AOTEA NEWS
– CLINICAL UPDATE

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FROM THE **EDITOR**

We are pleased to present to you the first edition of Aotea News – Clinical which replaces the clinical articles and commentary section from Aotea News. By separating this from the more direct laboratory information content of Aotea News we can expand the space and scope of articles and commentary relevant to our referrers.

We trust you will find this expanded publication of use in your practice and we welcome comments on the material provided and any topics you would like to see covered in future editions.

As in recent years we will endeavour to produce three editions per year, and from next year we will distribute Aotea News between issues of Aotea News – Clinical to keep you informed on laboratory news and services along with changes in testing protocols, testing methodologies or test reporting.

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NON-FASTING SAMPLES FOR CARDIOVASCULAR RISK ASSESSMENT AND SCREENING FOR DIABETES

Non-fasting samples can be used in cardiovascular risk assessment and screening for diabetes.

The traditional recommendation is that lipids are measured after an overnight fast. In fact, there is no good evidence that fasting lipids are superior to non fasting lipids for cardiovascular risk prediction.

There is substantial evidence that the requirement for fasting is difficult for many people to observe and is a significant barrier to identifying those who should be on treatment.

Several large studies have found that lipid fractions, including triglycerides, do not change significantly in most people after normal food intake. In particular, the total cholesterol: HDL cholesterol ratio does not change and remains valid for use in risk prediction tools. In those in whom triglycerides are significantly elevated after a meal there is emerging evidence that these levels are better predictors of cardiovascular risk than fasting levels.

Measurement of non fasting cholesterol and HDL cholesterol is accepted in the guidelines of the National Cholesterol Education programme (USA) and the United States Preventive Services Task Force.

Medical centres in Denmark use non fasting lipid profiles as standard practice.

The New Zealand Guidelines for Cardiovascular Risk Assessment and Screening for Diabetes (2009) indicate that if a fasting profile is not possible, measurement of non fasting cholesterol and HDL cholesterol is acceptable, with HbA1c replacing fasting glucose.

Now the most recent guideline on screening for diabetes recommends that, in most circumstances, HbA1c is the preferred test to screen for and diagnose diabetes. The reasons include the substantial advantages of lack of need for fasting, reduced biological variability and equally good relationship with retinopathy and CVD risk, compared with fasting glucose and OGTT.

Thus, use of a non fasting specimen for the initial combined cardiovascular risk assessment and screening for diabetes is a sensible option. This should make testing more acceptable to patients and relieve pressure on collection services in the early morning thus reducing waiting times for phlebotomy. Fasting lipids should be reserved for when decisions are being made to treat or when LDL cholesterol is being monitored.

Dr Michael Crooke
Chemical Pathologist

PRACTICE **POINTS**

- There is no evidence that fasting lipid measurements are superior to non-fasting lipids in cardiovascular risk assessments.
- Given the advantages to patients, non-fasting lipid profiles are encouraged and can be combined with HbA1c testing to screen for diabetes in a risk assessment setting.
- Fasting lipid measurement is still recommended when decisions are being made to treat or when LDL cholesterol is being monitored.

EARLY DETECTION OF PROSTATE CANCER: WADING THROUGH THE SWAMP OF OPINION AND DEBATE

Few issues in modern healthcare have generated more heat and light than the ongoing debate around the value of offering asymptomatic men screening for the detection of early prostate cancer.

Various players expound very different points of view – it is not that one group holds the "truth" and another is incorrect but rather that each examines the issue through the lens of their particular experience and bias.

Health action groups are made up of men who, until they had PSA testing, were well and have now had a malignant disease detected and effectively treated – to them PSA screening saved their lives and is to be aggressively advocated.

Pathologists every day examine prostate needle biopsies containing adenocarcinoma detected through opportunistic screening.

Urologists and Oncologists are exposed to the misery of symptomatic advanced prostate cancer patients and feel strongly that early detection and treatment averts this most unpleasant of outcomes.

Public Health physicians on the other hand view the matter from a public good perspective and examine the epidemiological evidence that casts doubt on the long term survival benefits of early prostate cancer detection and point out that in certain situations screening offers the risk of more harm than benefit.

There are now more position statements from various expert groups in multiple jurisdictions on screening for early prostate cancer than any practitioner would wish to read and digest.

What do you offer an asymptomatic 45 year old male patient who consults you for his "health check-up"?

Below is a brief distillation of some of the current wisdom which may assist, or further confuse, your thinking!

- Prostate cancer is the most commonly diagnosed cancer in New Zealand men and the third most common cause of male cancer deaths. Approximately 3,000 new cases of prostate cancer are diagnosed each year, and around 560 men die of the disease each year. Prostate cancer is rare before age 50 years and the majority of deaths due to prostate cancer occur after age 75 years.
- Despite neutral to discouraging recommendations from the NZ Ministry of Health and the National Health Committee in the last 10 years around 40% of New Zealand men over the age of 50 years have been offered opportunistic PSA screening by general practitioners.
- In 2009 two randomised trials of prostate cancer screening reported. The PLCO trial was completed in the United States and the ERSPC in Europe. These trials did not establish that screening populations for prostate cancer has clear overall benefit. One of the trials found a 20 percent relative reduction of risk of death from prostate cancer in men who underwent screening and the other found none. In September 2010 the BMJ published a meta-analysis of the results of six major randomised trials to determine whether screening using PSA testing reduces prostate cancer mortality. The six trials included the ERSPC, PLCO and the later Göteburg study. The meta-analysis found that screening for prostate cancer did not reduce mortality from prostate cancer or overall mortality but that screening increased the probability of being diagnosed with prostate cancer by 46 percent ; 95% being early stage disease.
- Given the evidence to date no country has recommended the introduction of a national organised screening programme based on PSA testing with or without digital rectal examination. Controversially the U.S. Preventive Services Task Force (USPSTF) is about to recommend against even opportunistic prostate-specific antigen (PSA)-based screening for prostate cancer for asymptomatic men concluding the harm to benefit ratio is unfavourable regardless of age, race, or family history[1].
- In July 2011 the NZ House of Representatives Health Committee released its report into an "Inquiry into early detection and treatment of prostate cancer"[2]. The key recommendation is that asymptomatic men be offered from age 45 years (possibly when visiting their general practitioner for a formal cardiovascular risk assessment "warrant of fitness.") consistent, clear, and accessible information on the pros and cons of prostate cancer testing. This evidence should be up-to-date and easily readable, and have reference to a website that contains more detailed material and enable informed decision on whether to undergo PSA testing and/or rectal examination. Men with a strong family history of prostate cancer should be advised of the choice of undergoing a full history, clinical examination, PSA testing, and rectal examination from the age of 40.
- The key will be the development of a useable decision aid tool for general practice to assist consumers to understand the options. Current tools need to be reworked in the light of the published trials that show that for men aged 70 years and older, screening has no mortality benefit and for men aged 50 to 69 years, the evidence suggests that the reduction in prostate cancer mortality 10 years after screening is small to none. The Ministry of Health is deciding who should develop the decision-aid, and how groups with an interest in prostate cancer might be involved in the process.
- The conclusion from the USPSTF is worth reproducing:

  "An individual man may choose to be screened because he places a higher value on the possibility of benefit, however small, than the known harms that accompany screening and treatment of screen-detected cancer, particularly the harms of overdiagnosis and overtreatment. This decision should be an informed decision, preferably made in consultation with a regular care provider and no man should be screened without his understanding and consent."

Dr Peter B Bethwaite
Pathologist

[1] See http://www.uspreventiveservicestaskforce.org/draftrec3.htm
[2] See http://www.parliament.nz/en-NZ/PB/SC/Documents/Reports/a/1/3/49DBSCH_SCR5250_1-Inquiry-into-early-detection-and-treatment-of-prostate.htm

DABIGATRAN: SOME PRACTICE POINTS AND LABORATORY ASPECTS

Dabigatran was listed on the pharmaceutical schedule on 1st July 2011, fully funded and without restriction.

It is licensed for use in New Zealand only for stroke prevention in non valvular atrial fibrillation (AF), and for prevention of thrombo-embolism (VTE) post major orthopaedic surgery.

The drug was approved for use in AF in October 2010 in the USA and Canada and in 2011 in Japan and some European countries. The recommendations for its use in AF are based on the industry sponsored Randomised Evaluation of long term Anti-coagulation Therapy (RE-LY) trial. This was a large randomised noninferiority clinical trial that compared two doses of dabigatran (100mg to 150mg) given twice daily to Warfarin treatment (INRs of 2-3) in over 18,000 patients with atrial fibrillation. The 150mg dabigatran dose was found to be superior to warfarin for the prevention of stroke or systemic embolism and the twice daily Dabigatran 100mg was found to be equivalent ("not inferior") to warfarin.

The potential advantages of dabigatran are:

- A more rapid onset of action — 36 hours
- A more rapid return to normal coagulation after discontinuation (48 hours)
- Less requirement for intensive laboratory monitoring
- A wider therapeutic window with a more predictable effect on coagulation irrespective of age, ethnicity and weight
- A fixed daily dose; although with twice daily dosing poor compliance can compromise effectiveness
- A lower interaction rate with other medicines and with food when compared to warfarin

In the RE-LY trial there was an increased risk of the intracranial haemorrhage on warfarin and gastrointestinal haemorrhage in patients on dabigatran. There were no significant differences in mortality rates from any cause between either treatment groups.

Dabigatran is predominantly renally excreted so patients must have creatinine clearance /eGFR of > 30ml/min. It should be used cautiously in patients with creatinine clearance /eGFR between 30 — 50 ml/min. Prescribers should be aware that older patients with apparently normal serum creatinine may have a lower creatinine clearance /eGFR. These facts may explain some of the bleeding cases that have been related with the recent introduction of dabigatran which have led to comments in the lay press. The reader is referred to the BPAC publication which gives an excellent discussion of dabigatran dosing in patient with renal impairment (http://www.bpac.org.nz/magazine/2011/september/dabigatran.asp)

The potential adverse effects of dabigatran include bleeding, dyspepsia and gastrointestinal haemorrhage. There are potential interactions with, verapamil, aspirin, clopidogrel, ketoconazole and NSAIDS.

LABORATORY TESTING IN PATIENTS ON DABIGATRAN

Routine coagulation monitoring is not required for patients taking dabigatran because of the rapid onset of action, a wide therapeutic window and predictable pharmacokinetics.

There is currently no test available to routinely guide dabigatran dosage — in particular, INR is not useful for monitoring dabigatran.

Laboratory testing (activated partial thromboplastic time (APTT) and thrombin time (TT)) has a limited role and can be used to test whether there is evidence of dabigatran in the patient (used to test compliance), in patients taking the drug who are bleeding to see if there is still significant anticoagulant effect from the medicine, or in managing patients in a preoperative setting.

- If neither the APTT nor TT is prolonged there is no significant residual anticoagulant activity.
- If both of the above tests are prolonged there is likely to be a significant effect from the dabigatran present in the patient.
- If the TT only is prolonged, there is some residual anticoagulant effect, but at a low level only.

BLEEDING ON DABIGATRAN

Unlike warfarin and heparin, no specific antidote is available to reverse the effects of dabigatran. Management of bleeding complications in patients taking dabigatran should be individualised; dabigatran should be stopped and the source of bleeding investigated. Unless the bleeding is mild and able to be managed within the community, patients with bleeding should be referred urgently to secondary care

Details of the management of moderate, severe or life-threatening bleeding is available from: http://www.pharmac.govt.nz/2011/06/13/Dabigatran%20bleeding%20management.pdf

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DABIGATRAN DOSING AND OPERATIVE PROCEDURES

Anticoagulation management prior to surgery for patients on warfarin has required careful consideration and the same will apply to dabigatran use. Guidelines for laboratory testing and perioperative management for patients on dabigatran have been prepared by local haematologists and surgeons and again these are found on the Pharmac web site http://www.pharmac.govt.nz/2011/06/13/Dabigatran%20testing%20and%20perioperative%20management.pdf.

The links given in the article have also been added to the Aotea Pathology Website (clinical information menu) for ease of access if desired. http://www.apath.co.nz/

PRACTICE **POINTS**

- Dabigatran is predominantly renally excreted, so patients must have creatinine clearance /eGFR >30 mL/min. It should be used cautiously in patients with creatinine clearance between 30 — 50 mL/min. Older patients with normal serum creatinine may have low creatinine clearance.
- No specific monitoring test is available for anticoagulant effect and routine monitoring is not required. INR testing has no place in management.
- Although CNS bleeding risks are lower than patients on warfarin, GI bleeding risks are increased. No reversal agent is available.
- Laboratory testing (APTT) / (TT) has a limited role and can be used in patients who are bleeding to see if there is still significant anticoagulant effect from the medicine or in managing patients in a preoperative setting.
- Unless the bleeding is mild and able to be managed within the community, patients with bleeding on dabigatran should be referred urgently to secondary care.

THE RISE AND RISE OF ANTIBIOTIC RESISTANCE: ESBLS

Bacteria are the ultimate survivors in our ecosystems and we need to "manage" how we are to co-exist with them, especially in the confrontation that results in disease.

One expression of this is in the development of bacterial resistance to therapeutic agents. If you were asked "name a multi-resistant bacterium" you would likely respond "MRSA!" This is a correct answer – but there are now better answers, and the current best answer is "ESBL"!

ESBL (Extended-Spectrum Beta-Lactamases) is not the name of a bacterium, but refers to the potent mechanism of antibiotic resistance which is becoming increasingly common amongst the Gram-negative enteric bacteria commonly referred to as "coliforms" and gives resistance to virtually ALL of the penicillins and cephalosporins but not, mercifully, to the "penem" class of antibiotics (Imipenem, meropenem and Ertapenem).

The evolution and survival of coliforms which possess these resistance mechanisms is further guaranteed by them being resistant to most other classes of antibiotics as well – aminoglycosides, quinolones, tetracyclines to name a few. For these organisms we have precious few therapeutic options.

The rise of the phenomena of ESBL-producing bacteria can be summarised as follows:

- ESBL-producing bacteria of clinical significance emerged in heavily populated countries where there was uncontrolled use of antibiotics in agriculture and the community.
- The first cases of infection in New Zealand, in the late 1990s, occurred in patients who had travelled to and had been admitted to hospitals in these countries.
- In the early 2000s, outbreaks of ESBL-producing E. coli occurred in long term care facilities, particularly in the Hawke's Bay area. The potential to spread resulted in the development of surveillance systems in many hospitals so as to provide an "early warning system".
- Two organisms with extended-spectrum Beta-lactamases predominate: *Escherichia coli* – typically found in the community outside hospitals and often seen in long-term care facilities and *Klebsiella pneumonia* more frequently found in hospitalised patients.
- In New Zealand in 2010 there were over 7000 cases of ESBL-producing coliforms isolated from patients (annualised data from ESR). There is a "North to South gradient" with far greater numbers of cases in the Auckland area (see below).
- Typically, the ESBL-producing bacteria isolated in this region are multiply-resistant and susceptible only to Imipenem and Nitrofurantoin. An increasing number are now resistant to nitrofurantoin. A very few isolates are susceptible to other antibiotics and this significantly changes how we report these organisms when we isolate them from clinical specimens.
- ESBL-producing bacteria, hitherto, were not regarded as aggressive pathogens but to be associated with colonisation of mucosal surfaces. This situation has changed recently in many countries where blood stream infections with these organisms are now commonplace.
- ESBL-producing bacteria have now replaced MRSA as the commonest multiply-resistant organism requiring the provision of isolation facilities at Wellington Hospital. ESBL-positive patients now outnumber MRSA-positive patients by a factor of 10:1.
- We should hope for new antibiotics to arrive! Until then we have some old antibiotics we might have to revive. The re-introduction of colistin and fosfomycin is a distinct possibility. Future antibiotic susceptibility testing may well incorporate these agents in the near future.

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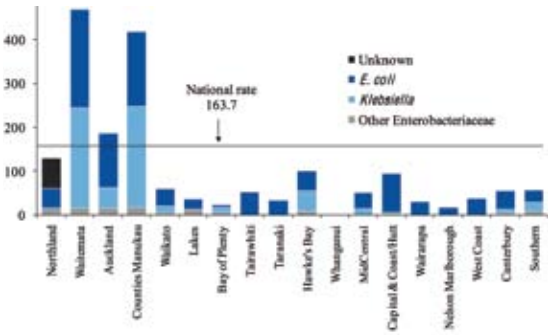
Antibiotic Susceptibility Test showing *E.coli* resistant to all but two antibiotics (Imipenem and Nitrofurantoin) based on measurement of zone sizes.

Distribution of ESBL-producing bacteria, 2010



No. of isolates per 100,000 from each DHB (from ESR surveillance report, 2011)

PRACTICE **POINTS**

Can anything be done to slow down the epidemic?

- Only prescribe antibiotics in situations where they are likely to succeed.
- Successful treatment of infections with ESBL-producing bacteria is very difficult in the community. Nitrofurantoin is the only orally-available antibiotic. Intravenous administration of a penem antibiotic is necessary to treat aggressive infections.
- Early communication is vital if you are transferring a known ESBL-positive patient to an acute hospital as isolation precautions offer the best method of preventing transmission.
- These organisms commonly transfer on hands, so compliance with hand hygiene protocols are vital.