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EDITORIAL

Dr John O'Neill MD, FRACP

CONSULTANT NEUROLOGIST

EDITOR, *PROCEEDINGS*

The 28th Issue of *Proceedings* leads with an excellent article by Professor David Ma, haematologist. David highlights the unjustifiably high cost of certain new pharmaceutical agents, especially with respect to cancer treatment. David critically analyses the usual arguments for justification of the spiralling costs of new pharmaceutical agents. He points out that some of these new drugs provide only minimal benefit to patients who, along with their families, can be clutching for straws to survive end state malignant disease. David emphasises that doctors, ultimately the primary gate keepers of the economics of health, must be able to critically analyse the cost/benefit of these newly marketed drugs in order to make sure that patients are not given false hopes and that costs are reasonably limited so that our health care system remains economically sustainable.

The issue of cost/benefit analysis becomes apparent in the following article by Associate Professor Mark Danta, gastroenterologist. Mark provides a scholarly discourse on Hepatitis C. He particularly highlights new but very expensive anti-viral therapies. Despite their short term high cost, these drugs appear to have a great benefit with the realistic potential to completely eradicate Hepatitis C as a disease in our community.

The 2016 Sandra David Oration was given by the highly popular journalist, Geraldine Doogue. In my edited version of her oration, I hope I have adequately represented her thought on the hopes and dreams for an ideal Australia for our children and grandchildren.

Breast cancer is the most commonly diagnosed cancer in women. Unfortunately the incidence has risen steadily over the past three decades. Surgery remains the mainstay of breast cancer treatment. Drs Warren Hargreaves and Elias Moisisidis have

written an excellent article on breast reconstruction after breast cancer surgery. They particularly highlight the possibility of "direct to implant breast reconstruction" wherein reconstruction is performed at the same time as the mastectomy for cancer.

Professor Bernard Haylen provides an update on disorders of pelvic floor dysfunction and the surgical management of pelvic organ prolapse.

In order to enhance education across various specialties, the Medical Imaging Department of St Vincent's Private Hospital now electronically circulates a "case of the month" which aims to correlate a clinical presentation and the diagnostic imaging, some cases being quite unusual. As Editor of *Proceedings*, I have decided to have a recurring article from radiology highlighting some of these interesting monthly case presentations. In this Issue, Doctors Sebastian Fung and some of his radiological colleagues have presented three cases of interest across three different speciality groups.

Dr Kalanie and Associate Professor Michael Neil, orthopaedic surgeons, have provided an update on the current use of hip arthroscopy in orthopaedic practice with special reference to the entity of femoroacetabular impingement.

Finally, Associate Professor Janet Rimmer, respiratory physician, explains in detail a new but relatively simple test (the measurement of the fraction of exhaled nitrous oxide) in the respiratory diagnostic armamentarium. She points out that this simple bedside test now significantly influences the day to day treatment protocols for asthmatic patients.

The St Vincent's Clinic Foundation has this year provided \$828,000 in research grants, awards and scholarships. The recipients of these grants and their topics of research are shown on the inside back cover. Thanks are again due to Mr Ted Harris, President of the Board of Trustees of the Foundation, and the members of the Scientific Committee.

Finally may I thank Mr Chris Thomas, publicist and the support of Ms Michelle Wilson, CEO of the Clinic.



INTRODUCTION

In Australia, the cost to the Pharmaceutical Benefit Scheme (PBS) of cancer drugs rose from \$65 million in 1999-2000 to \$466 million in 2011-2012, an average increase of 19 per cent per annum. In USA, 12 of the 13 new cancer drugs approved by the US Food and Drug Administration (FDA) in 2012 were priced above \$100,000 per annum. The launch price of cancer drugs in the USA has increased by 10 per cent per annum over almost 20 years and the price of an average cancer drug has increased by 10-fold over 10 to 15 years, from \$5,000-\$10,000 before year 2000 to over \$100,000 in 2013. It is important that we as providers of healthcare services are aware of cost-effectiveness of new drugs for our society to ensure health care remains sustainable. In this article, we focus on the high pricing of new anti-cancer drugs by pharmaceutical companies and provide approaches to resolve this important issue.

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The Spiralling Cost of New Cancer Drugs: What can we do?



Professor David DF Ma

IS CURRENT PRICING OF NEW CANCER DRUGS JUSTIFIED?

A number of arguments have been put forward to support the high pricing of new cancer drugs. However, evidence disputing these claims are presented below:

1. Rising costs of drug development

The Tufts centre for the study of drug development announced in November 2014 that it cost USD\$2.6 billion to develop a new drug, up from the centre estimate of \$802 million in 2003. The detailed analysis of their claims was not transparent. A key assumption that more than 80 per cent of new compounds are abandoned at some point during their development, is factored-in to the cost estimate, thus pushing up the cost of the development of a drug by including costs of other failed drugs. Importantly, the Tufts estimate had not taken into account that the research and development cost had largely been borne by the public. One study has shown that publicly funded research from non-profit, university-affiliated centres have contributed to the development of more than 84 per cent of all basic research for

discovering new drugs. Thus, in many cases, the public and not drug companies bear the bulk of the risks. Pharmaceutical companies remain among the most profitable companies in the USA, which further argues against the need for high pricing of new cancer drugs to recover the development cost.

2. The market force will lead to lowering of drug prices

A phenomena noted in recent years, is that older drug prices appear to increase rather than decrease every year. For example, imatinib was priced at \$30,000 per year in the USA when released in 2001, and was increased to \$92,000 per year in 2012, despite: all research costs being accounted for in the original price; new indications being developed and approved by the FDA; and the population of patients taking imatinib had increased. Similar trends were observed in Australia. As an example, thalidomide, an old drug, had a price increase of nearly five times increased from \$5-\$6 per pill in 1990s to \$28.50 per pill in early 2000 when it was used to treat myeloma. Moreover, pricing of cancer drugs is inconsistent among countries. The price of imatinib in South Korea, for example, costs only 20-30 per cent of the price in USA, due to market competition with a locally discovered and developed drug.

Clearly, free market force alone has not been effective in moderating prices of new cancer drugs.

There are a number of anti-competitive strategies that explain why free market forces *do not lead to lowering of drug price*. They are discussed below:

– In the USA, due to legislation prohibiting Medicare from negotiating drug prices, drug pricing was determined entirely by the pharmaceutical companies. Pharmaceutical companies use a so-called Market Spiral Pricing Strategy, in which the price of a certain cancer drug is priced 10-20 per cent above the price of an existing similar drug. For example, imatinib, which was priced at \$2,200 per month, or \$30,000 per year in 2001, was based on the price of interferon, which was then the standard

treatment. Pricing of subsequent tyrosine kinase inhibitors including nilotinib, dasatinib and ponatinib were then based on pricing of imatinib (118, 132 and 180 per cent price increase relative to imatinib respectively), as shown in Figure 1.

– “Game theory”: or *collective collusive behaviour*, where there is an agreement among competing drug companies to maintain high drug prices to maximise profits.

– The *patent system*: designed to protect intellectual property, is an intrinsically anti-competitive mechanism. Once a drug is patented, no biosimilar drugs can be marketed for the life of the patent, which is 20 years.

– *Reduced competitiveness of generic brands*: In the USA, there is a Medicare cap at six per cent for generic drugs, which means that even when there is shortage of supply, pharmaceutical companies that produce generic medicines cannot increase the price by greater than six per cent for any 6-month period. This in effect prevents generic prices from increasing to competitive levels for years to come. As a result, there is very little incentive to invest in the generic medication market, further reducing competitiveness.

– *Pay-for-delay*: An agreement is established between the pharmaceutical company and its generic competitor to delay the launch of the generic medication, keeping the drug prices high for a longer period of time.

– *Product hopping*: Here a pharmaceutical company discontinues an old formulation of a drug when the patent is expired or soon to be expired, in an attempt to force consumers to change to a drug’s new patented formulation. Due to its anti-competitive nature, product hopping is currently forbidden by US law if there is evidence that the strategy is coercive and used to restrict fair competition.

– *Disincentives for research for cheaper alternatives*: Because of the expense of the patented drug, clinical trials involving new cancer drugs become very expensive. Due to commercial interest, pharmaceutical companies of the patented drug will be unlikely to initiate this type of research. For a third party to perform these comparative studies, it will have to purchase both the patented drug and its cheaper alternative, in addition to incurring the fixed costs of running a trial. The incentive to do these trials is further reduced if the patent drug has a marginal benefit, such as is the case for many new cancer drugs. This is because

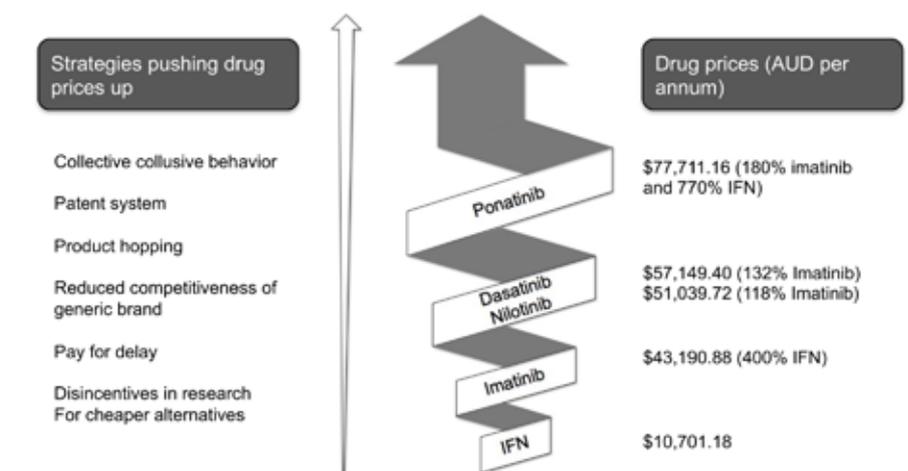


Figure 1. Example of the spiralling cost of cancer drugs, from the advent of interferon (IFN) to Tyrosine Kinase inhibitors in the treatment of Chronic Myeloid leukaemia.

the cheaper alternative has to be of equivalent efficacy to the patented drug, or at least of permissive inferiority (eg 80 per cent effective), but at the same time it is better than placebo treatment, which is hard to achieve if the benefit is only marginal.

3. Cancer drugs are potentially life-saving.

While some cancer drugs, such as imatinib, are life-saving for patients with chronic myeloid leukaemia, many others do not fall into this category. Cetuximab, an anti-EGFR monoclonal antibody, costs \$80,000 per patient with advanced non-small cell lung cancer to increase the overall survival by 1.2 months; and bevacizumab costs \$90,000 per patient with metastatic breast cancer to increase survival by 1.5 months. In fact, only one of the 12 new anticancer drugs approved in 2012 in the USA provides survival gains of greater than two months. It is hard to justify paying excessively high prices for such a relatively small survival gain, as the health resource is finite and the same resource is also needed to fund other competing treatments where the cost-effectiveness ratio is more favourable.

HIGH PRICING OF CANCER DRUGS, DOES IT MATTER TO PATIENTS?

Effects of overpricing of cancer drugs in patients based on published evidence include:

1. inability for patients to pay bills, resulting in loss of basic needs such as food;
2. the financial burden of expensive drugs may undermine patients’

adherence to the medications vital for their health;

3. patients are not able to access effective new cancer medications due to high costs unless it is under PBS subsidy;
4. financial distress often leads to emotional distress and overall distress in cancer patients; and
5. cancer patients who have severe financial distress have increased mortality.

In a study in North Carolina, 42 per cent of 254 cancer participants reported a significant or catastrophic subjective financial burden, 46 per cent reduced spending on food and clothing, and up to 24 per cent of patients have been non-compliant with their medications. Furthermore, Ramsay et al from the Fred Hutchison Cancer Research Center showed an increased mortality in cancer patients who suffered from severe financial stress requiring bankruptcy protection.

WHAT CAN WE DO TO ADDRESS FINANCIAL TOXICITY OF NEW CANCER DRUGS (TABLE 1)?

It is important that we as a country find ways of reducing drug prices so patient care is improved while at the same time ensuring those pharmaceutical companies which develop an effective drug will still be viable and profitable. The experts in chronic myeloid leukaemia believe that this is doable. They argue that lowering prices will increase patient compliance and adherence to treatment, so these patients will live longer and continue to stay on therapy, thereby increasing revenues to pharmaceutical companies by increasing sales.

We as health professionals have a duty of care to our patients to make our medical system sustainable. Oncologists at Memorial Sloan Kettering Cancer Center, for example, stopped prescribing a drug for the treatment of colorectal cancer at more than \$11,000 a month, which had shown no survival advantage over an existing drug. As a result of this public stance, the manufacturer agreed to reduce the price by half. Moreover, health professionals should be educated in critically assessing the current clinical evidences, with the inclusion of cost-effectiveness in our assessment of treatment value.

Professional bodies, such as the Australian Medical Association (AMA), have an important role to play and this includes resisting influences from big pharmaceutical companies and sponsorship. Where sponsorships for meetings are required, support from local institutions should be sought first. Professional bodies also need to resist endorsing drugs which have marginal benefits, including the presentations related to these drugs in plenary sessions at the annual congress meetings. The Royal Australian College of Physicians, for example, has recently published guidelines relating to ethical relationships between physicians and industries. Moreover, it is important to include sessions where cost effectiveness and value of a treatment is discussed and to educate the public about the ongoing over-pricing of drugs. The American Society of Clinical Oncology (ASCO), for example, has recently announced that it will develop scorecards of different cancer treatments, ranking them by their benefits, adverse effects and costs. This will better inform oncologists as to the value of their treatments, aiding decision making for patient management.

The Pharmaceutical Benefits Advisory Committee (PBAC) has the un-enviable task to assess cost effectiveness of a new cancer drug for approval to be subsidised by the Australian Government, which ultimately comes out of tax-payers' pockets. There are a number of potential strategies that can be adopted to improve the efficacy of the PBAC process, as discussed below.

Firstly, we need to reconsider if progression free survival (PFS) is a valid endpoint for approval, particularly if overall survival is not improved, or the improvement of PFS is not associated with an improved quality of life. Also,

Table 1. Suggested strategies to address the spiralling cost of new cancer drugs

Medical professionals need to:

- justify the use of cancer drugs with marginal survival advantage;
- be educated about cost effectiveness and value of new cancer treatments; and
- promote public awareness of this healthcare issue.

Professional bodies need to:

- seek sponsorship from local institutions before considering support from pharmaceutical companies;
- resist publicly endorsing drugs with marginal benefits, such as presentations in plenary meetings;
- develop guidelines on value of therapies with cost-effective analysis;
- educate the public on awareness of overpricing of new drugs; and
- support oncologists / haematologists who do not wish to treat patients with drugs that have marginal benefits.

Regulatory bodies (PBAC) need to:

- use clinical meaningful endpoints to assess cost-effective benefits;
- fund research on cost-effectiveness of new drugs;
- consider indication-based pricing of cancer drugs; and
- increase transparency in drug pricing and assessments.

marginal benefits, such as a survival advantage of 1-2 months, need to be re-evaluated as to whether they are good enough reasons to warrant approval for subsidy, even if the survival difference is statistically significant. It is important to realise that statistical significance is not a good surrogate marker for efficacy, as a large patient sample size in a study could provide statistical significance even for small difference in survival. A larger difference in a smaller study should alternately be advocated, in order to justify the value of treatment.

Cost effectiveness of a given medication can also be improved by identifying a subgroup of patients where efficacy is better, using a molecular diagnostic biomarker. For example, a biomarker that will identify the patients with colorectal cancer that will respond to cetuximab may improve the current response rate of 10-15 per cent, and the PBAC can refine PBS subsidy to this particular subgroup. The recent ASCO recommendation of not using cetuximab in colorectal carcinoma if a KRAS mutation in codon 12 or 13 is detected is a good start of fine-tuning the indication of cancer drugs based on a molecular biomarker. It will be cost-saving for the Australian community in the long run to invest in clinical trials.

Another way to reduce overall cost includes the modification of the pricing strategies of drugs. Currently, the cost of a drug is the same for all clinical indications for the particular drug, although the efficacy of the drug is different for different indications. An

alternative strategy is indication-based pricing. In this way, a drug is priced according to its efficacy in different indications, so a drug may cost more when it is more efficacious and less when it is less efficacious.

Last but not least, it would be helpful to have greater transparency surrounding the assessment of the value of a new drug, as well as price negotiations between government bodies and pharmaceutical companies. Currently, these assessments and negotiations occur behind closed doors, largely because of the perceived need for commercial confidentiality. The transparency on the assessment and negotiations will better inform clinicians how decision of access is made, as well as the information about the value of a particular therapy. Clinicians in turn will be better equipped in providing the most appropriate treatment to patients, making the health system more sustainable.

CONCLUSION

New cancer drugs are over-priced, and often for unjustifiable reasons. Moreover, financial toxicity will adversely impact patient outcomes and the healthcare system will become unsustainable. It is important that we as clinicians are informed about the current situation and start questioning why pharmaceutical companies have set unreasonably high prices for new cancer drugs. Quality of care in oncology has long been focused on our ability to manage or cure cancer. Its time we also consider the financial toxicity of new drugs to both patients and society.

Associate Professor Mark Danta

SUMMARY:

- Australia has 230,000 chronically HCV infected individuals.
- HCV does not integrate into human genome which means that treatment eradicates the infection.
- No successful vaccine exists.
- Over 30 years approximately 25 per cent will develop cirrhosis with the associated risk of hepatocellular failure and hepatocellular carcinoma.
- Assessment of HCV is based on HCV genotype, viral load and degree of liver fibrosis.
- The new direct acting antiviral (DAA) therapies have eradication rates of 90-95 per cent with finite (8-24 week) courses of therapy, depending on genotype and degree of liver disease.
- While the DAA therapies are very expensive, the PBS has funded treatment for any individual with HCV.

INTRODUCTION

Describing his revolutionary times, Lenin declared: "There are decades where nothing happens; and there are weeks where decades happen." From the perspective of HCV we are living in revolutionary times. HCV is a major global health issue but since HCV was identified we have now developed treatments so effective that eradication through treatment is being considered.¹ This review will outline the issues of HCV infection and detail the newly available therapies that offer so much promise to those infected with the virus.

A/Prof Mark Danta; MD, MPH, DTM&H, FRACP; St Vincent's Clinical School, University of New South Wales; Faculty of Medicine UNSW, St Vincent's Clinical School

The Hepatitis C Virus (HCV) Revolution – The Direct Acting Antiviral (DAA) era



Associate Professor Mark Danta

VIROLOGY:

Hepatitis C is a positive-sense Flavivirus of 9600 base pairs. It does not have a proof reading polymerase and, consequently, mutates at an exceedingly high rate, estimated at 107 virions/day.² The consequences of the extremely high mutation rate are three-fold. First, it explains the sequence variation between HCV separated by geographies. HCV that has been separated geographically through time with a genetic divergence of >30 per cent are classified as different genotypes. There are six major genotypes (1-6), with the two most common in Australia being genotypes 1 and 3. These have different implications for treatment response, outlined below. Second, there is variability within the infected host that results in different strains of HCV, termed quasispecies, and this allows the virus to evade the immune response, explaining the level of chronic infection following exposure to the virus. Third, HCV variability explains the development of drug resistance, which will be outlined below (see Resistance) and has implications for vaccine development which, to date, has been unsuccessful. An important concept

to understand is that unlike hepatitis B and HIV infection, HCV does not integrate into the human genome. This means that it can be eradicated and cured, as opposed to requiring long-term suppressive therapy.

EPIDEMIOLOGY:

Hepatitis C is a chronic blood borne viral infection. With over 150 million individuals infected world-wide, it accounts for approximately 1 million deaths each year.³ In Australia, there are 230,000 individuals currently HCV infected.⁴ HCV transmission usually requires blood-to-blood parenteral exposure. The risk factors include: blood product exposure, intravenous drug use and other factors such as iatrogenic and tattoos. In Australia this usually means intravenous drug use (IDU), which is responsible for over 80 per cent of transmission. The Australian incidence at its peak was 16,000 new cases per year but with the introduction of needle syringe exchange and a reduction in IDU, the HCV incidence rate has fallen to about 8-9,000/year.⁴ Specific risk groups also account for different transmission routes. These include immigrants. For example, Egypt suffered such a catastrophic rate of infection following the schistosomiasis prevention programs in the 1960s that resulted in a 14 per cent prevalence rate.⁵ HIV infected men who have sex with men (MSM) are also a specific group who are at risk of percutaneous transmission due to high-risk sexual exposure.⁶ Interestingly, the rate of HCV transmission in heterosexual couples is negligible and currently barrier contraception is not recommended.⁷

Until recently there has been little overall impact of treatment related to: poor access to treatment, and the poor uptake of treatment due to high rates of side effects and relatively low efficacy. Interestingly, Australia has one of the world's highest proportion of diagnosed HCV cases, with approximately 80 per cent of infections diagnosed.⁸ In Australia, it is estimated that there are

approximately 20,000 individuals with HCV-related cirrhosis.⁴ This is the at-risk population for hepatocellular failure and hepatocellular carcinoma.

NATURAL HISTORY:

Following acute infection with HCV, 75 per cent of individuals will become chronically infected.⁹ This is a result of a failure of both the innate and adaptive immune systems to clear the infection. We know from extensive immunological studies that to clear the infection a combined broad and vigorous humoral and cell-mediated immune response is required, particularly to the nonstructural proteins of the HCV virion.¹⁰ Interestingly, polymorphisms in the region of IFNL3 (also known as IL28) interferon signaling gene strongly influences spontaneous clearance.¹¹ In part, the failure to clear HCV relates to the high mutation rate of the virus and also to specific immunological effects of HCV proteins. Significantly, only a small proportion of individuals are acutely symptomatic, as a result of the poor immune response, which has contributed to the ongoing transmission and prevalence of HCV.

Viral, host and environmental factors combine to determine the natural course of HCV. It has been estimated that over 30 years the rate of cirrhosis development is 25 per cent. The risk is increased in older age, obesity, males, immunosuppressed HIV infected individuals and post-liver transplant HCV recurrence.^{12, 13} The complications of HCV usually occur in the context of cirrhosis. The rate of developing decompensated liver disease, including ascites, encephalopathy, coagulopathy, variceal haemorrhage is estimated at 3-5 per cent/year in cirrhosis. The rate of HCC development in cirrhosis is 2-4 per cent/year. Once these complications develop the prognosis is poor with a mortality of decompensated liver disease in the region of 50 per cent at two years. It is clear that prevention of cirrhosis will have significant and long-lasting clinical impacts. Interestingly, HCV is also associated with a number of extrahepatic manifestations which need to be evaluated. These include: cryoglobulinaemia with skin and renal manifestations, porphyria cutanea tarda and splenic lymphoma.

CLINICAL ASSESSMENT OF HCV:

The assessment of HCV involves the characterization of the virus and the determination of the degree of liver disease as this determines the type and length of treatment.

Serology with the anti-HCV antibody will identify individuals who have been exposed to HCV. It does not determine whether the person is currently infected. This is defined by nucleic acid amplification to detect HCV RNA, which can be either quantitative or qualitative. HCV RNA is usually detectable in the first 2 weeks and the anti-HCV seroconverts up to six weeks after infection. If the HCV RNA is positive then a genotype and viral load needs to be done as these will determine the specific therapy and length of treatment. Chronic infection is defined arbitrarily as infection for than six months.

The stage of liver disease is defined by the degree of liver fibrosis, which used to be based on liver histology. With progress in non-invasive technologies liver biopsies are now rarely needed to stage HCV-related liver injury. Non-invasive technologies include: imaging with liver elastography and serum-based investigations. Fibroscan is the most widely used of these technologies in Australia and uses elastography to determine liver stiffness.¹⁴ It has an excellent correlation with cirrhosis, which is the most important determinant of prognosis and treatment length.^{15, 16} Newer ultrasounds can perform shear-wave elastography and acoustic radiation force impulse (ARFI), which is a similar method to determine degree of fibrosis, in particular cirrhosis. Internationally, there are a myriad of blood test algorithms that are a combination of serum factors that correlate with liver fibrosis. The serum-based tests available in Australia are: APRI, Hepascore, FibroGENE and ELF test. However, in Australia imaging techniques are the most accessible methods.

Finally, an assessment of co-factors that can influence disease progression and treatment response are important to evaluate and include: alcohol consumption, weight, co-infection with HBV or HIV, medication and comorbidities.

TREATMENT:

Until 2016 the treatment of HCV was interferon-based. This non-specific immunomodulator had an overall efficacy of 55 per cent when combined with ribavirin but was associated with significant and often debilitating side effects. For the majority of HCV patients we have now entered the interferon-free age with the new all oral regimens. These regimens have eradication rates of 90-95 per cent with 8-24 week courses of therapy. This has been outlined in a recent Australian consensus statement.¹⁷

Australia lagged behind the rest of the developed world in our access to these new classes of medications. However, the new therapies were approved and listed on the PBS from March 1st 2016. The government has committed \$1 billion AUD over the next five years to treat patients with HCV. Unlike many other regions of the world, all individuals infected with HCV can access HCV therapy, irrespective of liver fibrosis stage. With some foresight, the PBS has approved not only specialists but also general practitioners to prescribe these new therapies on the S85 Schedule, thereby significantly expanding access to therapy. In some ways, the delay in approval has resulted in Australia becoming a model for delivering these exceptional therapies to the population.

The new direct acting antiviral therapies (DAAs) have specific actions on the HCV viral proteins, as outlined in Figure 1.¹⁸ While many agents have been investigated these novel therapies act on three HCV proteins: The NS3/4a protease, the NS5b polymerase and the NS5a co-factor. By disrupting the function of these proteins, viral replication is inhibited and the virus can eventually be cleared. Similar to HIV infection, combinations of at least two of these agents must be used to achieve eradication.

NS3/NS4a: These nonstructural proteins combine function to act as a serine protease which cleaves the HCV polyprotein at four sites.¹⁹ The protease inhibitors (PIs) act on these proteins. The first generation protease inhibitors were Telaprevir and Boceprevir, which have now become redundant with the newer generation PIs. The new PIs include: Grazoprevir, Parataprevir and Simeprevir with improved efficacy

and broader genotype effect, better pharmacokinetics allowing once daily dosing and less side-effects. Resistance is an issue.

NS5a acts a co-factor for the NS5b polymerase.²⁰ It has no known direct enzymatic function. However, inhibition of NS5a is a potent inhibitor of HCV replication. While they are often pangenotypic, meaning that they act across different HCV genotypes, they often have a low genetic barrier predisposing to the development of resistance. The NS5a inhibitors are: Daclatasvir, Ombitasvir and Ledipasvir. The two newer agents, Velpatasvir and Elbasvir have a higher genetic barrier to resistance.

NS5b is the HCV RNA-dependent RNA polymerase that is essential for the amplification of the HCV genome.¹⁹ Similar to HIV, this can be inhibited by nucleotide inhibitor (NI: Sofosbuvir) or non-nucleotide inhibitors (NNI: Ombitasvir). The NIs are chain terminators and are highly effective with high barrier to resistance and broad effect across all genotypes. In contrast, the NNIs act by binding to the polymerase leading to conformational change that inhibits function of the enzyme. The NNIs are weaker inhibitors with lower efficacy and potential for resistance, although this is rare.

The treatment endpoints are eradication of HCV, which is termed sustained virological response (SVR). This is defined as negative HCV RNA PCR 12 weeks after completion of HCV treatment. It used to be assessed at 24 weeks but this has almost a perfect correlation with the week 12 results, which is now used. Often patients are monitored for the on treatment response at week 4 to determine that the treatment is suppressing HCV. This is usually defined as an HCV load <1000 IU/ml. Using the current DDAs, almost all treated patients are negative on treatment with a small proportion relapsing following cessation of therapy. This usually occurs within four weeks of stopping.

TREATMENT COMBINATIONS:

As outlined in the recent Australian HCV consensus statement the combination therapies and length of treatment are determined by the genotype of HCV, presence of cirrhosis and previous treatment exposure.¹⁷

Figure 1: Site of DAA therapy in HCV lifecycle (Adapted from Dore and Feld CID 2015)(18)

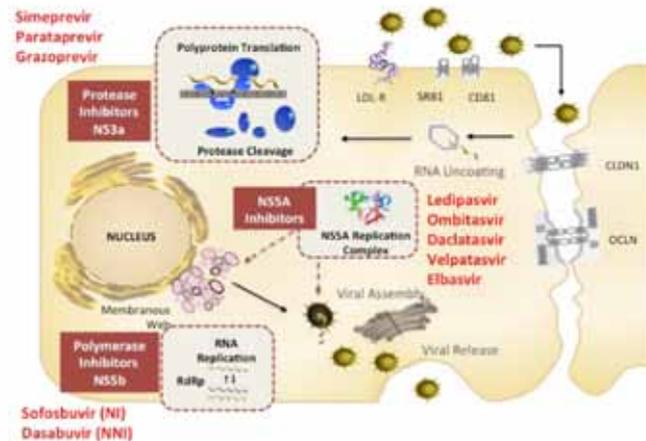
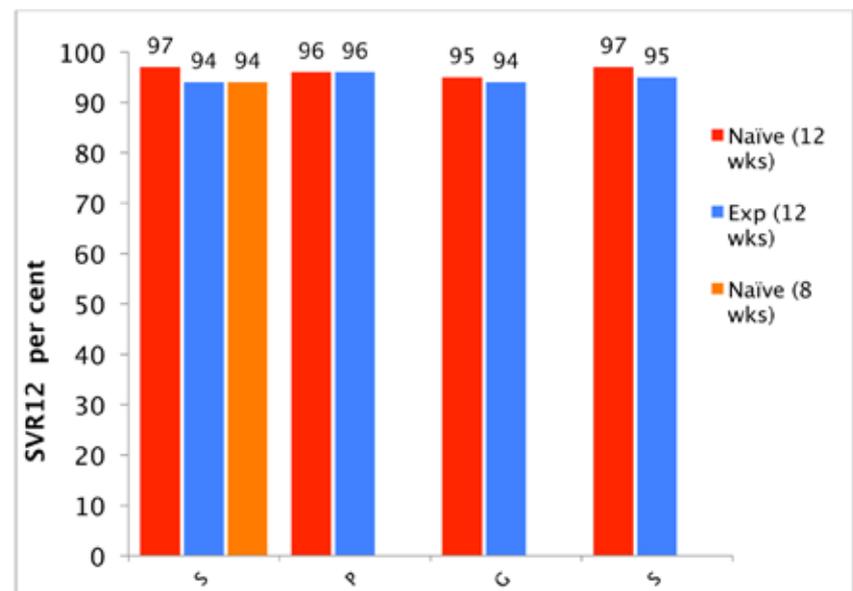


Figure 2: Summary DAA therapy for genotype 1 HCV.(21, 23, 24, 27, 34)

Zeuzum, NEJM 2014; Afdhal, NEJM 2014; Kowdley, NEJM 2014; Feld, NEJM 2014; Zeuzum, ILC 2015; Kwo, ILC 2015



Genotype 1 (Table 1 and Figure 2):

Genotype 1 is the most prevalent HCV in Australia with a prevalence of 55 per cent. There are three current regimens for G1 HCV, including: Sofosbuvir/Ledipasvir (Harvoni), Parataprevir/Ritonavir/Dasaburvir/Ombitasvir +/- Ribavirin (Viekira Pak) and Sofosbuvir with Daclatasvir. Interferon can be used if required. In the next year it is likely that two new combinations will be added including Sofosbuvir with Velpatasvir, and Grazoprevir with Elbasvir (Zepatier). All have similar SVRs but different pill burden, side effects and drug interactions. The overall SVR with these different regimens is 95 per cent based on the large registration studies, outlined below.

Sofosbuvir and ledipasvir is co-formulated into one tablet called Harvoni. The overall SVR is 95 per cent in the large registration studies.^{21,22} In patients with low viral load and no significant liver fibrosis (<F3) 8 weeks of therapy can be used. In cirrhosis (F4) the outcomes are similar to those without cirrhosis, unless the patient has failed previous therapy, including interferon and first generation protease inhibitors Telaprevir and Boceprevir. In this case, there is an advantage to increasing treatment length to 24 weeks.

Viekira Pak is the combination of parataprevir/ritonavir/dasaburvir/ombitasvir +/- ribavirin with the medication taken twice daily. The parataprevir is ritonavir boosted and

this can cause problems with CYP450 pathway interactions. In addition, G1a subtype HCV requires ribavirin which carries with it a number of side effects, including anaemia, rash and insomnia. The outcomes are similar to the Harvoni course with 95 per cent overall SVR.^{23,24} In the context of cirrhosis, longer treatment is required for treatment experienced patients, and 24 weeks is recommended. Ribavirin, the older more toxic HCV therapy, must be used in G1a infection but can be avoided in G1b. There is now a contra-indication to using Veikira Pak in decompensated cirrhosis (Child Pugh B and C). Newer combinations are looking even more exciting and the combination of sofosbuvir and velpatasvir has SVRs >95 per cent across all genotypes.²⁵

Genotype 2 (Table 2)

Genotype 2 accounts for 5 per cent of the HCV in Australia. It is the most sensitive HCV genotype to the new DAA treatments. While the more expensive options for HCV G2 are excellent, the PBS has approved sofosbuvir and ribavirin for 12 weeks for G2 HCV, irrespective of degree of liver fibrosis, with a SVR of 90 per cent.^{26, 27}

Genotype 3 (Table 2)

Genotype 3 is the second most common HCV genotype in Australia, with a prevalence of approximately 30 per cent. Interestingly, while it was the most responsive genotype to interferon therapy, it is now the most resistant to the new therapies with overall response rates to the DDAs of 90 per cent.^{26,27} The current available combinations are: sofosbuvir and daclatasvir, or sofosbuvir with the addition of interferon and ribavirin.

Genotype 4,5 and 6 (Table 3)

While there is good data to support the use of the DAA regimens for genotypes 4,5 and 6 HCV, these are currently not supported on the PBS. As a result, the current recommended treatment is sofosbuvir with pegylated interferon and ribavirin for 12 weeks. The outcomes are >90 per cent eradication rate with this combination. In the future, the all-oral combinations will likely be funded, especially with the new pangenotypic combinations.

Table 1: Treatment of HCV genotype 1 (modified from Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016).(17)

Regimen		Geno		Treatment duration				Efficacy SVR
				No Cirrhosis		Cirrhosis		
				Naïve	Experienced	Naïve	Experienced	
Sofosbuvir 400mg + Ledipasvir 90mg		1a/b	8 or 12 weeks	12 weeks	12 weeks	24 weeks	>95 per cent	
Sofosbuvir 400mg + Daclatasvir 60mg +/- Ribavirin 1000/1200mg		1a/b	12 weeks	12 or 24 weeks	12 weeks+ Ribavirin or 24 weeks (no ribavirin)	12 weeks+ Ribavirin or 24 weeks (no ribavirin)	>95 per cent	
Paritaprevir-ritonavir 150mg/100mg n OD + Ombitasvir 25mg OD + Dasabuvir 250mg BD +/- Ribavirin 1000/1200mg		1a 1b	12 weeks+ribavirin	12 weeks+ribavirin	12 weeks+ribavirin	12 or 24 weeks+ribavirin	>95 per cent	

Table 2: Treatment of HCV genotype 2 and 3 (modified from Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016).(17)

Regimen		Geno		Treatment duration				Efficacy SVR
				No Cirrhosis		Cirrhosis		
				Naïve	Experienced	Naïve	Experienced	
Sofosbuvir 400mg + Ribavirin 1000/1200mg OD		2	12 weeks	12 weeks	12 weeks	24 weeks	>90 per cent	
Sofosbuvir 400mg + Daclatasvir 60mg		3	12 weeks	12 or 24 weeks	24 weeks	24 weeks	>85 per cent	
Sofosbuvir 400mg + Ribavirin 1000/1200mg		3	24 weeks	24 weeks	24 weeks	24 weeks	59-95 per cent	
Sofosbuvir 400mg + PegIFN weekly + Ribavirin 1000/1200mg		3	12 weeks	12 weeks	12 weeks	12 weeks	>85 per cent	

SPECIAL GROUPS:

HIV: While the impact of HIV on HCV has been shown to be detrimental with accelerated rates of liver fibrosis and reduced rates of HCV clearance with interferon-based therapy, the new DAAs have been shown to be equally effective in HCV mono-infection and HCV/HIV co-infection. In the recent C-Edge study using Grazoprevir with Elbasvir (Zepatier) for HCV with and without HIV, the outcomes were the same.²⁸

Renal failure: End stage renal failure is a group where the treatment needs to be tailored to the individuals. Unfortunately, sofosbuvir is renally excreted and is contraindicated when the GFR is <30 ml/min. Currently, the only regimen is Viekira Pak with outcomes similar to normal renal function. Based on the C-Surfer study new regimens such as Zepatier will be effective and safe.²⁹

DRUG-DRUG INTERACTIONS:

Every patient starting on these new DAA combinations should have interactions checked to avoid complications. Important drugs to consider include: proton pump inhibitors, statins, St John's wort, antimicrobials, anti-epileptic agents, amiodarone, immunosuppressive agents and antiretroviral agents. This is especially an issue with the ritonavir-boosted regimen Viekira Pak. There is an excellent resource for determining any interaction with these new medication which has been developed by the Liverpool University, UK. It is available online at: <http://www.hep-druginteractions.org/>

RESISTANCE:

The HCV polymerase is non-proofreading which means that it is error prone with development of multiple genetic mutations.³⁰ As a result, each individual patient has a number of circulating quasispecies, or variants of HCV. These variants have different levels of 'fitness', which describes the virion's ability to replicate. It has been shown that variants that are resistant to the new DDA therapies actually exist before exposure to the DAAs. When these individuals are treated the sensitive virus is suppressed and the resistant virus flourishes. This is termed virological failure and is a reason for treatment failure. Given the extremely high level

Table 3: Treatment of HCV genotype 4,5 and 6 (modified from Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016).⁽¹⁷⁾

		Treatment duration				Efficacy SVR
		No Cirrhosis		Cirrhosis		
Regimen	Geno	Naïve	Experienced	Naïve	Experienced	
Sofosbuvir 400mg + PEG Interferon alpha weekly + Ribavirin 1000/1200mg weight-based	4,5,6	12 weeks	12 weeks	12 weeks	12 weeks	>90 per cent

of success with treatment it does not make sense to look at the variants before starting treatment as they are likely only significant in a small proportion of individuals. The sites where the resistance usually occurs is the NS3a protease and NS5a polymerase co-factor site. Often resistance can be overcome with longer therapy and different classes of DAA.

FUTURE:

The future for HCV is very promising. The foresight of the Australian government in funding these new therapies for all on the PBS has made Australia a leader in the developed world as far as access to treatment. Access is critical. Even with treatments that are 100 per cent effective, there would be no impact on the burden of disease unless a significant proportion of the disease population is treated. In the initial four months of the DAA program (March to June 2016), an estimated 22,470 patients initiated therapy, with possibly 40,000 to be treated in 2016 representing 17 per cent of the total chronic HCV infection population in Australia.³¹ This exceeds the annual number needed to treat to have an impact on the liver disease and mortality burden.³² Consequently, there is now talk of HCV eradication in Australia.

There are now a number of projects that are exploring the concept of "treatment as eradication", which has derives from the HIV research community's "treatment as prevention".

Given that HCV is eradicated with a finite course of treatment in 95 per cent of individuals it is clear that this is possible if focused in high-prevalence groups. The current projects include treating the IDU populations, prison populations and the HIV co-infected to reduce the reservoir of HCV infection. In time this would reduce transmission and may eventually lead to eradication of HCV. Modeling of IDU populations has explored the rates of treatment needed based on prevalence of infection to achieve a 90 per cent reduction in disease burden.³³ These treatment rates are now clearly achievable.

Finally, new combination medication will become available that will be shorter course, more effective and pangenotypic meaning that there may be a one-size-fits-all treatment such as Sofosbuvir and Velpatasvir. Eventually, it may be that a patient is diagnosed with HCV and then treated without any of the current assessments.

We live in revolutionary times and Australia is placed to consolidate these changes so that HCV will become the TB, if not the small pox, of the 21st Century.

Australian HCV consensus statement: <https://www.asid.net.au/documents/item/1208>

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The Sandra David Oration

Hopes and Dreams for an ideal Australia

What is an ideal Australia that I'd like to see my children and grandchildren flourish in?

I realised how little I thought about this, how little I considered the medium to long term, the very thing people like me in the media report on. The truth is, and it's probably true for you, very busy people, *living a good life* means attempting to live a reasonably broad existence: that is, meeting current deadlines, keeping up with friends, keeping up with one's profession (in my case what I'd call the developing story of the 21st century world), keeping vaguely fit, doing some meditation and contemplation for one's serenity, and if really working down the base of a good pyramid, having some sort of hobby, doing some sort of voluntary work.

But thinking seriously about a future Australia, rather than merely reacting? Well, that is often *unploughed ground*.

The more I read about Sandra David and her family, and grasped the nature of their patient, diligent commitment to this institution and all it represented, the more I thought that in order to honour them, this Oration should prompt me to think a bit deeper.

Many of us like to say that we're driven by the needs of those to come, those we love; but certainly in my industry, there's a lot of ego. Yes, there's a lot of commitment too and of course it is such fun, which hopefully spreads some of the best about the community to each other. I certainly try to operate on the basis of "do no harm".

But what about *imagining* how things might be better than just doing no harm; how might we thrive?

I'm not inclined to think Utopian thoughts because I'm too pragmatic. And I'm not one to seek how to "smash the system" because I think terrible vacuums are created in those circumstances, very bad for the most vulnerable.

So what does a relatively orthodox woman, originally from WA, now dream of?

Well first and foremost, of course, I desperately hope our children and



Geraldine Doogue, Broadcaster

(Taken from the actual oration by Geraldine Doogue).

grandchildren live in a time of *peace*. Mercifully my generation inherited the yield of our parents' lives, imbued as they were by the Depression and World War II and frankly the older I am, the more I experience a sense of unbelievable relief that I was born in the 1950s and not the late 30s.

So while I may look back on immense social change and turmoil, I personally feel I've escaped pretty scot-free by comparison with my immediate forebears. And I would love my grandchildren to have a reasonable expectation that they could too.

My role, as an elder, is to keep constant vigilance about any subtle drift to war, or a growing appetite for the glamour of war. I'm not a pacifist, by the way. And I don't believe it will forever go away. Lest you do, I invite you to cast your mind back to the "100 years of peace" after the end of Napoleonic Wars (100 years of essential peace; don't tell the Chinese that, given the Opium Wars etc which are still framing our world I might add!!) but arguably Europe became so complacent they just let World War I drift into view, because they couldn't quite imagine war

or really the critical need to throw absolutely everything into avoiding it.

I also yearn for these children of mine to grow up in and contribute to, an Australia that thinks BIG: that keeps its eye on-the-big-map! That they live in among their elders who think it's right (not hubris) to participate in conversations that tilt at being "a great country," that wonderful message of George Megalogenis' terrific doco series last year, on ABC-TV earlier this year and based on his book.

No, I don't want us to *brag* and *preen* ourselves or to become complacent because I realise it is a very competitive world and especially during times of a technology revolution, such as we're living through. This can mean that very established groups (such as venerable institutions like St Vincent's or my ABC) can avert their gaze, because they are truly so busy and fail to see that their situation is deteriorating.

Be alert and maybe alarmed, I suppose! But don't let the alarm *paralyse* us. Because I'd really like us to revel in and explore the innards of our success, as well as our still-to-comes: to know that underneath all the "Aussie, Aussie, Aussie" bravado that frankly drives me mad, that we have created a very interesting young society here, based on an incredibly old one.

I'd like us to really believe that our *neighbourhood*, next to Asia, is a ripper of a neighbourhood; that we are in a sweet spot, living during the Asian century (real pity the Coalition junked that), if only we could see the real benefits of this, really come to know its peoples, its *modern dilemmas*; not its well-known traditional ones, comfortably antiquated village issues (with which we often feel more comfortable) but modern dilemmas.

A lot of the things we worry about, in terms of family life, the way we eat or exercise, treat elderly people, are just played out *so much more intensely* in Asia, careering along at an extraordinary rate of change that leaves people gasping. Not only do we have a chance to provide services to emerging Asia, but there's so much in it for us to understand.

I'd love much more of the coverage of Asia to be of the *shared-dilemma* kind,

The Sandra David Oration

rather than the us and them type: us, the predictable, the sophisticated; them, the exotic, the infantile; without ever dodging, I might add, the very real issues that do seem to bedevil them, like difficulties in succession planning, in handovers of power, which I've come to realise increasingly, is the genius of our tradition of democracy, developed over centuries, and not easily donned.

I'd like our children to grow up in a *fairer society*, where money does not open all doors yet where the generation of wealth, prompted from within by our brains and our institutions, is really praised; where there is genuine pride in these achievements, not merely in those who win the Dally M or Brownlow medals!

But we do need stocks of capital to accumulate to invest in some of these good ideas from within and not to rely on overseas or feel that the only real money to be made in Australia is in real estate or mining; that these kids grow up explicitly contributing to what we have come to see as a *knowledge-led joint venture*, building on our strengths, not dwelling on our deficits.

We need well-functioning capitalists and entrepreneurs who actually believe the best societies are those that mind the gaps! Capitalists and entrepreneurs who develop fine-tuned political messages along those lines so that we don't have political parties and governments who are consistently pandering to the moneyed-crowd. It isn't essentially us, I don't think, but it could become us, without a lot of vigilance. It creeps in. Capitalism was born in America where they purport to have a log-cabin-to-president mentality but where, in effect, that other truism I think holds more sway: that the business of America is business. I think it produces a very vibrant form of capitalism, yes, but also a very ruthless one, with too little checks and balances on the siren song of money.

Ours, I believe, has been much more built along the lines of honouring The Little Aussie Battler, a person who in the USA would be called The Little Loser. And what a world of difference exists there! If we sideline this as a guiding ethic, we'll lose something of our very young soul: it matters, in other words, the myth one fosters in the country and the language.

I really want a deep-seated embedding of the thought that inequality is bad, very bad, for communities: to explore the idea that wage/salary rates ought to roughly sit in an alignment between the highest and average wages, that of the average man/woman in the street.

Japan's figure sits at a figure of about 13 times difference; I think the USA has gone to about 350 times, last time I looked. I think we are at about 160 times.

The average Fortune 500 CEO in the US makes about \$12 million per annum (Washington Post article Sept 25, 2014, drawn from the Harvard Business School), \$5 million or thereabouts in Switzerland, then Germany and Spain is at \$4.1 million. The typical worker at Starbucks or Maccas takes more than 6 months to earn what each company CEO earns in an hour!

Various researchers, Thomas Piketty and earlier versions, Richard Wilkinson and Kate Pickett in "The Spirit Level: Why More Equal Societies Almost Always Do Better", have convinced me anyway that all-round, in terms of general thriving in health, education, cohesion and pleasantries, societies without huge, presumed hierarchies actually do better.

I do accept hierarchies by the way. There are hierarchies of talent and preparedness for pressure and risk. I'm not blind to this. But I believe the more we perceive ourselves to be in "rough parity", *the more we recognise each other, the better for our longer-term health and for our kids to thrive*, whatever talents they turn out to have.

And by the way, hand-in-hand with this, what I don't like is the growing dependency on government handouts. I was a bit surprised late last year (Aug/Sept) to be reading just how many Australian families now accept some form of Government support: I think it was 80% whereas 20 years ago it had been about 67%, and of course far lower earlier. I don't think that's a healthy trend, I really don't.

I really believe in good government, again unlike the underlying driver of a lot of USA attitudes, but not in ever-growing government unless we want rising taxes. Again, I'm not opposed to that per se but ideally for plugging market failure gaps and for good leadership, to prompt activity where the usual entrepreneurial activity is proving very sluggish.

I don't favour government expenditure as a presumed, ongoing safety net except in crises with the expectation that it will be a passing phase.

And need I say, I sincerely hope our children and grandchildren grow up in a political culture which while robust, observes the conventions that have governed our superb inheritance of the Westminster tradition from the British. It will be "war without blood", that great definition of the adversarial nature of a good democracy but not with an "anything goes" quality as we sometimes sadly experience.

One of my clever young friends said to me about 20 years ago, as debate around women/men raged: "I'd like to be born 100 years ago or 100 years hence when it's all settled!" Well I'm here to tell you that contrary to all your worst imaginings, things may be improving.

How we re-insert good, healthy boundaries into our lives is emerging as a vital undertaking: vital to model, vital to eulogise, vital to find the language for. A version of take-the-best-and-leave-the-rest of technology will need to bubble up to top-of-mind of good parents and grandparents. That is, the need to build useful fences which leaves some room to contemplate and to play.

Maybe even a subset is restoring some form of the Sabbath, dare I say! Now that would be a very interesting challenge to set oneself.

There's now so *much choice* rather than obligation, if you think about it, about human interaction particularly in families. In some ways, it's a refreshing development, to escape those cloying non-negotiable commitments.

But as I watch family life, or the creation of quasi-families in big cities, I see that those where there's an onus on people to make dates for common, shared time (and stick to them) thrive and grow, by comparison with the "up to you" sensibility; the no-dramas mode of each-to-his own.

In the words of Samuel Beckett, we must continue to try, fail, try again and fail better.

Breast Reconstruction – Pushing the Envelope



Dr Warren Hargreaves



Dr Elias Moisisdis

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women and the incidence has risen steadily over the past three decades. The risk of diagnosis by age 85 was one in 12 in 1982 and one in eight in 2012, while total case numbers increased from 5,311 to 15,050.¹

Fortunately, due to a combination of earlier diagnosis and more effective treatment, the risk of death has decreased from 30/100,000 women in 1982 to 20/100,000 in 2012.¹

Surgery is still the mainstay of breast cancer treatment and is performed in all patients who have a curative treatment intent. In general, cancer surgery will remove either part (partial mastectomy plus radiotherapy) or all (total mastectomy) of the breast. Landmark studies performed over four decades have shown equivalent long-term outcomes provided by these two different procedures.^{2,3,4}

Contemporary breast cancer management results in mastectomy for 35 per cent of patients in the USA and 40 per cent in England.^{5,6} In Australia there is 39 per cent mastectomy rate for women up to 80 and 50 per cent in women over 80. A survey of accredited

breast centres in the USA in 2011 also showed that 11 per cent of women underwent bilateral mastectomies for unilateral disease.⁵

Breast reconstruction has been shown to improve most measures of psychosocial wellbeing in women undergoing mastectomy yet rates of reconstruction remain low.^{8,9,10,11} Rates of breast reconstruction following mastectomy also vary widely by country, ranging from four per cent to 81 per cent.¹² Despite the benefits of breast reconstruction only around 50 per cent of women who have a mastectomy are willing and able to have a reconstruction.¹⁸

Although breast-conserving surgery remains the first choice of breast cancer treatment for many women, mastectomy is still a common option for surgical management of the disease. Mastectomy also has a place in cancer risk-reduction for patients who carry high-risk gene mutations such as BRCA1 and BRCA2. Contralateral prophylactic mastectomy is becoming increasingly popular with patients citing “peace of mind” as the main motivation for surgery in the healthy breast.^{5,19}

Breast reconstruction is a process that aims to restore form after mastectomy and generally involves multiple operations including breast mound creation, a

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procedure aiming to improve symmetry with the contralateral side and then nipple reconstruction and subsequent nipple-areola tattooing.

Traditionally, breast reconstruction has been performed after the completion of adjuvant therapies as it was felt that additional surgery, subsequent to cancer removal, would potentially delay those treatments. However, technical developments and recognition of the importance of breast reconstruction have led to the practice of immediate breast reconstruction – that is, performed at the same operation as removal of the cancer and often before adjuvant therapies.

Rates of immediate breast reconstruction (IBR) have increased as the safety has been recognised.^{12,14,15,16} The Royal Australasian College of Surgeons Breast Audit showed IBR was performed for 13 per cent of patients diagnosed in 2008, but it has been reported as high as 41 per cent in contemporary surgical practice.¹⁷

AUTOLOGOUS BREAST RECONSTRUCTION

To recreate the breast form, volume is derived from alloplastic (silicone implants) or autologous (fat and or muscle) sources. If autologous tissue is used there will be a donor site in a region other than the breast (Figure 1). This may be on the abdomen (Transverse Rectus Abdominis Myocutaneous [TRAM] flap and Deep Inferior Epigastric Artery Perforator [DIEP] flap), the back (Latissimus Dorsi flap), the buttock (Superior Gluteal and Inferior Gluteal Artery Perforator flaps – SGAP and IGAP) or the inner thighs (Transverse Upper Gracilis –TUG myocutaneous flaps).^{20,21,22,23,24}

There are advantages to autologous breast reconstruction as natural tissue is soft, supple and responds to gravity with a more natural shape. It will also usually change size with weight gain and loss. Disadvantages include longer operating and recovery times, donor site morbidity including extra scarring and a small but real risk of partial or complete flap necrosis necessitating further surgery. Donor site complications are not uncommon but are usually more of an inconvenience than a significant clinical concern and can be managed by conservative means. Complications

include seroma, haematoma, infection and delayed wound healing.

ALLOPLASTIC BREAST RECONSTRUCTION

An immediate breast reconstruction (IBR) is performed during the same operation as the mastectomy, while a delayed breast reconstruction (DBR) takes place during a separate operation, some time after the mastectomy.

The option of performing DBR at virtually any time after mastectomy is an advantage but it also creates a particular problem. As the original mastectomy excises the breast tissue and overlying skin, reconstruction requires not only a replacement volume but also soft tissue coverage (“the envelope”). An autologous reconstruction brings both volume and skin coverage, whereas an implant (alloplastic source) provides only volume, necessitating creation of a new soft tissue envelope to cover the implant (Figure 2a). The envelope is created by recruiting existing local skin and muscle in a process known as tissue expansion. A pocket is created deep to the chest wall soft tissues by mobilising and approximating the free borders of the pectoralis major and serratus anterior muscles. The volume of the soft tissue pocket is then increased over several months using a tissue expander. The device is expanded by serial instillation of saline, usually in 50-100ml aliquots (Figure 2b). Once the desired size has been reached a second operation is performed to remove the expander and replace it with the definitive implant (Figure 2c). Nipple reconstruction usually takes place in a third stage, under local anaesthetic as an outpatient procedure.

The main advantages of implant based reconstructions include shorter operating times, more rapid recovery and avoidance of a donor site and hence any morbidity that may be related to this additional site. However, implants are foreign bodies and as such are firmer, have a fixed shape (although there is a wide range of forms they cannot be custom-made) and do not change position when the patient sits up or reclines. In addition they do not change size if the patient gains or loses weight. Other potential complications include asymmetry, malposition, rotation, rippling, capsular contracture and implant rupture and leakage. The



Figure 1. Immediate right skin sparing (nipple sacrificing) mastectomy and free Deep inferior Epigastric Artery Perforator (DIEP) flap with nipple reconstruction and tattooing, showing the typical donor-site scar on the lower abdomen.



Figure 2a. Delayed 2-stage expander/implant breast reconstruction. Preoperative photograph showing loss of volume and mastectomy scar.



Figure 2b. During the tissue expansion process. The chest wall skin is over-expanded to create some degree of breast ptosis.



Figure 2c. Following insertion of the definitive implant (a left-sided augmentation has also been performed)

likelihood of these complications can be reduced by placing the implant within a soft-tissue pocket that fully encloses it deep to the skin envelope. As described above, a muscular pocket of sufficient volume to cover an implant can only be created using a tissue expander.

The technique of tissue expansion is also used if a patient wishes to increase her post-mastectomy breast size from the current volume.

DIRECT TO IMPLANT BREAST RECONSTRUCTION

The reasons most commonly cited by patients for not having a breast reconstruction are the wish to avoid further surgery after the cancer operation and a desire to avoid operations at other body sites.

There is now a technique that allows breast reconstruction using implants to occur in a single operation and without

the need for a donor site. The procedure, known as “direct to implant” (DTI), has been made possible by the advent of materials that can “fill the gap” between the pectoralis major and serratus anterior muscles and allow complete soft tissue coverage of the implant. This removes the need for tissue expanders to create the pocket. The material used to complete the pocket is an “acellular dermal matrix” or ADM.

The ADM is tissue that has been chemically and mechanically processed removing cellular material. The remaining extracellular matrix includes proteoglycans, hyaluronic acid, collagen, fibronectin and elastin and ideally maintains the structure of the source tissue. Ideally the product will result in minimal inflammation, undergo gradual degradation of the matrix over time and completely integrate with the host tissue. Acellular dermal matrix (ADM) products are derived from sources such as human

dermis, bovine collagen, porcine pericardium and porcine small bowel submucosa.

The more compatible the final product is with host extracellular matrix, the less likely it will elicit an adverse reaction. An immunological/inflammatory reaction is currently seen in up to 10 per cent of patients and results in a condition called “red breast syndrome”.^{25,26,27} This is generally self-limiting but in some cases requires steroid treatment.

Single-stage DTI immediate breast reconstruction involves a mastectomy to remove the breast tissue but with preservation of the breast skin and soft tissue (“the envelope”). Unlike the conventional simple mastectomy this operation is referred to as a “subcutaneous” or “nipple-sparing” mastectomy. Breast reconstruction is then carried out via insertion of a breast implant of an appropriate size and shape. The implant

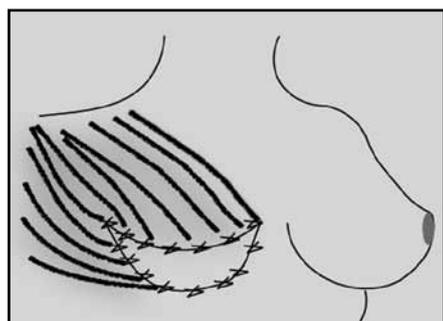


Figure 3a. Schematic of the ADM sutured to the serratus anterior and pectoralis major muscles. The lower pole of the implant is covered by the ADM.

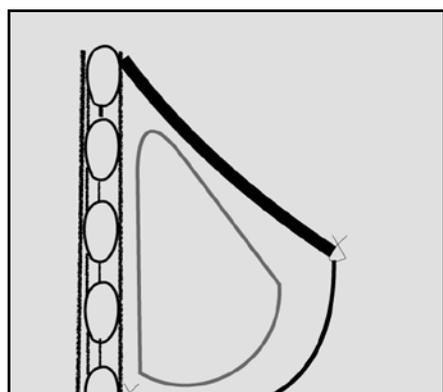


Figure 3b. Schematic of the position of the implant sitting in the pocket formed by the pectoralis major muscle and the ADM.

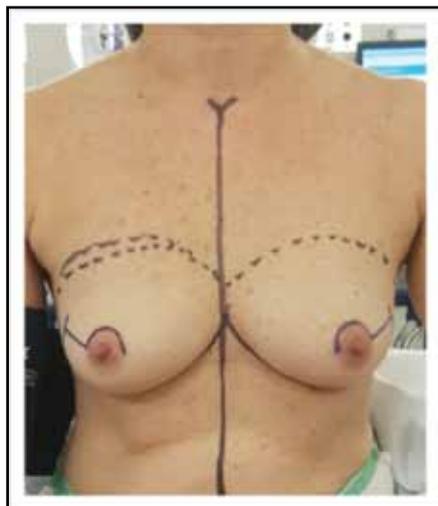


Figure 4a



Figure 4b

Figures 4a and 4b. Preoperative photographs of a patient about to undergo bilateral nipple-sparing mastectomy and immediate direct to implant breast reconstruction



Figure 5a



Figure 5b

Figures 5a and 5b. Early postoperative photographs of the patient in Figure 4 showing nipple-sparing mastectomy and immediate implant reconstruction. The profile view (Figure 5b) shows a natural projection of the implant-reconstructed breast.

is placed into a pocket formed by the elevation of the pectoralis major muscle from its origin on the chest wall and ADM is sutured along the lower border of the pectoralis major muscle and the inframammary fold – see schematic, Figures 3a and b. The ADM secures the free lower border of the pectoralis major and maximizes implant coverage. The added vertical dimension allows for a greater lower pole projection whilst supporting the implant in the desired position. Additionally, ADM use is associated with reduced capsular contracture rates. Figures 4 and 5 show the pre- and postoperative appearance in a patient who underwent DTI reconstruction.

The chief concern with the nipple-sparing/DTI procedure is preserving the vascularity of the mastectomy skin flaps. The vascularity of the breast envelope needs to be maintained in order to cover the implant and the ADM. If mastectomy skin flap necrosis occurs it has significant implications for the underlying ADM and implant. Further surgery may be required to debride non-viable tissue.

CONCLUSION

On St Vincent's Campus we are able to offer all patients the opportunity to undergo breast reconstruction in the public or private sector. A multidisciplinary discussion of treatment requirements and options allows the development of an optimal treatment plan prior to the patient's first operation.

Breast reconstruction may be immediate or delayed and may involve either an autologous or alloplastic graft. Historically, if a patient wished to have an immediate reconstruction then an autologous flap was required, whereas if the patient wished to avoid the second surgical site necessitated by an autologous graft then a multi-stage reconstruction was required in order to provide space for an alloplastic implant.

A "Direct to Implant with ADM" breast reconstruction is a safe and effective option in selected patients. It provides good volume and symmetry and can result in a reduced total number of operations for patients undergoing breast reconstruction. Donor site morbidity is also eliminated. There are particular advantages for patients undergoing bilateral immediate reconstruction as the goal of a symmetrical breast reconstruction is more likely to be achieved if both breast volumes are formed with similar tissue or material. This symmetry extends to breast shape,

breast size, the degree of ptosis as well as the change in shape over time and with different patient postures (upright or recumbent). This technique adds to the options available to patients who are considering breast reconstruction and can be of significant benefit in selected patients.

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Progress in Disorders of the Pelvic Floor

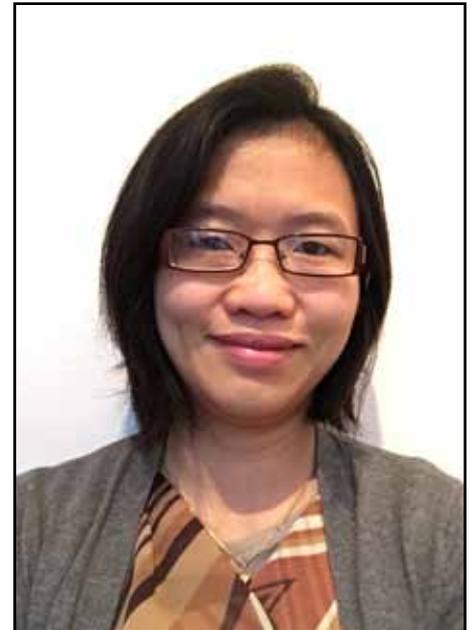
INTRODUCTION:

Since 2010, there has been surety and stability in the main diagnoses of pelvic floor dysfunction and the means of assessment. There has been steady progress in the different medical managements. In contrast, progress in the surgical management of pelvic organ prolapse (POP) has trended away from the use of vaginal prosthetic implants (meshes) where there has been a worldwide, highly publicized medico-legal controversy. Continence surgery using suburethral synthetic tapes (slings) have been subject to ongoing re-design and re-evaluation with elimination of a number of types from the marketplace. Overall, those remaining tapes represent an effective procedure with low morbidity in experienced hands.

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MAIN DIAGNOSES OF PELVIC FLOOR DYSFUNCTION (PFD)

In January 2010, the first female-specific terminology for PFD was published jointly by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) in their respective Journals.¹ This gave ongoing surety and stability to around 250 definitions clinicians might require, in particular those for the six (three new) main diagnoses, i.e. those with at least a 10 per cent prevalence in women presenting for the assessment of symptoms of PFD. These diagnoses, which remain useful and non-controversial, are:

- **Urodynamic stress incontinence (USI)** – urodynamically proven stress incontinence.
- **Detrusor overactivity (DO)** – urodynamically proven abnormal bladder contractions.
- **Pelvic organ prolapse (POP)** – symptomatic abnormal descent of pelvic organs, most commonly bladder, uterus, rectum, vaginal vault.
- **Voiding Dysfunction (VD)** – abnormally slow or incomplete

micturition as judged by abnormal urine flow rate and/or postvoid residual (PVR) measurement.

- **Recurrent Urinary Tract Infections (UTI)** – 3 or more symptomatic and medically proven in a 12 month period.
- **Bladder Oversensitivity** – Increased bladder sensation and decreased bladder capacity (during cystometry).

Assessment of Pelvic Floor Dysfunction (PFD)

There have been no major changes to assessment with a careful history and examination at a primary care level perhaps prompting a range of conservative measures. Physiotherapy or a trial of appropriate medications might be options considered. More complex or severe symptoms and signs might prompt specialist referral with urodynamic investigation remaining the “gold standard” for diagnostic precision. This would involve as a minimum clinical reassessment, uroflowmetry, PVR and filling and voiding cystometry. Even basic 2-D ultrasound imaging is extremely useful for PVR, bladder neck, urethral mobility and intercurrent pelvic pathology. More advanced 3 / 4-D ultrasound can additionally detect more

subtle diagnoses including obstetric related trauma.

Medical Management of Recurrent Urinary Tract Infections (UTI)

This diagnosis involves a clear history, hopefully backed up by relevant mid-stream urine (MSU) data. A urinary tract ultrasound can be a useful investigation at primary care level with calculi or an elevated PVR more common possible contributing causes. Common causes for elevated PVR are POP and urethral stenosis whereby a specialist assessment may be needed. Most commonly, no clear cause for the recurrent UTI is found. An effective regimen for prevention is required.

Cochrane studies support the efficacy of the following for UTI prophylaxis:

- Low dose antibiotics – This involves generally a daily dose of cephalexin, nitrofurantoin, trimethoprim or norfloxacin over a number of months initially till the UTI are controlled. Regimens might rotate between different antibiotics. Post-coital antibiotics, in selected cases, have supportive evidence.
- Hexamine (Hiprex) with Vitamin C – Both of these act as antibacterial agents, best in a combined use twice a day. Hexamine is 1 Gram with Vitamin C 500-1000mg. Again initial longevity of treatment might be a number of months depending on the level of control of the UTI.
- Vaginal oestrogens – There is evidence for vaginal though not oral oestrogens assisting recurrent UTI control. Twice weekly ovestin or vagifem can be tried though the latter is now marketed in a lower dose, the efficacy of which in this circumstance is uncertain.
- There is presently insufficient evidence to support the efficacy of cranberry, d-mannose or other commercially available preparations. Whilst personal hygiene is relevant, there is no evidence to support any particular initiative.

Medical Management of Voiding Dysfunction

This can often be the same as that for recurrent UTI² as incomplete micturition can be a common factor in what can be similar patient groups.

A chronic PVR of 30mls or more can lead to a significantly increased risk of recurrent UTI.³ Vaginal (Figure 1) or translabial ultrasound allows accurate and ‘immediate’ PVR measurement (within 60 seconds of voiding or repeat voiding). As voiding dysfunction might have an inflammatory basis, it is reasonable to initiate some of the UTI prophylactic treatments mentioned above.

As the prevalence of high PVRs and voiding dysfunction overall increases with age and POP, specialist referral with a view to possible surgical initiatives such as a urethral dilatation (urethral stenosis) or a POP repair may be required.

Medical Management of Bladder Oversensitivity

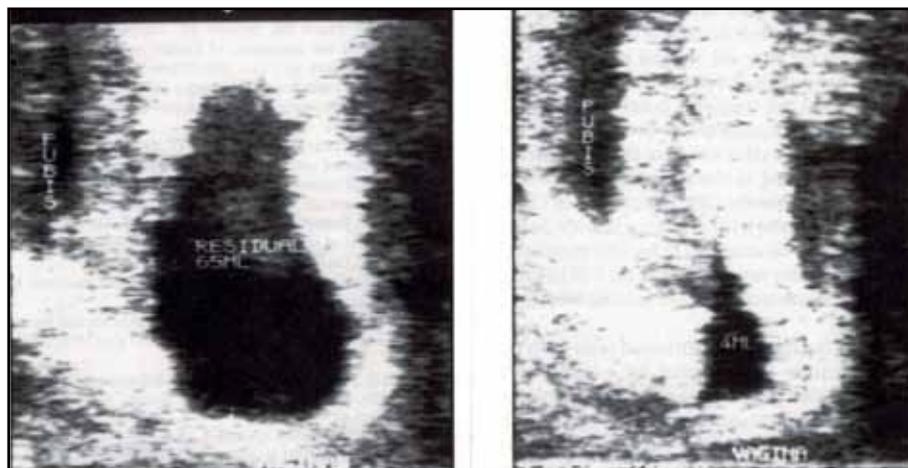
This is a strictly urodynamic diagnosis confirming a reduced bladder capacity (at least under 400mls where 500mls might be normally expected) in women particularly with frequency, nocturia and urgency symptoms. Often it reflects some ongoing inflammation with coexistent diagnoses, such as voiding dysfunction or recurrent UTI, relatively common. The

presence of pain during bladder filling (cystometry) may point to interstitial/ other cystitis. If bladder (detrusor) contractions are noted, the diagnosis becomes detrusor overactivity rather than bladder oversensitivity, the two diagnoses perhaps on a similar clinical spectrum.

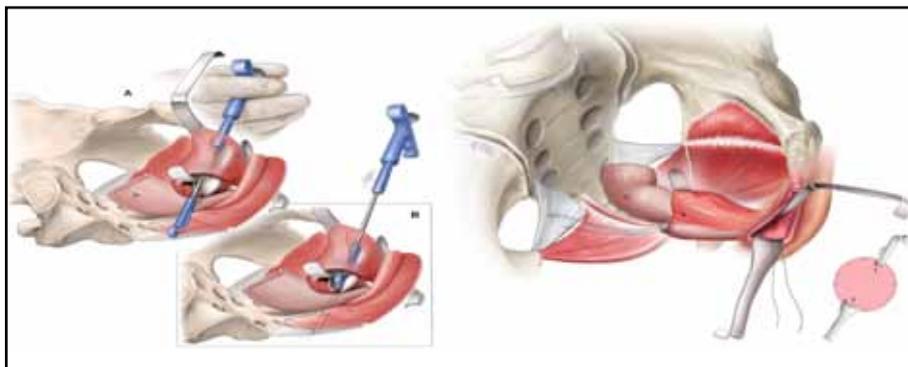
Most patients will have a response to the medical management of recurrent UTI. This will also depend on the presence of intercurrent diagnoses.

Medical Management of Detrusor Overactivity (DO)

Solifenacin (Vesicare), an antimuscarinic medication, has been available as a frontline treatment for DO for around 10 years. Limitations to use can be cost (non-PBS), dry mouth and visual acuity side-effects. The dry mouth can be less than the anticholinergic oxybutynin (Ditropan – PBS). Transdermal oxybutynin (Oxytrol twice weekly patches) are on the PBS also to reduce the dry mouth side-effect, though skin irritation can be a problem. Detrusitol (non-PBS) remains a further alternative.



Figures 1A and 1B: Transvaginal ultrasound measurement of an initial post-void residual (PVR) of 65mls reducing to 4mls with a subsequent attempt at voiding.



Figures 2A and 2B: Use of the Capio Slim © Boston Scientific to insert sacrospinous colpopexy (hitch) sutures with minimal dissection for vaginal vault support.⁴

Over the last 2 years, Betmiga (non-PBS), a beta-agonist has become available with studies and experience confirming efficacy. Main caution is hypertension, particularly if poorly controlled. Side-effects seem to be otherwise few. Research trends are aiming towards the use of combined therapies such as Vesicare and Betmiga combined.

Surgical Management of Pelvic Organ Prolapse

Patient morbidity, class action litigation and payouts have resulted in a major decline in mesh use as well as corporate withdrawal of mesh and even cases of corporate closure. At St Vincent's, the possibility (though not the extent) of this controversy was anticipated very early with a limited initial trial of mesh abandoned in favor of renewed research into pelvic floor anatomy and surgery using patient's own (native) tissues. This has resulted in predictable, reproducible POP surgical outcomes based on exact vaginal measurement of anatomical defects and appropriately addressing these areas. In the posterior vaginal compartment (where a rectocele might be evident), our findings are that main defects at time of repair occur at the vaginal vault (84 per cent cases) and introitus (100 per cent cases) rather than mid-vagina, opposing the traditional view of rectocele as being a rectovaginal "hernia".³ This means that effective both posterior vaginal and overall POP repairs generally require both: (i) secure vaginal vault support eg: sacrospinous colpopexy (Figures 2a and b),^{3,5} achieved with minimal dissection using modern suture placement devices; (ii) perineal restoration,⁴ simply by excision of thinned out (generally obstetric damage) medial tissue and repair (Figures 3a-c)⁴ Others share our view that more efficient vaginal native

tissue surgery is the way forward for POP.

The mesh options most open to debate are vaginal meshes not applicable to intraabdominal (generally laparoscopically inserted) meshes for uterine (hysteropexy) or vaginal (sacrocolpopexy) support for POP. These endoscopic options are well regarded for their success in terms of anatomical support, generally in recurrent prolapse cases, though morbidity rates are variable, as for any intra-abdominal surgical option, and surgeon experience dependant.

With vaginal vault support being at the forefront of vaginal surgeons treating POP, the introduction of more ergonomic devices to insert sutures from the vaginal vault to the main supportive (sacrospinous) ligament has result in a quantum leap in terms of reduced dissection and morbidity. This has also greatly assisted the predictability and reproducibility of surgical anatomical outcomes referred to above.

Surgical management of Stress Urinary Incontinence (SUI)

Suburethral tapes inserted vaginally have been used in Sydney since 1998 as an effective treatment for SUI with high success rates and relatively low morbidity. Care has to be taken with adjusting the tension in the tape at insertion with the title "Tension-free tape" used from the beginning to ensure postoperative voiding dysfunction is minimized.

The number of tape options had expanded enormously over time. Improvements have been made to the original and best-regarded (over time) retropubic approach in terms of the design and size of the insertion device. Tape size, around 1cm width, and material (large pore polypropylene)

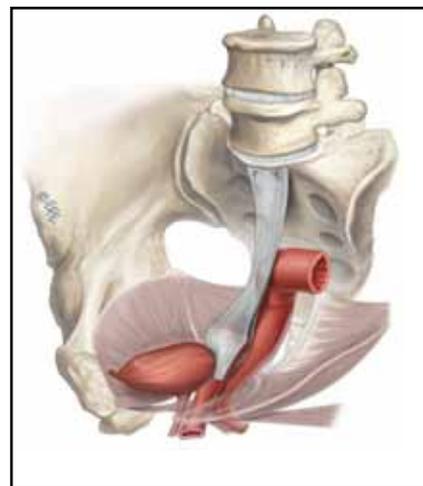


Figure 4: Laparoscopic sacrocolpopexy.⁴

has remained relatively constant. More lateral (transobturator) and shorter length (mini-slings) have achieved satisfactory success rates, with groin pain a potential side-effect in the former option. Recently, some pelvic floor surgical device companies have completely abandoned the market and closed operations in view of the extent of litigation (particularly in the USA) on vaginal mesh insertion for POP. This has reduced the number of tape options considerably, placing pressure on those remaining companies to satisfy much increased demand for their tape products. There remains a degree of uncertainty regarding future trends in the pelvic floor prosthetic market.

CONCLUSION

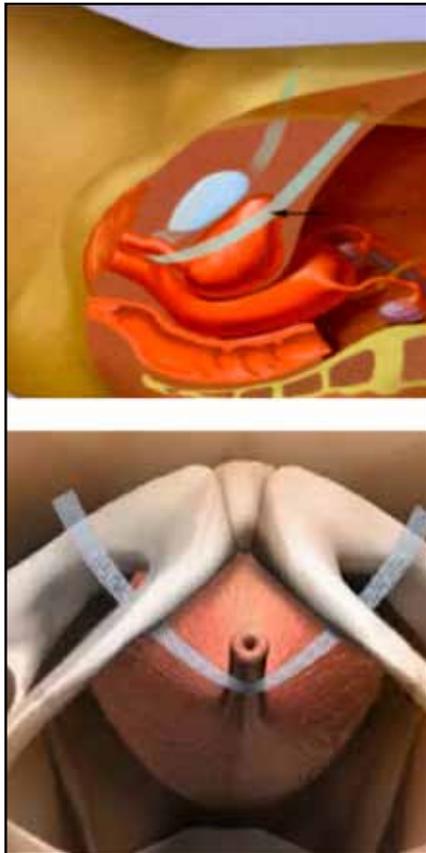
The last six to eight years have seen improved understanding, terminology, assessment and medical management of most aspects of pelvic floor dysfunction. Tapes (slings) for stress urinary incontinence will remain a mainstay of treatment for SUI, perhaps with more limited options. There will continue



Figures 3 A-C: Perineal restoration as part of a posterior compartment repair⁵

to be a marked decline in the use of vaginal mesh options. Vaginal vault support will continue to be a key factor in POP surgery with an ongoing debate likely between native tissue vaginal and laparoscopic mesh options.

Acknowledgements: Figures 3,5,7 involve the work of medical illustrator Dr Levent Efe. leventefe@gmail.com



Figures 5A and 5B: Suburethral (retropubic) Tension-free Vaginal Tape (a) retropubic; (b) transobturator

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Lessons in Medical Imaging



Dr Sebastian Fung



Dr Nita Durham



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CASE 1: GRANULOMATOUS MASTITIS

A forty-two year old woman was referred for a CT scan of her chest, thoracic and lumbar spine because of intermittent chest pain. The CT scan report included an incidental finding of a mass in her right breast (Figure 1).

Ultrasound demonstrated two definite hypoechoic masses and a probable third mass deep in her right breast (Figure 2). Because of her large, dense breasts and the difficulty in evaluating the deeper lesions, MRI was recommended.

MRI demonstrated four ovoid masses in her right breast, all of which exhibited thick irregular rim enhancement. Kinetic analysis demonstrated mainly rapid washout and plateau curves, a pattern

which is very suspicious for malignancy (Figures 3 a-c).

Two of the masses were then biopsied. Pathology reported active inflammation with granulation tissue. Two of the masses were subsequently aspirated to dryness and the residual lesions excised surgically.

LESSON:

Granulomatous mastitis is a very rare inflammatory disease of unknown origin that can clinically mimic carcinoma of the breast. It typically affects younger women, usually within 6 years of pregnancy.

The prognosis is usually good, although local recurrence has been reported. Primary treatment is usually excision biopsy. Corticosteroid therapy has also proved effective.

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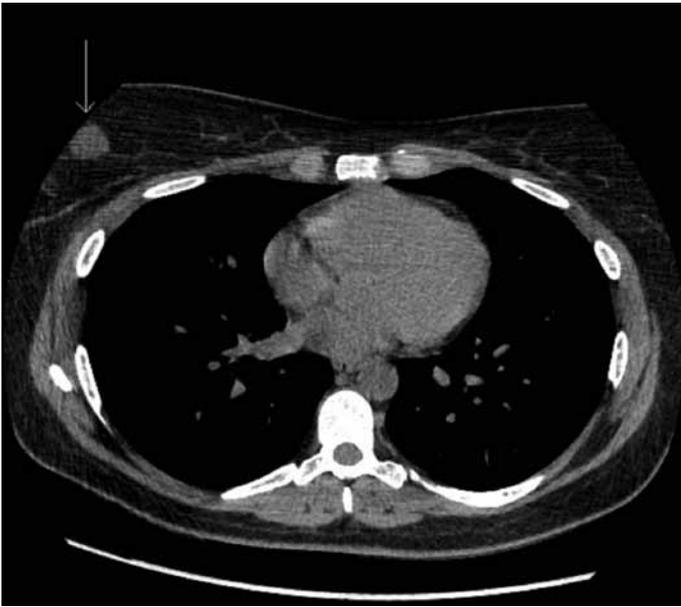


Figure 1: CT scan showing an incidental soft tissue lesion in the right breast

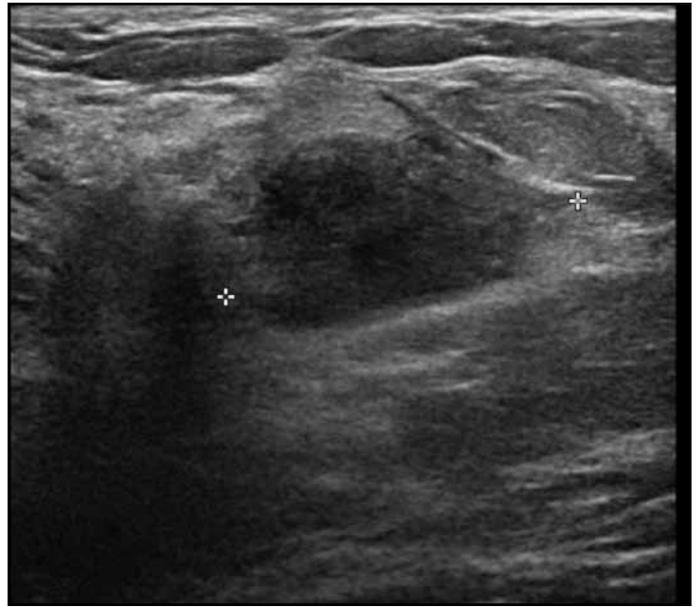


Figure 2: Ultrasound demonstrating one of the hypoechoic masses in the right breast

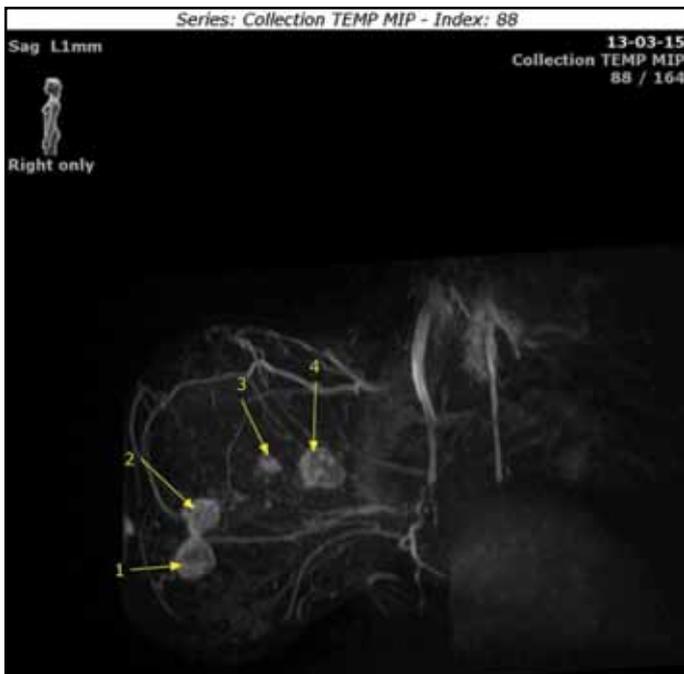


Figure 3A

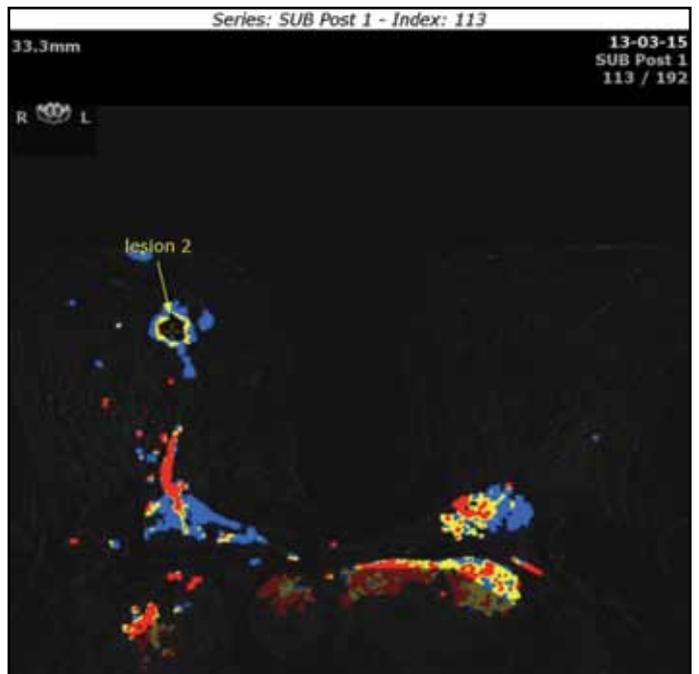


Figure 3B

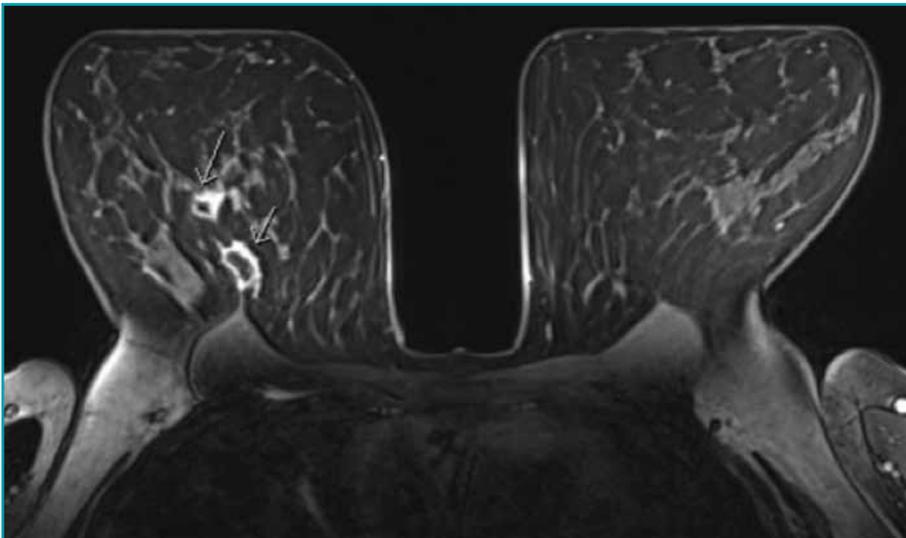


Figure 3C

Figures 3(a-c) Kinetic analysis showing 4 ovoid masses in the right breast.

CASE 2: BISPHOSPHONATE – INDUCED PROXIMAL FEMORAL STRESS FRACTURES

68yo female with long history of Crohns disease, seronegative arthropathy and osteoporosis on long term Biphosphonate therapy.

She presented with acute proximal left leg pain. A stress fracture in the proximal lateral left femur was noted (Figure 1), and was treated operatively with a long femoral stem left total hip arthroplasty.

Three months later there was a right proximal stress fracture requiring operative treatment with a right femoral nail.

In retrospect, previous plain x-rays showed the lateral proximal femoral cortical thickening and “beaking” that can precede overt fractures (Figure 2).

LESSON:

Biphosphonates are widely used and highly effective at limiting the bone loss and deterioration of bone microarchitecture that occurs in osteoclast-mediated bone resorption including senile osteoporosis. The widespread introduction of biphosphonates into clinical practice occurred after FDA approval of Alendronate in 1995.

Relatively recent reports have documented an association between chronic biphosphonate use and proximal femoral insufficiency fractures. These patients are at risk of a new variant of proximal diaphyseal femoral stress fractures, often preceded by thigh pain, vague discomfort and subjective weakness. The early radiological changes as seen in Figure 2 may be evident at that time. A bone scan would show high uptake of radionuclide. These fractures are typically sustained with a low energy mechanism or spontaneously and the majority progress to fracture completion. There is a high failure rate with conservative management and prophylactic fixation of femoral stress fractures reduces hospital admission times.



Figure 1 Stress fracture left proximal femur (arrow)



Figure 2 – Bilateral cortical beaking (arrows)

CASE 3: LYMPHOMA AFTER LUNG TRANSPLANTATION

A 53 year old male (post lung transplant for cystic fibrosis) presents with clinical features of acute on chronic sinusitis.

CT of the sinuses (Figure 1) demonstrated evidence of previous functional endoscopic sinus surgery and near complete opacification of all the paranasal sinuses with erosions of the right frontal sinus inner table and mild subcutaneous swelling above the right orbit. Clinically there was concern for the condition of "Potts puffy tumour". This was supported by MRI of the sinuses (Figure 2) which demonstrated subtle dural thickening and enhancement over the right frontal lobe as well as periosteal enhancement of the right frontal sinus outer table. Empirical antibiotic therapy was commenced.

A progress MRI (Figure 3) study 12 days later demonstrated worsening of the findings, now with what appeared as a collection. This was seen superficially over the right frontal bone, extending through the right ethmoidal cells and into the right orbit. This presumed collection also demonstrated diffusion restriction on the DWI sequence (Figure 4). Diffusion restriction is a non-specific imaging finding that can be seen with purulent collections, densely cellular material such as rapidly growing tumours and infarcts. Provisional diagnosis was that of an abscess or aggressive infective process. The patient was neutropaenic at this time.

Endoscopic sinus surgery was performed and revealed the diagnosis of B-cell lymphoma.

Following a month of treatment with Rituximab, the MRI findings of the subperiosteal periorbital collection, diffusion restriction and dural reaction were near resolved.

LESSON:

Post-transplant lymphoproliferative disease (PTLD) is a well-recognised complication of both solid organ transplantation and haematopoietic stem cell transplantation and is the most common post-transplant malignancy. This case of PTLD was unusual in that the clinical and imaging findings mimicked that of a suppurative infection. However given that the patient was neutropaenic a suppurative collection would have been very unlikely.

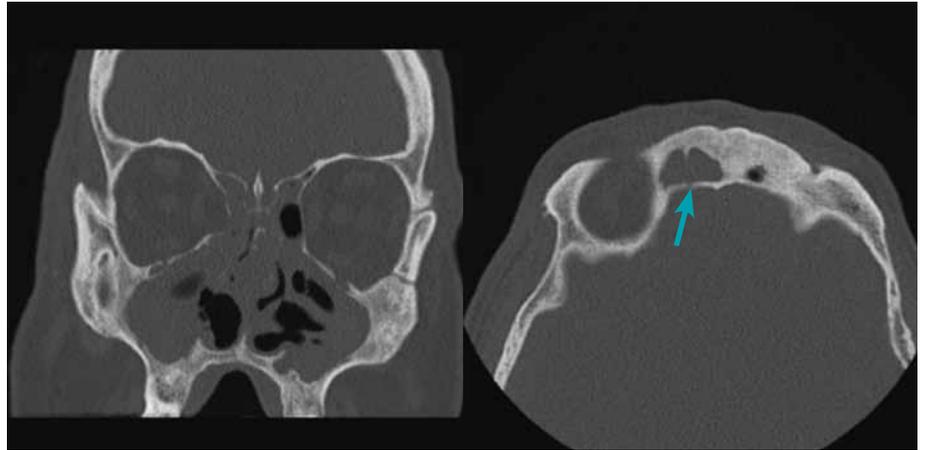


Figure 1 Coronal CT of the paranasal sinuses demonstrating extensive sinus opacification on a background of "osteitis" of the maxillary sinuses from chronic sinusitis and changes of prior endoscopic surgery. Axial CT at the level of the right frontal sinus showing an opacified sinus with focal erosion of its posterior wall (arrow). Subtle swelling of the soft tissues anterolateral to the right frontal sinus is also noted.

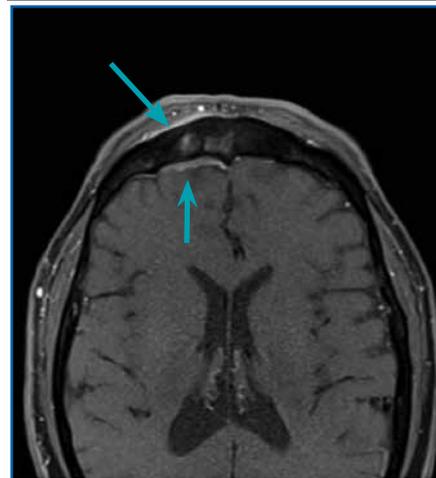


Figure 2 Axial MRI brain T1-weighted image post contrast showing enhancing periosteal and dural reaction anterior and posterior to the opacified right frontal sinus respectively (arrows).

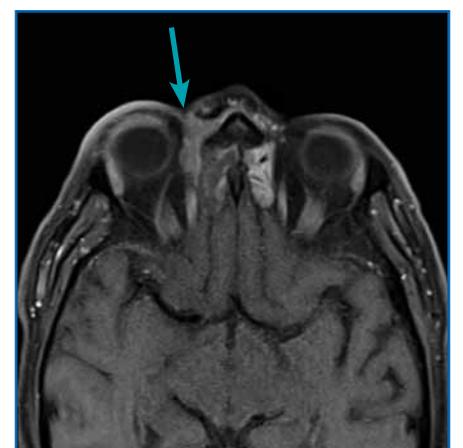
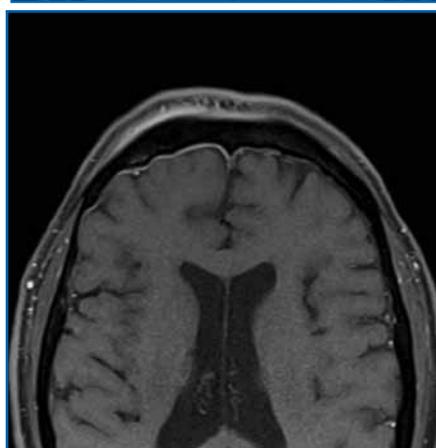


Figure 3 The MRI at 12 days demonstrating progression of findings: now with increased enhancing material extending through the right anterior ethmoidal cells, right orbit and anteriorly above the medial orbital rim.

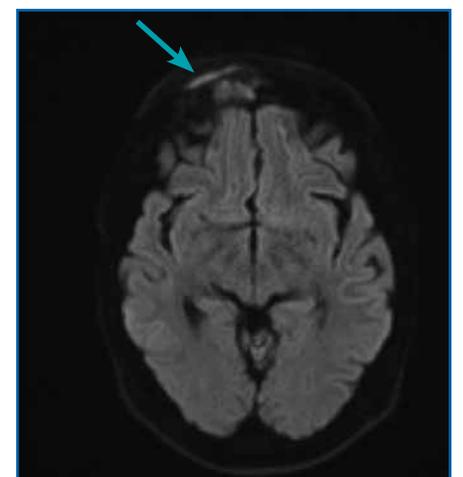
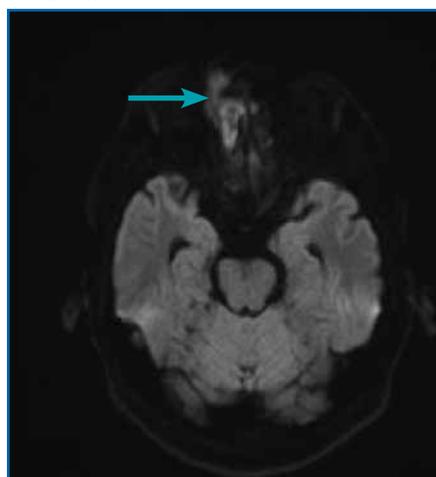


Figure 4 DWI sequence demonstrating diffusion restriction of the soft tissue changes in the right anterior ethmoidal cells and periosteal enhancing tissue.

Dr Amir Kalanie
Professor Michael Neil

BACKGROUND

Arthroscopic surgery of the hip joint was first described by Burmann as early as 1931, however no major advances were made in the field until the early 2000s. This came about as a result of our increased understanding of hip impingement, a concept popularized by a Swiss hip surgeon by name of Ganz. This new found understanding along with improvements in surgical instrumentation and techniques have given rise to today's modern arthroscopic hip techniques that not only allow treatment of Femoroacetabular impingement (FAI) but also a myriad of other pathologies in and around the hip.

Although the most common indication for hip arthroscopy is FAI along with an associated labral tear, there are a number of other pathologies that can be successfully addressed including:

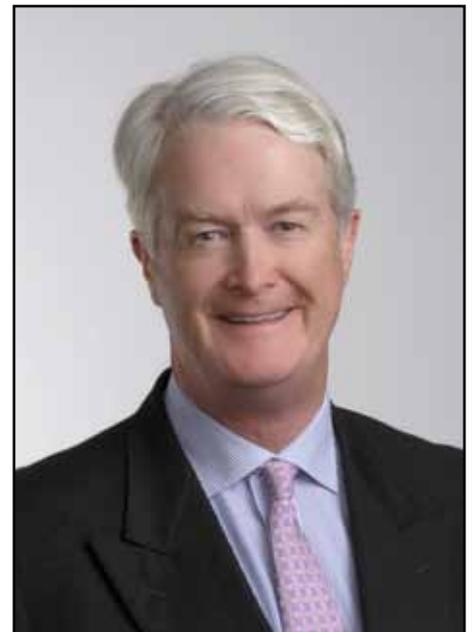
- *Trochanteric bursitis (discussed in this article)*
- *Gluteal tendinopathy/tear*
- *Hip Instability*
- *Psoas tendon impingement/tendinitis*
- *Loose bodies*
- *Synovial osteo-chondromatosis*
- *Ligamentum teres tears*
- *Ilio-tibial band or psoas tendon snapping syndromes*
- *Synovitis*

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Current Role of Hip Arthroscopy in Modern Orthopaedic Practice, with Particular Focus on Femoroacetabular Impingement



Dr Amir Kalanie



Professor Michael Neil

FAI/LABRAL TEAR:

Morphologic and radiologic changes:

There are three types of FAI: Cam and Pincer and mixed cam and pincer (Figure 1)

Cam impingement denotes proximal femoral asphericity due to excessive bone formation at the 1-2 o'clock region of the femoral head/neck junction. This leads to abutment of the cam lesion on the acetabular edge causing pain in flexion and internal rotation. Structurally this constant abutment results in tearing of the acetabular labrum and damage to the adjacent articular cartilage. Cam impingement is most commonly encountered in young male athletes.

Pincer impingement is the result of acetabular over coverage; once again resulting in early, abnormal contact between the acetabular rim and femoral neck causing damage to acetabular labrum and articular cartilage. This type of FAI is more commonly seen in middle aged female patients.

The third and the most frequently encountered type of FAI is mixed impingement with features of both cam and pincer impingement are present.

Clinical findings:

Pain in and around the hip joint in a young active patient without overt radiologic osteoarthritis is a notoriously difficult problem to diagnose. In the majority of cases the persistent hip pain is wrongly attributed to soft tissue strain or contusion and the concomitant FAI pathology is often missed.

The diagnosis of symptomatic FAI is very much a clinical one and highly dependent on a thorough history and examination. The majority of patients tend to be young (in their 3rd-5th decade of life) active and often involved in cutting, pivoting and kicking sports. These patients present having suffered from long standing activity related groin pain that has an insidious onset and often deteriorates with time. Patients have often tried a number of non-surgical remedies including physiotherapy, activity modification and intra-articular steroid injections with mixed results. They tend to complain of groin pain and point to the anterolateral aspect of their hip in what is known as the "C-sign" (Figure 2).

Due to the extreme stiffness of the hip joint, the rotational forces normally born by the hip are transferred to surrounding joints resulting in concomitant pathologies such as osteitis pubis (Figure 3), adductor and rectus abdominus tendinitis, and less commonly lower back pain with resultant radiation of the pain into their upper thigh, trochanteric region or lower abdominal area.

On examination one tends to find a hip that is extremely stiff, not in keeping with otherwise normal or near normal appearing X-rays. The hip is generally irritable with painful restricted flexion, well preserved external rotation and severely restricted internal rotation.

The two most commonly used tests to detect FAI and labral tears are the Impingement test and FABER test (Figures 4a & b). The impingement test involves flexion to 100 degrees, internal rotation and adduction. This forces the bony cam at the head/neck junction against the acetabular labrum and the adjacent articular cartilage causing pain in the groin. FABER stands for Flexion, Abduction and External rotation which can be painful for the patient in the presence of any intra-articular pathology. Both these tests have a low sensitivity but almost 100% specificity which makes them a very good screening tool in the clinical setting.

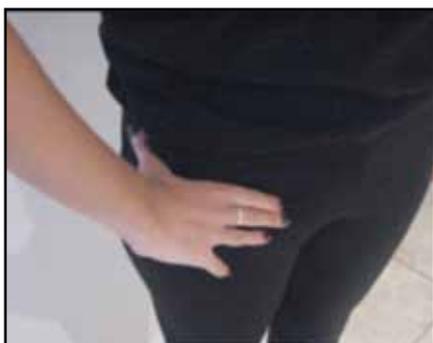


Figure 2. patient with labral tear demonstrating the "C-sign"

Other structures that should be closely examined are the symphysis pubis, adductor tendon origin and the trochanteric area looking for osteitis pubis, adductor tendinitis and trochanteric bursitis respectively. A thorough examination of the lumbosacral spine is also recommended.

Imaging for FAI

Plain radiography:

Plain radiographs are very helpful in demonstrating bony morphology associated with FAI and are considered the first line of investigation. To be able to optimally visualise the associated bony abnormalities in FAI, a FAI-series needs to be performed. However these images

need to be ordered in centres with a specialized musculoskeletal radiologist who can ensure the quality of the images and also their correct interpretation.

One such image is a Dunn view which is helpful in diagnosis of cam impingement as seen in Figure 5.

Pincer impingement is mainly assessed on AP view using the centre edge angle (CEA) as seen in Figure 6a. A CEA of 45degrees or greater is considered consistent with pincer impingement. Another radiologic feature suggestive of pincer impingement is the cross-over sign seen in Figure 6b.

In the majority of cases, X-rays in conjunction with the clinical findings allow the diagnosis of FAI to be firmly

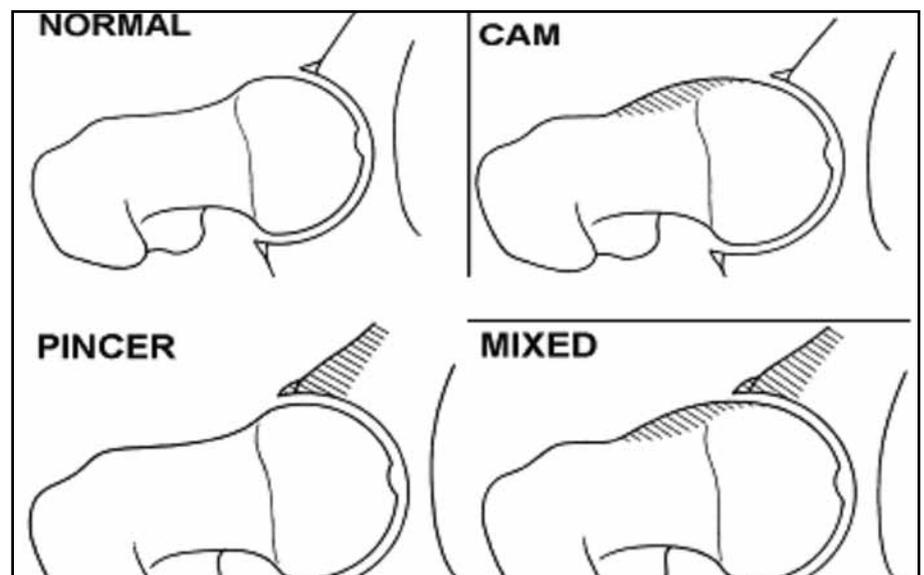


Figure 1. showing the three recognised FAI morphologies

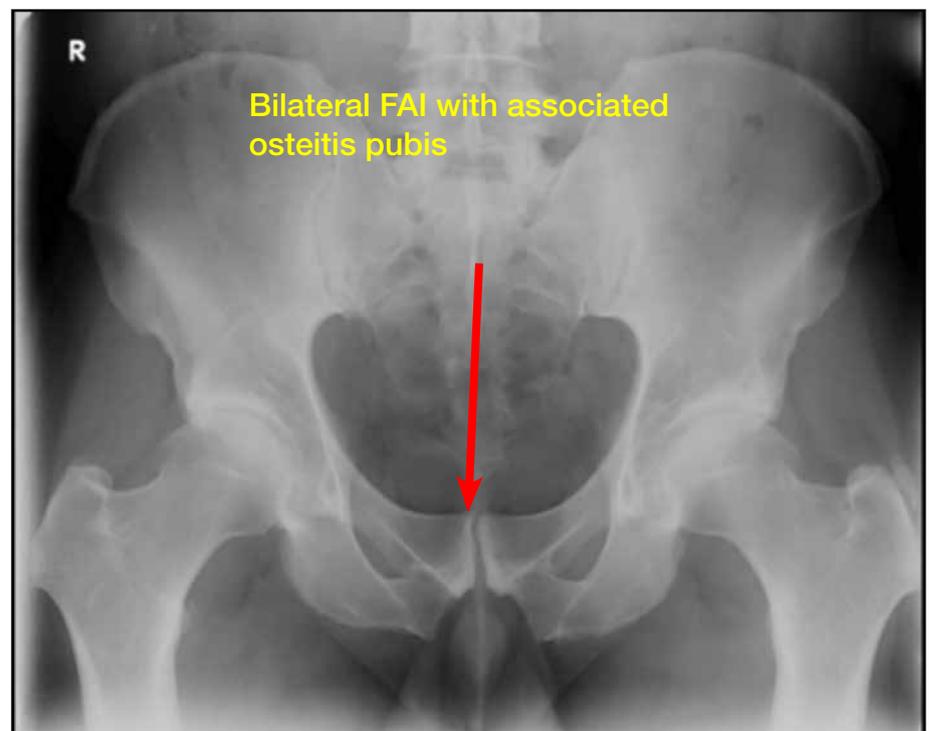


Figure 3. patient presenting with osteitis pubis and associated FAI

made. However in instances where doubt remains or there is concomitant pathology that needs further clarification then CT and/or MRI scans may be helpful adjuncts.

Treatment:

The association between FAI and OA of the hip has now been validated by a number of publications, therefore once diagnosed it is important to initiate treatment in a timely fashion.

The first line of treatment for symptomatic FAI/labral tears should be non-surgical. A combination of rest, NSAID, activity modification and targeted physiotherapy may help a portion of patients, especially those presenting acutely.

However if this line of treatment along with activity modification fails to clear the patients symptoms then arthroscopic surgery of the hip can be contemplated. The aim of arthroscopic surgery is to reshape both the aspherical portion of the femoral head (Figure 7) and the acetabular over coverage to prevent further damage to the adjacent labrum and the articular cartilage. Following the bony remodelling attention is turned to the tear of the acetabular labrum (Figure 8) and the associated adjacent chondral injury (Figure 9).

Every attempt should be made to repair/preserve the native labrum as it is an important anatomic structure that plays a crucial role in maintaining the healthy function of the hip joint. If repair is not deemed possible then labral reconstruction should be considered.

Following surgery patients are able to weight bear without restriction, start on a structured physiotherapy programme, aim to return to full daily activities by six weeks and high level sport by three months.

EXTRA-ARTICULAR DISORDERS

The two most common extra-articular disorders that are dealt with arthroscopically are recalcitrant Ilio-psoas tendinitis (IPT) and trochanteric bursitis/gluteal tendinopathy. However

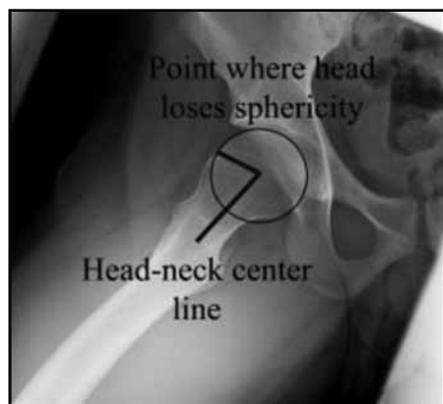


Figure 5. demonstrating the technique for measuring alpha angle on a Dunn view. Angles >60 support the clinical diagnosis of cam impingement

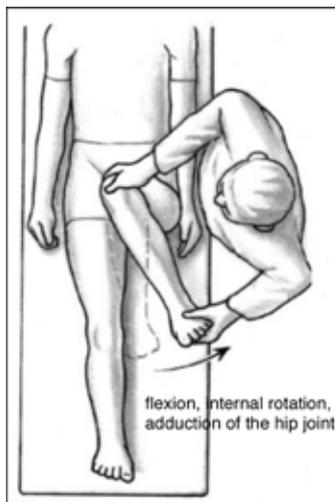


Figure 4a. Impingement test

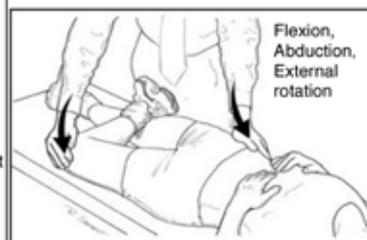


Figure 4b. FABER test

only trochanteric bursitis will be discussed here.

Trochanteric bursitis is a commonly encountered musculoskeletal condition that can be difficult to treat. The pathophysiologic mechanism of the disease is most likely due to tenuous blood supply and high tensile forces at the gluteal insertion, causing accumulation of micro-trauma to the gluteal tendon with a resultant trochanteric bursitis. Clinically this presents as lateral hip pain, weakness and limp. The commonest complaint is trochanteric based pain with increased intensity at night with inability for the patient to lie on the affected side.

The first line of treatment remains physiotherapy, NSAIDs and judicious use of steroid injections. In the recalcitrant cases, it is possible to endoscopically partially lengthen the ilio-tibial band which is often tight and contributes to the pathology, debride the bursa and perform radiofrequency stimulation of the gluteus medius tendon with good short to medium term results. If large tears of the tendons are found, then endoscopic repair can also be performed.

COMPLICATIONS OF SURGERY

Although in the majority of cases hip arthroscopy is a safe and effective tool in the hands of an appropriately trained surgeon, as with any surgical procedure it has a number of rare but well documented

complications.

The commonest of complications are transient nerve palsies around the hip secondary to direct pressure due to intra-operative traction. Pudendal and sciatic nerves are the most commonly affected. However the incidence of nerve palsies is much less when using the lateral position since the pressure is applied to the inner thigh rather than the perineal region as in the supine position. The majority of nerve palsies are transient and resolve by six weeks to three months.

Other major complications include avascular necrosis (AVN) and femoral neck fracture. Both of these are due to excessive intra-operative excision of the femoral cam lesion. Thankfully the incidence of both the above complications is very low locally and internationally.

FUTURE

One of the exciting prospects on the horizon is the advances made in robotic surgery. One such machine is the MAKO which has been used extensively in North American institutions over the last decade and is now arriving in Australia. The advantage that the robot can bring is precision and reproducibility when it comes to excising the cam and pincer lesions. This process involves obtaining a CT scan of the affected hip

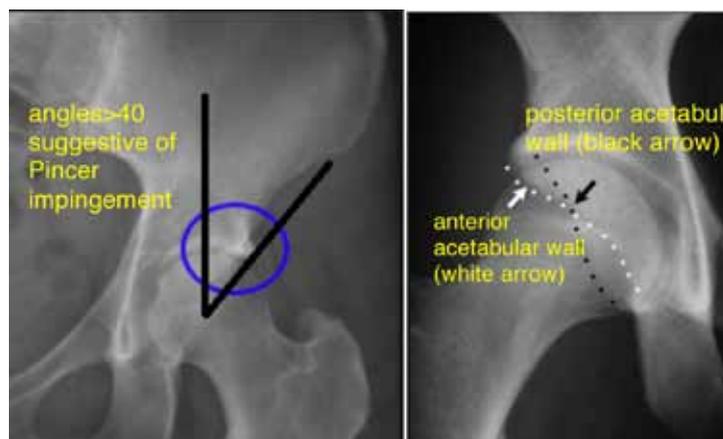


Figure 6A showing the method for measuring CEA. **Figure 6B** showing the presence of cross-over sign

followed by 3D reconstruction. These images can then be loaded onto the robot which will establish the exact geometry of the bone and can therefore remove the correct amount of bone more precisely and evenly, reducing the risks of AVN, femoral neck fracture, iatrogenic instability and the need for revision surgery.



Figure 7a demonstrating a large cam lesion. **Figure 7b** showing femoral head/neck junction post arthroscopic excision of the cam.



Figure 8a: an arthroscopic probe distracting a labral tear. **Figure 8b:** labral repair using suture anchors



Figure 9a showing full thickness chondral delamination. **Figure 9b** picture after debridement of the loose chondral fragment, followed by subchondral microfracture

Associate Professor Janet Rimmer

SUMMARY:

Exhaled nitric oxide (FENO) is a surrogate marker for the measurement of airway eosinophils. The development of simple to use portable devices which measure exhaled nitric oxide (FENO) non-invasively has led to an increased utilisation of this test in clinical practice. This article reviews the background of FeNO and usefulness of this test in clinical practice.

BACKGROUND HISTORY

NO has long been known as an atmospheric pollutant present in vehicle exhaust emissions and cigarette smoke.

In 1987, experiments on coronary arteries showed that NO was the long sought after endothelium-derived relaxing factor. Subsequently it was realised that NO had numerous biological roles including as a bactericidal, vasodilator, bronchodilator, neurotransmitter roles and a pro-inflammatory mediator.

NO was first detected in exhaled breath samples in 1991 and in 1993. Researchers from the Karolinska Institute in Sweden were the first to report increased FENO in asthmatics.¹

Today, NO is not only used in breath tests but also as a therapeutic agent for conditions such as pulmonary arterial hypertension and possibly for the treatment of acute respiratory distress syndrome.

ABBREVIATIONS:

FENO: fraction of exhaled nitric oxide
NO: nitric oxide
NOS: nitric oxide synthetase

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Exhaled Nitric Oxide and Relevance in Clinical Practice, Especially the Treatment of Asthma



Associate Professor Janet Rimmer

NO AND THE RESPIRATORY TRACT

The exhaled breath contains volatile factors such as NO, carbon monoxide (CO), ethane and pentane as well as nonvolatile substances in the liquid phase of the exhaled air called breath condensate such as hydrogen peroxide. NO is measured as exhaled breath in parts per billion (ppb) and is measured as the fraction of exhaled NO or FENO.

Exhaled nitric oxide is produced in both the upper and lower respiratory tract airways. It diffuses into the lumen by gaseous diffusion down a concentration gradient. Measured FENO from the lower respiratory tract has contributions from the upper and lower airways but probably little from alveolar and gastric sources. The method of sampling exhaled breath NO or FENO aims to minimise upper airway and ambient contamination.

In humans, NO is produced from L-arginine as it is converted to L-citrulline by three enzymes called nitric oxide synthases: constitutive NOS produced by endothelial and neuronal cells and also inducible NOS. The former two have constant low level activity whereas inducible NOS is low in normals but

increased by factors such as airway inflammation and infection. Exhaled breath NO or FENO is constitutively expressed in small quantities of <20ppb.

In normals the level of NO is low but it is increased by factors which up-regulate inducible NOS such as airway inflammation. Inducible NO is expressed in sinus and nasal epithelial cells as well as the epithelial cells of the lower respiratory tract. Inducible NOS produces x1000 more NO than endogenous forms of NOS; it is upregulated by proinflammatory cytokines such as IL4 and IL13. Exhaled NO is produced from the whole of the lower respiratory tract but most comes from the larger airways. In asthmatics 90 per cent of FENO is produced by inducible NOS.

FENO LEVELS IN NORMAL AIRWAYS

There are now simple and standardised methods using chemiluminescence available to measure FENO non-invasively in the clinic hence it could have an increasing role in the assessment of airways disease. FENO is measured by inhaling to tidal lung capacity and then exhaling at a steady flow rate (50mL/second) for six seconds. The distribution of FENO levels in a normal population is shown in Figure 1.^{2,3}

FENO AND ASTHMA

Traditionally asthma has been defined by symptoms and airway function but for a long time it has been recognised that airway inflammation is an important factor.

Patterns of inflammation in asthma are complex with the early phenotypes describing extrinsic (allergic) and intrinsic (non allergic) asthma. Over the last 30 years studies of inflammatory markers, cluster analysis and molecular/physiologic phenotyping aided by the use of biological therapies has led to the description of Type 2 high and Type 2 low asthma. Type 2 high asthma, which in some studies accounts for 50 per cent of asthmatics,⁴ is characterized by the involvement of Th2 cytokines: IL4,IL5,IL13 produced by a wide range

of cells including Th2 lymphocytes, basophils, mast cells, eosinophils. It is generally associated with elevated blood and sputum eosinophils, higher serum IgE, increased airway hyper-responsiveness, thickened basement membrane and steroid responsiveness. Biomarkers have been sought to identify this subtype and those described include blood and sputum eosinophils, FeNO, serum periostin, sputum IL13. Type 2 low asthma is more likely to be neutrophilic driven but there are no well characterized biomarkers in clinical use.

Asthma has also been divided into different cellular phenotypes on the basis of sputum cell differential counts.⁵ Hence approximately 50 per cent of asthmatics have an eosinophilic or Th2 high phenotype where sputum eosinophils are >3 per cent which relates to a FeNO cut off point of about 26 ppb (Figure 2). The other cellular or Th2 low phenotypes include neutrophilic and paucigranulocytic.

With the availability of targeted biological therapies such as omalizumab:anti-IgE (Xolair) and mepoluzimab:anti-IL5(Nucala) the need for asthma phenotyping will be increased. The ability to measure airway inflammation in samples such as bronchial biopsies, bronchial lavage or sputum is invasive and/or time consuming. Currently FENO is the easiest, least invasive measurement and provides the quickest result.

FENO is controlled by airway inflammation involving serum IgE, IL4 and IL13 pathways but not involving IL5.⁵ Initial targeted biological therapies have produced confusing results which in retrospect is likely due to poor selection or phenotyping of patients for therapy. Hence FENO measurements have correlated with symptom improvements in trials using anti-IgE, anti IL4, and anti IL13 therapies but not with anti IL5 therapy.⁵ All of these factors but particularly IL5 influence the eosinophilic airway response. This is part of the reason why there is not a complete correlation between airway eosinophils and FENO. Overall there are reasonable correlations between FENO levels and eosinophils in blood, sputum, bronchial lavage and bronchial biopsies. However the sensitivity and specificity of FENO to detect sputum eosinophilia ranges from 65-76 per cent and 70-83 per cent respectively so that false negatives and positives occur.

Airway eosinophilia is well established to be steroid responsive so a high FENO can be used to predict the likelihood of a steroid response while a low FENO predicts the lack of steroid

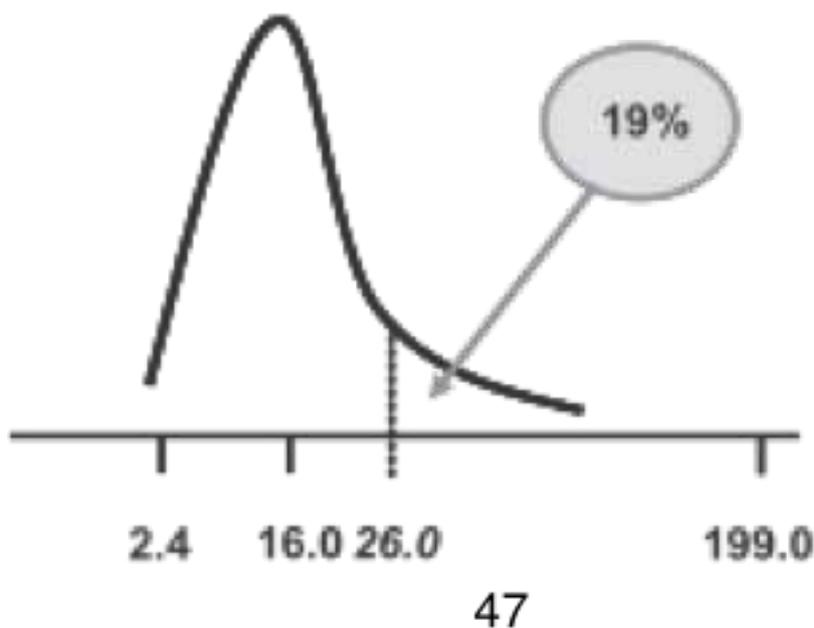


Figure 1: Distribution of FENO levels in an unselected population of 2,200 male and female subjects. The median value was 16.0 ppb (range of 2.4 to 199 ppb). 26 ppb is the optimum cut point for significant sputum eosinophilia (>3 per cent), but shows that 19 per cent would not have significant sputum eosinophils. 47 pp. is the cut point for steroid responsiveness in the asthma population.

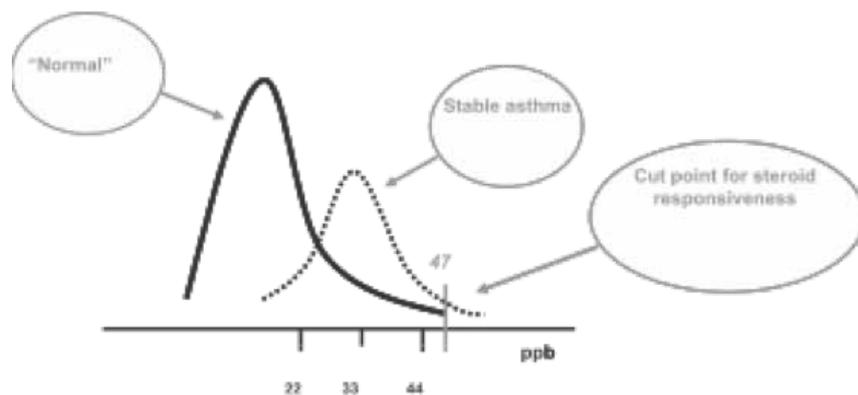


Figure 2. FENO values in the normal and stable asthma populations.

Table 1: Factors affecting FENO	
	Effect
Age	lower in children
Sex	lower in females
Height	lower with lower height
Smoking	lower
Atopy	higher
Medications	variable

Table 2: interpretation of FENO (ppb)levels in adults and children		
	Adults	Children
Low	<25	<20
Intermediate	25-50	20-35
High	>50	>35

responsiveness (see Table 3). As noted above FENO has also been identified as a biomarker responsive to biological therapies such as omalizumab (anti IgE), dupilimab (antiIL4/IL13) and lebrikizumab (anti IL13).

The inclusion of an airway inflammation parameter such as sputum eosinophils in asthma management has been shown to enhance asthma management compared with traditional monitoring alone.⁶ This has led to several guidelines recommending sputum eosinophils counts in the management of severe asthma.^{3,6,7} However sputum eosinophil measurements largely remain a research tool due to the fact that samples cannot be obtained in all subjects and the analysis is very time consuming.

It is currently proposed that a composite biomarker will be needed to define an asthma phenotype (see Table 4) particularly in the severe asthma population.⁸

Unfortunately many asthmatics do not have well controlled asthma even after optimising therapy.⁹ Several studies have now shown that FENO guided asthma management results in better outcomes in adults, children and pregnant asthmatics.^{10,11} In particular, asthma elevated FENO is associated with worse asthma symptoms, need for steroid therapy and is predictive of the response to steroid therapy.

In clinical practice FENO measurements can be used for the following reasons:

- to determine the etiology of respiratory symptoms;
- to identify the presence of eosinophilic airway inflammation;
- to assess whether airway inflammation is contributing to poor asthma control;
- to assist in the evaluation of treatment adherence;
- to determine a baseline FeNO for progress monitoring;
- to determine the choice of therapy; and
- to guide step up and step down medication changes

In short, the advantage of FENO in clinical practice is that the test is easy to perform and the result available within minutes allowing decisions in treatment to be made within a consultation. Preliminary data from our practice suggests that use of this device influences treatment decision-making in over 50 per cent of cases. In particular, the ability to back titrate or reduce doses of ICS is supported.

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Table 3: Interpretation of high/low FeNO levels

High FeNO	Low FeNO
eosinophilic airway inflammation	absent eosinophils
too low a dose of ICS	consider non ICS Rx if symptomatic (see Table 5)
steroid resistance	if asymptomatic reduce ICS safely
poor Rx adherence/technique	consider additional diagnoses such as reflux, obstructive sleep apnoea, vocal cord dysphonia, chronic rhinosinusitis.
continued allergen exposure	

Table 4: Biomarker score for asthma

	0	1	2
FeNO ppb	< 15	15 - <30	≥ 30
Blood eosinophils	< 150	150 - <300	≥ 300
Periostin ng/mL	< 45	45 - <55	≥ 55

Table 5 shows an algorithm for treatment changes in asthmatics being monitored by serial FeNO measurements.

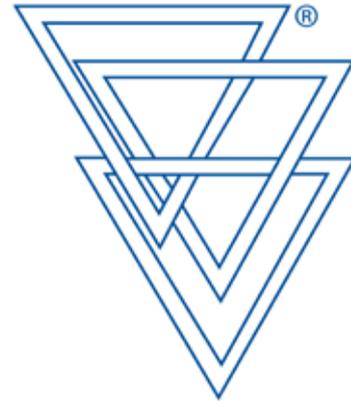
Table 5: Algorithm for Rx changes based on FeNO levels (adapted from 12)

FeNO level (ppb)	Symptom score (ACQ)*	ICS** change	LABA*** change
>29	NA	□ ICS	No change
16-29	≤ 1.5	No change	No change
16-29	>1.5	No change	□ LABA
<16	≤ 1.5	□ ICS	No change
<16	>1.5	□ ICS	□ LABA

* ACQ: asthma control questionnaire **ICS: inhaled corticosteroids, ***LABA: long acting beta 2 agonist, ACQ: asthma control questionnaire

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