type I and II diabetes and that it is related to the development and progression of diabetic vascular complications. In one of our studies on type I diabetic patients it was shown that ED (demonstrated by flow mediated endothelium dependent dilation) is inversely related to the extent of microalbuminuria (4).

Furthermore, the involvement of risk factors in ED is also supported by results of interventional studies that showed regression of ED with the treatment of risk factors. Improvement of ED may be achieved by eliminating risk factors, by substituting natural protective endothelial substances with L-arginine, by administrating inhibitors of endothelium-derived contracting factors (e.g. ACE inhibitors, angiotensin II receptor antagonists), by administrating cyto-protective agents (eg, free-radical scavengers such as superoxide dismutase, lipid-lowering drugs and by having the patient follow a diet and do physical exercise (3). In patients with poly-metabolic syndrome, we also observed improvement of ED through physical training. In growth hormone deficient patients, improvement of EF was registered with growth hormone replace-ment therapy (5).

These data show that the treatment of risk factors may help to restore a vascular function and that ED is reversible. ED promotes the progression of atherosclerosis and probably plays an important role in the development of thrombotic complications in the late stages of the disease.

As it has been shown that ED is a key underlying factor in the atherosclerotic process, markers of endothelial abnormalities have been sought. Different tests require the measurement of several different aspects of endothelial dysfunction such as endothelium-dependent vasomotion, as well as circulating markers of endothelial function. Most of the functional methods for in vivo endothelial testing examine the ability of the endothelium to cause vasodilation in response to pharmaco-logical and physiological stimuli that increase the endothelial release of NO.

Endothelial function may be tested non-invasively in the peripheral conduit arteries using high-resolution external vascular ultrasound. In this method, arterial diameter is measured in response to an increase in shear stress, which causes endothelium-dependent dilation, after the administration of sublingual nitroglycerine, an endothelium-independent dilation. The brachial arterial dilator response to increased blood flow during reactive hyperaemia has been shown to be caused mainly by an endothelial release of NO, to correlate significantly with endothelial function, as well as with the extent and severity of atherosclerosis.

Furthermore, endothelial injury may result in the release of various factors that can be detected in the circulation and that can be potentially used as markers of endothelial dysfunction. Circulatory markers of endothelial dysfunction most often used are: endothelin-1, von Willebrand factor, tPA and PAI-1 and adhesion molecules (VCAM, ICAM, P-selectin). With these tests, it is possible to follow the dose - response of harmful effects of risk factors, and the effects of preventive procedures on vessel wall function. Determination of ED also has important clinical implications. It was shown that ED is significantly and directly correlated with the occurrence of cardiac events and that cardiac events increased as ED worsens (6).

References available upon request

JOKES CORNER

Doctor's Strike

"Doctors at a hospital in Gaborone have gone on strike. Hospital officials say they will find out what the Doctors' demands are as soon as they can get a pharmacist over there to read the picket signs."

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Medical Term Needed

The man told his doctor that he wasn't able to do all the things around the house that he used to do.

When the examination was complete, he said, "Now, Doc, I can take it. Tell me in plain English what is wrong with me."

"Well, in plain English," the doctor replied, "you're just lazy."

"OK," said the man. "Now give me the medical term so I can tell my wife.

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Laxatives

A pharmacist comes back from his break and sees a man leaning against the wall, his face strained and nervous. He asks his assistant: "What's wrong with that man over there?"

"He came in looking for cough medicine," she replies. "I couldn't find any, so I gave him a whole bottle of laxatives."

"Oh great!" steamed the pharmacist. "He is going to sue us now. You don't give laxatives to a person with a cough!"

"Well," said the clerk defensively, "look at him. He's afraid to cough!"

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Cold....

One day it was so cold that all the lawyers had their hands in their own pockets!

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Mental health.....

Psychiatrists say that one out of four people are mentally ill. Check three friends. If they're okay, you're it!

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Peer pressure....

A reporter interviewed a 104-year-old man. "And what do you think is the best thing about being 104?" the reporter asked.

"No peer pressure," he replied.