ISSN 0041-6193

# THE ULSTER MEDICAL JOURNAL

Volume 86 (3) September 2017

# The Ulster Medical Journal

The journal of the Ulster Medical Society. First published in 1932.

Successor to the Transactions of the Ulster Medical Society (1862-1929), and the Transactions of the Belfast Clinical and Pathological Society (1854-1860)



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The journal is published in January, May and September, by the Ulster Medical Society, and typeset and printed in the UK by Dorman and Sons Ltd, Belfast. See inside back pages for institutional and personal subscriptions.

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# Guest Editorial

## Time for a new resistance against antibiotics

Resistance of pathogenic organisms to antimicrobial agents can seem far from a clinician's mind during everyday consultations with patients. A recent systematic review of clinicians' views about antimicrobial resistance reported that they believed that antimicrobial resistance was a serious (but distant) problem that was mainly caused by patients' incomplete adherence to prescriptions or self-medicating and was more important for hospital settings and other countries: that is, it was more important for other people.[1] Few clinicians believed that their own prescribing contributed to resistance.[1] There is now compelling evidence, however, that a single course of antibiotics prescribed by a general practitioner increases the risk of its recipient becoming colonised or infected with resistant bacteria, making it more difficult to treat infections, and resulting in further antibiotic use.[2] We now know that the prescribing decisions of doctors quickly and measurably alter the antibiotic flora of individual patients and of the population.

We are now seeing serious effects of antimicrobial resistance in everyday clinical practice: previously rare infections now occur with increasing frequency, causing harm to patients and to our population. The incidence of dangerous *Escherichia coli* bloodstream infection has nearly doubled in the last decade in Northern Ireland to around thirty cases per week, mirroring the dramatic increase seen in the rest of the UK.[3] About two-thirds of these infections start in the community, most often from a urinary source, and 30-day mortality is 15%.[4] Bacteria that are resistant to carbapenems (broad-spectrum antibiotics of last resort) are no longer strangers to our healthcare settings. When discovered in a clinical or environmental specimen, they prompt a response that consumes staff time and financial resources, disrupting patient care, closing rooms or wards to admissions, increasing the competition for a finite number of isolation rooms, and resulting in other patients being screened for bacteria by rectal swabs to investigate whether they too may have become carriers.[5] Antimicrobial resistance is already causing distress, illness and death for patients, and disruption, increased demands and stress for Health and Social Care staff.

The recent Review on Antimicrobial Resistance led by the economist Jim O'Neill projected vastly increased costs and deaths resulting from antimicrobial resistant organisms over the coming decades.[6] The Review recommended that the amount of 'inappropriate' antimicrobial consumption in humans and animals be greatly reduced and that there should be a particular focus on reducing healthcare-associated Gram-negative bloodstream infections. The UK government responded by setting ambitious targets to reduce 'inappropriate' antibiotic prescribing by 50%, with the aim of being a world leader in reducing prescribing by 2020 and to reduce healthcare associated Gram-negative bloodstream infections in England by 50% by 2020.[7] The Department of Health (Northern Ireland) has endorsed these aspirations and new collaborative programmes of work are underway to address the factors behind Northern Ireland's antibiotic use (the highest in the UK by a wide margin) and the factors that lead to healthcare-associated infections (HSS(MD) 6/2017). A new work programme to reduce healthcare-associated infections and to improve antimicrobial stewardship in all Health and Social Care settings in Northern Ireland is led by the Public Health Agency-chaired multi-agency, multi-disciplinary Regional Antimicrobial Stewardship and Healthcare-associated Infection Improvement Board.

It is important that the new effort to reduce harm from antibiotic use is not dismissed as a bureaucratic target conceived in an ivory tower, or as a cost-cutting measure: our profession has, in the past, misunderstood the balance of risk associated with antimicrobial use and we must together find a new equilibrium where prescribers and patients understand that prescribing an antibiotic is not necessarily the safer option when faced with diagnostic uncertainty.[2,8] The imperative to reduce antimicrobial prescribing comes at a time when the primary healthcare system has been in the news because of practices closing, a recruitment shortfall, and GP representatives reporting that demand currently exceeds capacity of the primary care system. Creating the circumstances that allow healthcare professionals to safely reduce the amount of antibiotics they prescribe is a complex challenge. It will mean designing a system that reduces the incidence of infections in the community through preventive strategies such as vaccination, hygiene and food safety; increasing the capacity of the public to safely self-care for minor illnesses;[9] aiding prescriber decision-making with point-of-care diagnostic testing, where it is appropriate; allowing clinicians enough time to have caring conversations with patients that don't necessarily end in a prescription for antibiotics; and providing intelligence to professionals about their own antibiotic prescribing and the resistance patterns in organisms from their patients. These changes will take time. Experience elsewhere suggests that expert clinicians may feel that scrutiny of their antibiotic prescribing is intrusive and undermines their professionalism, and we must therefore aim to bring about change in collaboration with clinicians and their representatives.[10] One step in this journey will be the introduction of the Royal College of General Practitioners-endorsed TARGET (Treat Antibiotics Responsibly, Guidance, Education, Tools) toolkit to Northern Ireland. [11] These resources aim to help GPs to safely reduce antibiotic

prescribing and include self-care resources for patients that have been designed using a behavioural science approach. Though a smaller fraction of antibiotics is prescribed in secondary than in primary care, antibiotics of last resort are more frequently used. Patients (and their bacteria) move between these two parts of the complex Health and Social Care system, with decisions in one setting having effects in the other: an open and constructive partnership between all stakeholders will be required to bring about change.

Ten years ago, a major outbreak of *Clostridium difficile* (a disease largely caused by antibiotics) resulted in a significant number of deaths in Northern Ireland.[12] A change in antibiotic prescribing practices was a major factor in ending the outbreak and in the wider decline in incidence of *C. difficile*.[13] We have been here before and succeeded in preventing harm by changing our prescribing behaviour.

This year, World Antibiotic Awareness Week runs from 13-19 November and European Antibiotic Awareness Day is Saturday 18 November. During this week, regional and local events will take place in Northern Ireland to raise public and professional awareness and to allow healthcare teams to share learning about changing prescribing practices. Details of events will be promoted through Health and Social Care organisations and social media. We will need doctors, nurses, pharmacists, allied healthcare, scientific staff and patients to champion the importance of antibiotic stewardship. Contact us by email if you want to get involved.

We have pledged to be Antibiotic Guardians. You can make a pledge too via http://www.antibioticguardian.com.

Declan Bradley (declan.bradley@hscni.net) and Lorraine Doherty, Guest Editors

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# ULSTER MEDICAL SOCIETY PROGRAMME 2017-2018

**President:** Ms Angela M Carragher MB BCh BAO (NUI) FRCS(Edin) MMed Sci (QUB) **Theme:** Aim Higher

## AUTUMN SEMESTER

| Date | Meeting | Speaker | Title | Location |
|---|---|---|---|---|
| **Thursday 5 October 2017** | **Presidential Address Associate Postgraduate Dean** | **Ms Angela Carragher** | **Aim Higher** | 8 pm North Lecture Theatre MBC G07NT |
| **Thursday 19 October 2017** | **Joint Meeting with NIMDTA & QUB. Research for Trainees - Opportunities, Presentations & Prizes** | **Prof Phil Kalra** Consultant Nephrologist, Chair of NIHR Renal Clinical Trials Network and Renal Association Academic Vice President | **"Reverse engineering" a clinical research career in the NHS** | 9 am – 4 pm Postgraduate Lecture Theatre BCH (Lunch 12 – 2 pm) |
| **Thursday 19 October 2017** | **Ulster Medical Society** | **Mrs Margaret Murphy** Chairperson World Health Organisation (WHO) | **Kevin's Story** | 8 pm North Lecture Theatre MBC GO7NT |
| **Thursday 2 November 2017** | **Joint Meeting with the Ulster Society for the History of Medicine** | **Prof John Duffy** Professor Emeritus | **Some Glimpses of Medieval Greek Medicine** | 8 pm Postgraduate Lecture Theatre BCH Harvard University |
| **Thursday 23 November 2017** | **Ulster Medical Society** | **Mary O'Rourke QC** Medical Lawyer | **Why do I defend doctors – Tales for a professional life doing so Defending Doctors** | 8 pm Postgraduate Lecture Theatre BCH |
| **Thursday 7 December 2017** | **The Robert Campbell Oration** | **Miss Sonia George** Consultant Ophthalmic Surgeon BHSCT | **Blind Sight – How children and adults with brain damage really see** | 8 pm Postgraduate Lecture Theatre BCH |

# Research for Trainees
# Opportunities, Presentations and Prizes

**Thursday 19 October 2017**
**Postgraduate Centre, Belfast City Hospital, Belfast HSC Trust**

| | | |
|---|---|---|
| 09.00 – 09.10 | **Registration** | |
| 09.10 - 09.20 | **Welcome** | **Professor Pascal McKeown, Head of Medical School, Queen's University Belfast (QUB)** |
| 09.20 – 09.35 | **Why do Research if you want to be a Clinician?** | **Dr Maurice O'Kane, Director, Northern Ireland Clinical Research Network** |
| 09.35 – 09.50 | **Why do research as a trainee and how it will be part of my career?** | **Dr Ronan Gray PhD Student (QUB) and Surgical Trainee (NIMDTA)** |
| 09.50 – 10.05 | **Research Opportunities in Medical Education** | **Dr Jenny Johnston, Academic General Practitioner, Centre for Medical Education, QUB** |
| 10.05 – 10.20 | **How can you combine Research and Clinical Work?** | **Dr Cecilia O'Kane, Senior Lecturer and Respiratory Physician, Centre for Experimental Medicine, QUB** |
| 10.20 – 10.35 | **Clinical Academic Pathways** | **Professor Peter Maxwell, Director, Clinical Academic Training Programme (QUB & NIMDTA)** |
| 10.35 – 10.50 | **How to obtain Funding to undertake research** | **Professor Ian Young, Chief Scientific Advisor DHSSPS, Director HSC Research and Development and Consultant Chemical Pathologist** |
| 10.50 – 11.10 | **Tea/Coffee and Networking** | |
| 11.10 – 12.00 | **Keynote Address:**<br>**"Reverse engineering" a clinical research career in the NHS** | **Professor Phil Kalra, Consultant Nephrologist, Chair of NIHR Renal Clinical Trials Network and Renal Association Academic Vice President** |
| 12.00 – 14.00 | **Lunch (Foyer)** | **DRAFT PROGRAMME FOR 2017** |
| 12.00 – 13.00 | **Meet the Researchers, Find out informally how to get research started and keep going (& Eat Lunch!)**<br><br>Opportunities to have brief interviews with QUB Research Centre investigators | **Centre for Cancer Research & Cell Biology**<br>Dr Gerry Hanna<br>**Centre for Medical Education**<br>Dr Gerry Gormley<br>**Centre for Experimental Medicine**<br>Professor Jose Bengoechea<br>**Centre for Public Health**<br>Professor Jayne Woodside |
| 13.00 - 14.00 | **Poster Judging & Eat Lunch** | **Case Reports & Case Series**<br>**Quality Improvement**<br>**Medical Education Research**<br>**Clinical Research**<br>**Basic Science Research**<br>**Dental Research** |
| 14.00 – 14.10 | **Welcome to Prize Presentations** | **Miss Angela Carragher**<br>**President, Ulster Medical Society** |
| 14.10 -15.40 | **Oral Presentations** | **Chair: Miss Angela Carragher**<br>**Judges; Dr John Craig; Professor Peter Maxwell; Professor Keith Gardiner** |
| 15.40 – 15.50 | **Award of Poster Presentation Prizes** | **Dr Michael McBride, Chief Medical Officer** |
| 15.50 – 16.00 | **Award of Oral Presentation Prize** | **Dr Michael McBride, Chief Medical Officer** |
| 16.00 – 16.10 | **Concluding Remarks** | **Dr Michael McBride, Chief Medical Officer** |

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*Grand Rounds*

# Understanding Acid-Base Disorders

Paul K. Hamilton[1], Neal A. Morgan[2], Grainne M. Connolly[3] and Alexander P. Maxwell[4]

Accepted: 8th January 2017
Provenance: externally peer-reviewed

*Case for consideration*

*A 25 year old mechanic is admitted in a very confused and drowsy state. His initial laboratory results are listed below. What diagnoses should be considered?*

| | *Reference Range* | | *Reference Range* |
|---|---|---|---|
| *pH 7.1* | *7.35-7.45* | *$Na^+$ 136 mmol/L* | *136-145* |
| *$PaO_2$ 13.4 kPa* | *11.0-14.0* | *$K^+$ 3.8 mmol/L* | *3.5-5.3* |
| *$PaCO_2$ 2.5 kPa* | *4.5-6.0* | *$Cl^-$ 95 mmol/L* | *95-108* |
| *Bicarbonate 5.3 mmol/L* | *22-29* | *Total $CO_2$ 6 mmol/L* | *22-29* |
| *Lactate 1.2 mmol/L* | *0.6-2.4* | *Urea 4.2 mmol/L* | *2.5-7.8* |
| *Ketones <1 mmol/L* | *Depends on context* | *Creatinine 92 µmol/L* | *40-110* |
| | | *eGFR >60 mL/min/1.73m²* | *>60* |

## INTRODUCTION

The accurate interpretation of laboratory tests in patients with acid-base disorders is critical for understanding pathophysiology, making a diagnosis, planning effective treatment and monitoring progress. This is an important topic particularly for junior medical staff who may encounter acid-base problems outside normal working hours when patients become acutely unwell. These clinical situations may be a source of confusion particularly because of the variety of terms used to describe and classify acid-base disorders. In this article, we aim to provide the reader with an overview of the key concepts necessary for developing a good working understanding of acid-base disorders that commonly present in clinical medicine. We start with some acid-base disorder definitions and then provide a series of case vignettes to illustrate the key points.

## DEFINITIONS

Acidaemia — An arterial pH below the normal range (pH<7.35).

Alkalaemia — An arterial pH above the normal range (pH>7.45).

Acidosis — A process lowering pH. This may be caused by a fall in serum bicarbonate and/or a rise in the partial pressure of carbon dioxide ($PaCO_2$).

Alkalosis — A process raising pH. This may be caused by a rise in serum bicarbonate and/or a fall in $PaCO_2$.

## ACID-BASE HOMEOSTASIS

Like temperature, blood pressure, osmolality and many other physiological parameters, the human body strives to keep its acid-base balance within tightly controlled limits. It is not the aim of this article to review in detail the physiology of acid-base homeostasis, but to provide a working knowledge of some key concepts that will help in the interpretation of results encountered commonly in clinical practice. More detailed free text reviews of acid-base homeostasis are available[1-5].

A buffer is a solution that resists a change in pH. There are many different buffer systems in the body, but the key one for understanding most acid-base disorders is the bicarbonate system present in the extracellular fluid. Like any buffer, this system comprises a weak acid (in this case carbonic acid, $H_2CO_3$) and its conjugate base (the bicarbonate ion, $HCO_3^-$), which exist in a dynamic equilibrium as shown in Equation 1[6]:

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$$

*Equation 1*

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The acidity of a solution is governed by the concentration of hydrogen ions ($H^+$) present. If a disease process results in an increase in the concentration of hydrogen ions, one would expect the body to become more acidic. However, the bicarbonate buffer system resists this change because the excess of hydrogen ions drives the reaction in Equation 1 to the right: hydrogen ions react with and "consume" bicarbonate ions and any change in acidity is minimised. This process requires an adequate supply of bicarbonate ions. The kidneys are vital organs in acid-base balance as they can both generate "new" bicarbonate buffer and reclaim filtered bicarbonate in the proximal tubules (Figure 1).

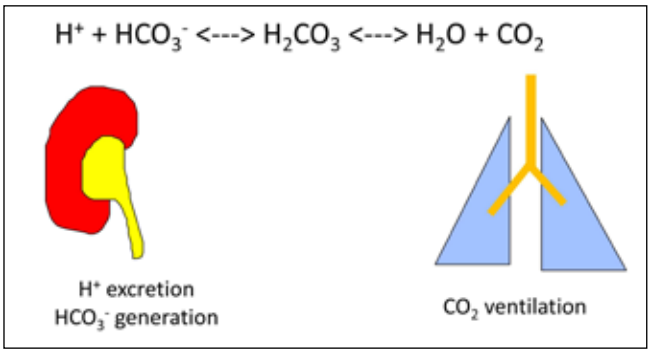



**Fig 1.** Acid-base balance is maintained by effective renal and respiratory homeostatic mechanisms

By rearranging and simplifying the above acid-base reaction, it is possible to derive the useful relationship shown in Equation 2:

$$H^+ \text{ is proportional to } \frac{PaCO_2}{HCO_3^-}$$

*Equation 2*

Equation 2 helps to illustrate how the body's hydrogen ion concentration can be regulated by altering the ratio of $CO_2$ to bicarbonate. Ventilation controls the $PaCO_2$ level and the kidneys regulate the bicarbonate level (Figure 1).

This makes it easy to see that the concentration of hydrogen ions increases in two settings: an increase in $PaCO_2$ or a reduction in plasma bicarbonate. One of the functions of ventilation is the elimination of $CO_2$ during exhalation. If a patient is tachypnoeic, they will tend to lose $CO_2$, while patients with a reduced respiratory drive will retain $CO_2$. An increased concentration of hydrogen ions (an acidosis) stimulates the respiratory centre to increase the rate of breathing (exhaling more $CO_2$). This mechanism is another key physiological response that helps to maintain acid-base balance.

Acid-base disorders are broadly classified into problems involving metabolic and/or respiratory processes. Metabolic processes primarily direct change in the level of bicarbonate and respiratory processes primarily direct changes in $PaCO_2$ (Figure 2).

The body adapts, or compensates where there is an acid-base disturbance in an attempt to maintain homeostasis[7].

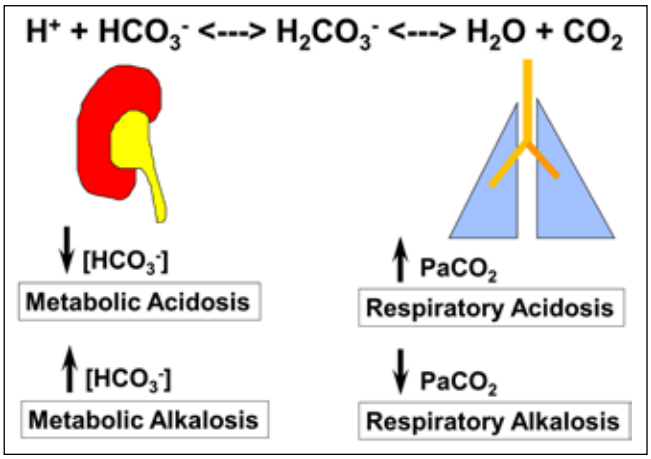



**Fig 2.** Changes in $PaCO_2$ level and bicarbonate concentration [$HCO_3^-$] can help identify the nature of the acid-base disorder.

If the primary acid-base problem is metabolic, then the compensatory mechanism is respiratory. The respiratory rate is altered, usually within minutes, in an attempt to keep the hydrogen ion concentration normal. If the primary acid-base problem is respiratory, then the kidneys adapt to counteract the change by altering their handling of hydrogen ions. This process in the kidneys usually takes place over several days.

## CAUSES OF ACID-BASE DISORDERS

Acid-base disorders are classified according to whether there is acidosis or alkalosis present (see pH section for details), and whether the primary problem is metabolic or respiratory (Figure 2). Bear in mind that there may be more than one problem occurring simultaneously and that the body may be compensating for the derangement. Table 1 outlines, with some clinical examples, acid-base disorders that are commonly encountered.

TABLE 1

*Definitions and main causes of acid-base disorders*

| | |
|---|---|
| Metabolic acidosis | Process that primarily reduces bicarbonate:<br>Excessive $H^+$ formation e.g. lactic acidosis, ketoacidosis<br>Reduced $H^+$ excretion e.g. renal failure<br>Excessive $HCO_3^-$ loss e.g. diarrhoea |
| Metabolic alkalosis | Process that primarily raises bicarbonate:<br>Extracellular fluid volume loss e.g. due to vomiting or diuretics<br>Excessive potassium loss with subsequent hyperaldosteronism |
| Respiratory acidosis | Process that primarily causes elevation in $PaCO_2$:<br>Reduced effective ventilation e.g. many chronic respiratory diseases or drugs depressing the respiratory centre |
| Respiratory alkalosis | Process that primarily causes reduction in $PaCO_2$:<br>Increased ventilation e.g. in response to hypoxia or secondary to a metabolic acidosis |

Remember, metabolic processes primarily direct changes in bicarbonate and respiratory processes primarily direct changes in $PaCO_2$ (Figure 2).

## MEASURED AND DERIVED INDICES

Some potentially confusing terminology is often used when discussing acid-base disorders. These terms include $PaCO_2$,

total bicarbonate, total $CO_2$, standard bicarbonate and base excess [8]. It is useful to know what these terms mean and how they are derived. Most blood gas analysis is carried out on point-of-care blood gas analysers, and these generally only measure two substances when it comes to acid-base reports: hydrogen ions (from which pH is calculated – see below) and $PaCO_2$. The 'bicarbonate' results that are given from such analysers are generally calculated using Equation 2.

Most laboratories measure total $CO_2$ concentration as part of the standard electrolyte profile. The reason behind this is that it is technically difficult to measure bicarbonate ions in isolation, but relatively straightforward to measure total $CO_2$. Total $CO_2$ represents the total amount of bicarbonate ions, dissolved $CO_2$ and other $CO_2$-containing substances in a solution. Since bicarbonate normally constitutes the majority of this, total $CO_2$ is normally used as a convenient surrogate measure of bicarbonate. The total $CO_2$ on the electrolyte profile may provide the first clue to the presence of an acid-base disturbance in a patient and should not be overlooked when reviewing electrolyte results. One cannot, however, diagnose acid-base disturbances from an isolated total $CO_2$ measurement. In order to characterise an acid-base disturbance, measures of pH, $PaCO_2$, total $CO_2$ or bicarbonate are required, as well as measurement of the anion gap.

Standard bicarbonate is a calculated index that attempts to provide information on what the bicarbonate concentration would be if the respiratory components of the disorder were eliminated. Base excess is another calculated index which will be elevated in the setting of metabolic alkalosis and reduced in metabolic acidosis. We will not consider the use of these calculated indices further in this article.

## UNDERSTANDING ACID-BASE DISORDERS – A FOUR STEP APPROACH

In order to understand the nature of an acid-base problem, we recommend a structured approach during which the following four questions should be asked.

### *Question 1: What is the pH?*

The first step in interpreting an acid-base problem is to look at the pH (or $[H^+]$) and decide if you are dealing with acidosis, alkalosis or normality. The concept of pH as a measure of acidity will already be familiar. With most human enzymes favouring physiologically neutral conditions, acidaemia is deemed to be present when the pH is less than 7.35 and alkalaemia when the pH exceeds 7.45. It is becoming increasingly common to directly quote the concentration of hydrogen ions ($[H^+]$) present in a solution. pH and $[H^+]$ are directly related using Equation 3:

$$pH = -\log_{10} [H^+], \text{ where } [H^+] \text{ is in mol/L}$$

*Equation 3*

Thus, pH 6.8 corresponds to $1.6 \times 10^{-7}$ mol/L $[H^+]$, pH 7.4 to $4.0 \times 10^{-8}$ mol/L, and pH 7.6 to $2.5 \times 10^{-8}$ mol/L, i.e. pH falls as $[H^+]$ rises.

Because the body compensates for acid-base disorders, it is possible that a disorder might be present even if the pH is normal. It should also be borne in mind that the body never over-compensates.

### *Question 2: What is the bicarbonate?*

The second step in interpreting an acid-base disorder is to consider the bicarbonate concentration relative to the normal reference range (which will vary from laboratory to laboratory, but is typically in the range 22-29 mmol/L).

A reduced bicarbonate concentration could mean that the body's main buffer is being used up buffering excess acid (hydrogen ion) production e.g. in lactic acidosis or ketoacidosis. Alternatively the reduced bicarbonate concentration could indicate a problem related to loss of bicarbonate from the gastrointestinal tract e.g. diarrhoea or a kidney problem i.e. failure to generate new bicarbonate or reclaim bicarbonate filtered into the renal tubules. **A reduced bicarbonate concentration is a hallmark of metabolic acidosis.**

An increased bicarbonate concentration may indicate that there have been substantial losses of acidic fluid e.g. loss of gastric fluid from persistent vomiting or prolonged nasogastric aspiration. Alternatively an increased bicarbonate concentration may be a chronic adaptation by the kidney to high $PaCO_2$ levels in persons with chronic respiratory diseases associated with $CO_2$ retention (see Equation 1 where elevated $CO_2$ levels drives the equation to the left producing more bicarbonate). **An elevated bicarbonate concentration is a feature of metabolic alkalosis.**

### *Question 3: What is the $PaCO_2$?*

The third step in assessing an acid-base problem is to measure the $PaCO_2$. This is helpful in determining whether the respiratory system is responding normally to an acid load and reducing the $PaCO_2$ to compensate for an acidosis i.e. the primary acid-base disturbance is a metabolic acidosis and this is compensated by an increased respiratory rate resulting in a secondary respiratory alkalosis. **A decreased $PaCO_2$ is a feature of respiratory alkalosis.**

Alternatively, if there is a primary respiratory problem, e.g. respiratory failure associated with chronic obstructive pulmonary disease, the retained $CO_2$ results in an elevated $PaCO_2$ (and will drive Equation 1 to the left) and produce a respiratory acidosis. It is also possible to develop a respiratory acidosis if drugs, such as opiate analgesics, depress the respiratory centre resulting in a critical reduction in the rate of ventilation resulting in $CO_2$ retention. **An elevated $PaCO_2$ is a feature of respiratory acidosis.**

*One can see that by examining the pH, bicarbonate and $PaCO_2$ it is possible to deduce the nature of the primary acid-base disorder present and the compensatory response.*

### *Question 4: What is the anion gap?*

The final step in assessing an acid-base disorder is to calculate the anion gap. Bodily fluids are electrically neutral, meaning that the number of positive charges (cations) present equals the number of negative charges (anions). The most abundant anions are chloride and bicarbonate; numerous other anions are not routinely quantitated, for example proteins and sulphate ions. Sodium is by far the most abundant plasma cation; other cations present in much lower quantities include potassium, calcium and magnesium. If it were feasible to measure all charged substances in blood, it could be shown that the sum of the positively charged particles is exactly balanced by the number of those substances carrying negative charges. It is routine practice to measure only four charged particles: sodium, potassium, chloride and bicarbonate ions. As discussed earlier, total $CO_2$ on the electrolyte profile may be considered as a convenient surrogate measure of bicarbonate and can be used in the calculation of the anion gap. When the numbers of cations (sodium and potassium) are added, one will always find that they outnumber the anions (chloride and bicarbonate). This difference is what is meant by the term 'anion gap[9]' and reflects the unmeasured anions in Equation 4 or Equation 5. An anion gap may be low, normal or high, and can be conveniently calculated using Equation 4:

$$\text{Anion Gap} = [Na^+] + [K^+] - [Cl^-] + [HCO_3^-], \text{ where all concentrations are in mmol/L.}$$

*Equation 4*

Since the extracellular fluid potassium concentration is very much lower than the sodium, chloride or bicarbonate concentrations and because it can only vary by a few mmol/L, it is often ignored making the anion gap calculation simpler as shown in Equation 5:

$$\text{Anion gap} = [Na^+] - [Cl^-] + [HCO_3^-]$$

*Equation 5*

The reference interval (normal range) for anion gap varies from laboratory to laboratory, and is inherently imprecise because of the number of measurements required for its calculation. An anion gap greater than 20 mmol/L is always considered to be abnormally elevated and a gap of less than 10 mmol/L abnormally low. There is some debate in the literature about the significance of anion gaps in the range 10-20 mmol/L, but a pragmatic approach would be to actively seek out causes of a high anion gap in patients with gaps exceeding 14 mmol/L (or 18 mmol/L if potassium is included in the equation.

TABLE 2

*Causes of metabolic acidosis (common causes are in bold)*

| Normal anion gap | High anion gap |
|---|---|
| Gastrointestinal losses of bicarbonate | Renal failure |
| Renal tubular acidosis | Ketoacidosis |
| Treatment with carbonic anhydrase inhibitors | Lactic acidosis |
| Urinary diversion procedures | Salicylate poisoning |
| Excessive administration of 0.9% saline | Glycol ingestion (ethylene glycol, propylene glycol) |
| | Methanol ingestion |

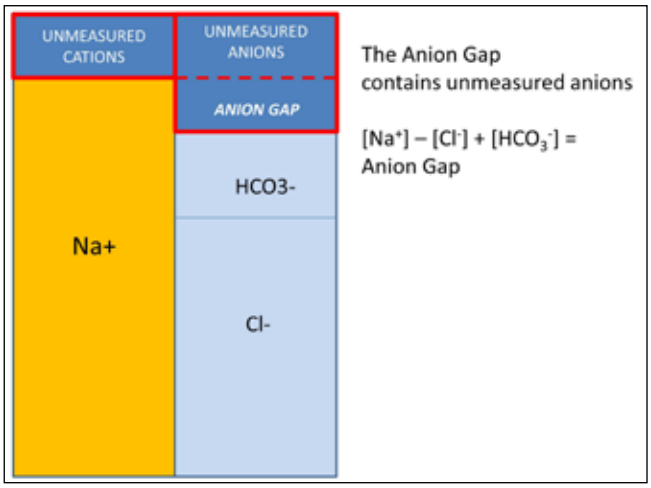
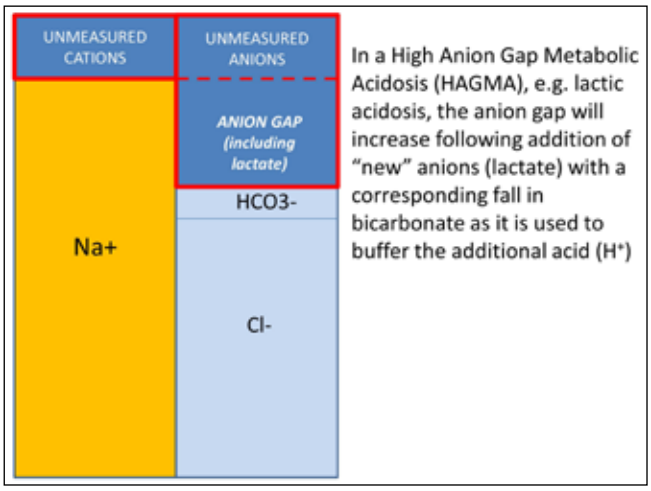



**Fig 3**

(a) Illustration of the "normal" anion gap




(b) High anion gap present in a metabolic acidosis

Consider the following normal electrolyte profile: $Na^+$ 136 mmol/L, $K^+$ 4.0 mmol/L, $Cl^-$ 100 mmol/L, $HCO_3^-$ (or total $CO_2$) 25 mmol/L. The anion gap is calculated as 140 – 100 – 25 = 11 mmol/L (or 15 mmol/L if potassium is included in the calculation). The Anion Gap is illustrated in Figure 3a.

TABLE 3

*Mnemonics for high anion gap metabolic acidosis*

| Mnemonic | Causes of a high anion gap metabolic acidosis |
|---|---|
| GOLD MARK | Glycols, Oxoproline, L-lactate, D-lactate, Methanol, Aspirin, Renal failure, and Ketoacidosis |
| KARMEL | Ketoacidosis, Aspirin, Renal Failure, Methanol, Ethylene Glycol, and Lactic Acidosis |
| MUDPILES | Methanol, Uraemia, Diabetes, Paraldehyde, Iron/Isoniazid, Lactate, Ethylene glycol and Salicylate |
| KUSMALE | Ketoacidosis, Uraemia, Salicylate, Methanol, Aldehyde, Lactate and Ethylene glycol |

Calculation of the anion gap is particularly useful in cases of metabolic acidosis since it can help in formulating a differential diagnosis[10]. There are two main categories of metabolic acidosis: high anion gap metabolic acidosis (HAGMA) and normal anion gap metabolic acidosis (NAGMA). A HAGMA is illustrated in Figure 3b. Common causes of HAGMA and NAGMA are detailed in Table 2.

Several mnemonics for common causes of HAGMA have been developed[11], and some of the more useful examples are included in Table 3.

From a clinical perspective, if a HAGMA is identified then the simplest approach to establishing a cause is to consider if the patient has one (or more) of the three common aetiologies (lactic acidosis, ketoacidosis or kidney failure)[12].

If these conditions are not present then the HAGMA may be linked to ingestion of a toxin e.g. methanol or ethylene glycol, or be due to the build-up of another acid such as 5-oxyproline (also known as pyroglutamic acid) which may accumulate with chronic paracetamol use in susceptible individuals[13].

As the laboratory tests for toxic alcohols are not rapidly available it can be useful in a patient with an unexplained HAGMA to assess the "osmolal gap"[14]. This "gap" is the difference between the calculated serum osmolality and the laboratory measurement of serum osmolality (from a U&E sample). The calculated osmolality can be simply derived by using Equation 6. A high osmolal gap suggests the presence of toxic alcohols such as methanol or ethylene glycol.

$$\text{Calculated osmolality (mmol/L)} = 2 \times [Na^+] + [\text{glucose}] + [\text{urea}]$$

*Equation 6*

Rarely, patients with short bowel syndrome or following bariatric surgery can develop severe D-lactic acidosis and an associated encephalopathy[15]. Unabsorbed carbohydrates act as a substrate for colonic bacteria to produce D-lactate. This will result in a high anion gap metabolic acidosis but the standard laboratory measured lactate (L-lactate) will be normal[15].

Calculated anion gaps that are low (below the reference interval) are uncommon. Causes include laboratory error or hypoalbuminaemia but rarely may be found in association with a paraproteinaemia or intoxication with lithium, bromide, or iodide[10].

## ILLUSTRATIVE CASES

### *Case 1*

An elderly man is admitted with septic shock. Shortly after admission, blood tests reveal the following:

pH 7.18, $PO_2$ 34.2 kPa, $PaCO_2$ 2.1 kPa, $HCO_3^-$ 7 mmol/L

$Na^+$ 138 mmol/L, $K^+$ 3.9 mmol/L, $Cl^-$ 95 mmol/L, Total $CO_2$ 8 mmol/L, Urea 8.2 mmol/L, Creatinine 102 µmol/L, eGFR >60 mL/min/1.73m$^2$

Question 1: What is the pH? The pH is low indicating an acidosis.

Question 2: What is the bicarbonate? Bicarbonate is low, indicating that the acidosis is metabolic in nature.

Question 3: What is the $PaCO_2$? The $PaCO_2$ is low, reflecting a respiratory alkalosis. The low level seen here is a reflection of the body's compensation in an attempt to correct the pH, i.e. a compensatory respiratory alkalosis is present.

Question 4: What is the anion gap? The anion gap is high, indicating HAGMA.

The most likely cause for this acid-base disorder is lactic acidosis due to poor tissue perfusion as a result of septic shock.

### *Case 2*

A woman is being treated for congestive cardiac failure on the coronary care unit. After several days of treatment, the following results are returned:

pH 7.49, $PO_2$ 11.6 kPa, $PaCO_2$ 5.8 kPa, $HCO_3^-$ 42 mmol/L

$Na^+$ 142 mmol/L, $K^+$ 3.0 mmol/L, $Cl^-$ 85 mmol/L, Total $CO_2$ 44 mmol/L, Urea 9.3 mmol/L, Creatinine 84 µmol/L, eGFR >60 mL/min/1.73m$^2$

Question 1: What is the pH? The pH is high indicating an alkalosis.

Question 2: What is the bicarbonate? Bicarbonate is high, in keeping with a metabolic alkalosis

Question 3: What is the $PaCO_2$? The result towards the higher end of the reference range reflects a degree of respiratory compensation for the metabolic alkalosis.

Question 4: What is the anion gap? The anion gap is 13 mmol/L which is normal.

The most likely cause for this acid-base abnormality is extracellular fluid volume loss and hypokalaemia due to treatment with diuretics.

### *Case 3*

An elderly woman with chronic obstructive pulmonary disease (COPD) is admitted with increasing confusion. Shortly after admission, blood tests reveal the following:

pH 7.21, $PO_2$ 8.2 kPa, $PaCO_2$ 11.1 kPa, $HCO_3^-$ 35 mmol/L

$Na^+$ 140 mmol/L, $K^+$ 4.7 mmol/L, $Cl^-$ 94 mmol/L, Total $CO_2$ 34 mmol/L, Urea 8.2 mmol/L, Creatinine 66 µmol/L, eGFR >60 mL/min/1.73m$^2$

Question 1: What is the pH? The pH is low indicating an acidosis.

Question 2: What is the bicarbonate? Bicarbonate is high, indicating that a metabolic alkalosis is present. The pH is low so the primary problem is an acidosis and is likely to be respiratory in nature.

Question 3: What is the $PaCO_2$? The $PaCO_2$ is very high and indicates a respiratory acidosis is present. The very high $PaCO_2$ level seen here is typical of a person with respiratory disease that results in retention of $CO_2$ i.e. the primary clinical problem is respiratory failure due to COPD.

Question 4: What is the anion gap? The calculated anion gap is 12 mmol/L i.e. normal.

The most likely cause for this acid-base abnormality is an acute exacerbation of COPD.

***Case 4***

An elderly man developed profuse diarrhoea following antibiotic treatment of a chest infection. He is thirsty and light headed. Shortly after admission, blood tests reveal the following:

pH 7.25, $PO_2$ 13.2 kPa, $PaCO_2$ 4.2 kPa, $HCO_3^-$ 17 mmol/L

$Na^+$ 134 mmol/L, $K^+$ 3.4 mmol/L, $Cl^-$ 104 mmol/L, Total $CO_2$ 18 mmol/L, Urea 9.3 mmol/L, Creatinine 102 µmol/L, eGFR >60 mL/min/1.73m$^2$

Question 1: What is the pH? The pH is low indicating an acidosis.

Question 2: What is the bicarbonate? Bicarbonate is low, indicating that a metabolic acidosis is present.

Question 3: What is the $PaCO_2$? The $PaCO_2$ level is just below the lower end of the normal range indicating a respiratory alkalosis is present. The pH is low so the primary problem is an acidosis (metabolic acidosis). The respiratory alkalosis therefore represents partial compensation of the metabolic acidosis.

Question 4: What is the anion gap? The anion gap is 12 mmol/L, indicating that this is a normal anion gap metabolic acidosis.

The most likely cause for this acid-base disorder is bicarbonate loss from the gastrointestinal tract due to diarrhoea.

Returning to our initial case…

Applying the four question approach to this case, it should now be apparent that the patient has a high anion gap metabolic acidosis with respiratory compensation. The common causes for this presentation can be quickly eliminated since his renal function is normal, and lactate and ketone levels are not elevated. A more unusual explanation for the presentation should be sought (see Table 2). In this case, the patient was subsequently found to have ingested 500 mL of screenwash containing ethylene glycol (antifreeze) in an attempt to end his life.

Prompt recognition of the likely cause of this patient's high anion gap metabolic acidosis helps inform further investigation and management. This would include quantitation of ethanol and toxic alcohol concentrations to confirm the type of ingested poison. Ethylene glycol and methanol are metabolised by alcohol dehydrogenase to very toxic metabolites. If this diagnosis seems likely it is important to urgently seek senior help. Fomepizole is an alcohol dehydrogenase inhibitor which is easy to administer and prevents metabolism of these alcohols to their toxic metabolites. Haemodialysis will rapidly clear ethylene glycol, methanol and their metabolites and should be started if the patient is severely acidaemic or has evidence of end organ damage e.g. renal failure or visual loss.

## CONCLUSION

Acid-base disorders are commonly encountered in clinical practice and a structured approach to assessment includes taking a history, performing a physical examination and careful interpretation of routine biochemical tests and arterial blood gas analysis. Additional investigations such as lactate, glucose, ketones or toxicology testing may be needed to more fully characterise a metabolic acidosis.

Answering four questions will help determine the problems present in the clinical scenario: What is the pH? What is the bicarbonate? What is the $PaCO_2$? What is the anion gap? Using this approach will help guide further investigations and management of the patient.

There are no conflicts of interest.

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*Ulster Med J* 2017;**86(3):**167-171

*Clinical Paper*

# Vaginal Hysterectomy using the ERBE BiClamp® Bipolar Vessel Sealing System: A Case Series

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Accepted: 17th December 2016
Provenance: externally peer-reviewed

**Abstract:** The ERBE BiClamp® BVSS appears to be a safe and effective method of vaginal hysterectomy in this small single surgeon, single institution study; demonstrating efficient operative times, minimal blood loss and intraoperative morbidity with acceptable surgical outcomes. Its use contributes to the advancement of minimally invasive gynaecology and should be encouraged.

## INTRODUCTION

Approximately 50,000 hysterectomies are performed annually in the UK[1]. With fewer complications and a quicker recovery, the vaginal route is preferred over its abdominal counterpart[2]. This is endorsed in the National Institute of Clinical Excellence (NICE) guidelines on heavy menstrual bleeding and a 34-study Cochrane review[2,3]. The American Association of Gynecologic Laparoscopists (AAGL) highlight that hysterectomy for benign uterine disease should be performed either vaginally or laparoscopically[4]. This affirms the American College of Obstetricians and Gynaecologists' (ACOG) statement that the vaginal approach should be primary whenever feasible due to better patient outcomes and fewer complications than laparoscopic or abdominal surgery[5]. AAGL have recently launched an online master course in vaginal hysterectomy (VH) to support this[6].

VH yields a speedier return to normal activity, fewer febrile episodes, shorter hospital admission, shorter operative time and less blood loss[4,7]. Despite this, there is a reluctance towards VH due to the challenging surgical technique with limited access to deep vascular pedicles making haemostasis and suture ligation potentially problematic[8]. Bipolar vessel sealing systems (BVSS) are proven to be safe and efficacious with possible advantages over conventional methods, namely less post-operative pain, reduced blood loss, shorter operative time and hospital stay[9-16].

The ERBE BiClamp® BVSS are insulated forceps with an automatic coagulation completion. The technique has similar anatomical principles to conventional methods, shortening the learning curve. It requires only two instruments; easing access and reducing trauma risk. Initial studies into VH using BiClamp® suggest that patients experience less post-operative pain and shorter operative duration[17]. Coagulation effects on innervation of the surgical field and the need for less downward traction on the uterus may explain improved post-operative pain tolerance[15]. These effects also prevent "back-bleeding", ensuring better haemostasis and reducing surgical field visual impairment. We investigated the use of ERBE BiClamp® BVSS in VH in terms of safety and efficacy with possible advantages over conventional suture ligation, namely less post-operative pain, reduced blood loss, shorter operative time and hospital stay.

## MATERIALS AND METHODS

The setting was a major district general hospital in Northern Ireland where a single surgeon began using the ERBE BiClamp® BVSS for VH in 2006, following a period of training with a recognised expert, Dr Henri Clavé in Nice, France.

We conducted a retrospective case review of all VH performed using the ERBE BiClamp® BVSS over a 7-year period (September 2006 – May 2014). Exclusion criteria were: VH performed by other surgeons within the same time period or using conventional suture ligation.

### *Details of surgical technique and device*

The technique is a variation of the classical form of VH using electro-surgery via the ERBE Vio® generator and the Bi-Clamp® forceps to achieve haemostasis. Following circumferential cervical incision, the anterior and posterior pouches are carefully opened to gain access to the peritoneal cavity. The Bi-Clamp® forceps are then used to sacrifice the pelvic floor ligamentous support and the uterine vascular pedicles before being transected with curved mayo scissors.

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The salient part of the operation is the amputation of the cervix after coagulation of the uterine arteries allowing uterine rotation, not traction. This is imperative in haemostasis and negates the need for uterine prolapse. Vaginal bilateral salphingoophrectomy (BSO) is also possible. The vaginal vault is closed with a continuous dissolvable suture with an effort to incorporate the anterior and posterior leaves of the pelvic parietal peritoneum.

*Outcome measures*

Data collected included patient demographics, type of procedure and indication, including additional vaginal or laparoscopic BSO or pelvic floor repair (PFR).

Primary outcome measures included:

- Operating time: from knife to skin until closure of the vaginal vault.
- Peri-operative blood loss: determined by haemoglobin (Hb) drop between pre-operative and post-operative values (g/dL).
- Complication rate: Intraoperative, short-term, within 2 post-operative weeks and long-term complications, indicated through outpatient review and re-referral patterns.
- Post-operative analgesia requirements: determined by analgesia consumption during post-operative hospital admission, as an average dose per day.
- Length of hospital stay: in post-operative days.

## RESULTS

A total of 200 patients were included over a 7 year period. (See Figure 1)

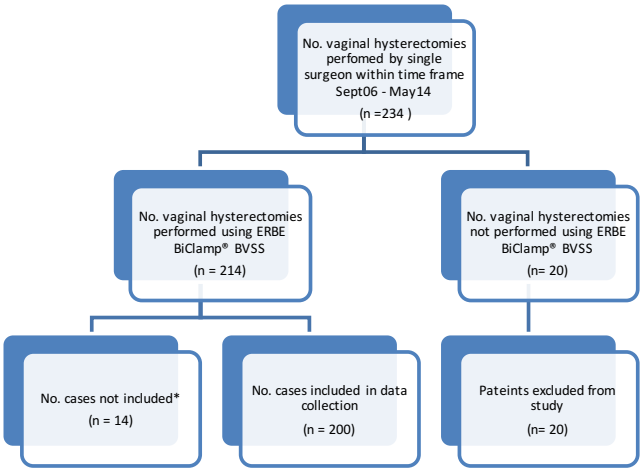


*Fig 1.* Formation of the study cohort
**Cases not included due to notes being unobtainable.*

Median age was 51 years (range: 24–83). Median Body Mass Index (BMI) was 28.5kg/m$^2$ (Interquartile range (IQR) 9.75), based upon 60.5% of patients as this was unobtainable in the remainder. BMI was greater than 35kg/m$^2$ in 23% of patients. Regional anaesthesia only was used in 4% of cases.

Median parity was 2 (IQR 2) with 19.5% of patients being nulliparous. Obstetric history was known in 70% of patients, of whom 7% had caesarean sections. Data on previous surgery was available in 70% of patients. Of these, 50% had had no previous pelvic surgery, with the commonest previous surgery being laparoscopic sterilization (11.5%). 5% of patients had underwent a previous laparotomy. Indications for VH are detailed in Table 1. VH alone occurred in 56% of patients with 44% having additional procedures; laparoscopic BSO (28.5%), vaginal BSO (13.5%), PFR (2%). Laparoscopic BSO was only conducted if vaginal BSO was unsuccessful or not feasible.

TABLE 1:

*Indications for surgery*

| **Indication for surgery** | % of patients |
|---|---|
| **Benign** | |
| Menorrhagia/failed conservative management | 23.9 |
| Cervical intra-epithelial neoplasia (CIN) | 11.7 |
| Endometriosis / Chronic Pelvic Pain | 7.8 |
| Uterovaginal Prolapse | 6.3 |
| Endometrial Hyperplasia | 4.8 |
| Other benign indications | 3.4 |
| **Malignant** | |
| Endometrial carcinoma | 36.5 |
| Cervical Carcinoma | 5.3 |

**Other indications for surgery included prophylactic (HNPCC/BRCA carrier or family history of carcinoma), 12 week sized fibroid, previous vulval angiomyxoma.*

*Operating time*

Median operating time for VH (+/- BSO or PFR) was 47 minutes (IQR 9, Mean 49.72+/-15.07, 95% CI 47.21-52.23). 83% of VH alone were <60 minutes. Median operating time for VH and Laparoscopic BSO was 75 minutes (IQR 27, Mean 75.65+/-20.31, 95% CI 70.16–80.14). 64% of all operations were <60 minutes. Operating time was not recorded in 2% of cases.

*Peri-operative blood loss*

Median Hb drop was 1.2g/dL (IQR 0.9, Mean 1.128+/-0.833, 95% CI 0.952–1.305), based upon 44% of patients as 48.5% did not have a post-operative Hb measurement and in 7.5% results were unobtainable.

*Complications*

93% of cases had no major intraoperative complications. The commonest complication was bladder injury (2.5%), but this wasn't associated with long term sequelae. In 2 cases, this was not due the BiClamp® forceps and occurred during dissection of the anterior fornix. There were no incidents of

bowel injury, labial or vaginal burns. Additional haemostatic sutures to pedicles were required in 4.5% of operations. Abdominal/laparoscopic conversion rate was 2%, due to bleeding with no subsequent long term complications. 2% of patients underwent conversion to laparotomy, all of whom had a BMI >35kg/m$^2$. Indications for conversion to laparotomy included bleeding (1.5%) and poor laparoscopic views (0.5%). In one case, ureteric injury resulted in anuria and acute nephropathy due to bilateral distal ureteric kinking with partial obstruction, secondary to vaginal vault closure. This necessitated ureteric stenting (which was removed six months following surgery) and bilateral nephrostomies. After follow-up, the patient was discharged with no long term complications. An American Society of Anaesthesiologists (ASA) physical status classification of >1 occurred in 65% of patients (of the 70% in which ASA was recorded), highlighting the extent of co-morbidity within our population. Consequently, in this high-risk group, anaesthetic problems, namely atrial fibrillation, asystole, which recovered, and chest pain occurred in 1.5% of cases.

Return to theatre occurred in 2.5%, indications being; bleeding, haematoma evacuation and ureteric injury. Vault haematoma occurred in 2.5% of patients with 1% returning to theatre. Two patients required transfusion of packed red blood cells, in accordance with UK Blood Transfusion Advisory Committee Guidelines[18]. Both patients returned to theatre on the first post-operative day due to bleeding. Urinary retention requiring an indwelling catheter on hospital discharge occurred in 2% of patients, none of whom experienced voiding dysfunction beyond 2 post-operative weeks. Direct microscopy-confirmed urinary tract infection (UTI) rate was 4%. Hospital readmission occurred in 2% of patients, indications being urosepsis, vault haematoma, post-operative ileus, and constipation. There were no recorded cases of venous thromboembolism or death related to surgery.

Long term follow up was conducted through telephone calls, outpatient review or re-referral and involved physical examination if warranted. 4% of patients were lost to follow up and duration ranged from 6 months-5 years. There were no long-term complications reported in 97% of cases. Prolapse requiring further surgery occurred in 1% of cases and persistent pelvic pain in 2% of cases, 50% of which pelvic pain and endometriosis were the initial indication for surgery.

*Post-operative analgesia requirements*

Simple analgesia was required by 76.5% of patients (Paracetamol, Codeine Phosphate or Non-steroidal anti-inflammatories). The average number of doses per day of Paracetamol (1g) or Codeine Phosphate (60mg) was 2.58 and of non-steroidal anti-inflammatory drugs (Sodium Diclofenac 75mg) was 0.8. 2.5% of patients received Tramadol and one patient received hyoscine butylbromide.

Opioid analgesia consumption occurred in 23.5% of patients, at an average of 0.98 doses per day (range 0.14–3.75) (1 dose = 5mg Morphine Sulphate). A patient-controlled analgesia system was used by 2% of patients, 75% of whom underwent conversion to laparotomy returned to theatre.

*Length of hospital stay*

37% of patients were discharged on the first post-operative day and 89% were discharged within 3 days. Median length of stay was 2 days (IQR 2, Mean 2.13+/-1.34, 95% CI 1.94–2.32). 79.5% of patients were admitted the night before surgery, to ensure bed availability, however length of hospital stay was measured in post-operative days. 10.5% of patients were admitted on the day of surgery and discharged on the first post-operative day.

## DISCUSSION

This retrospective case review suggests that ERBE BiClamp® BVSS is a safe and effective alternative to its conventional counterpart in VH. Intraoperative morbidity was minimal, 83% of VH alone were less than 60 minutes, median haemoglobin drop was 1.2g/dL, post-operative stay was 2 days and 76.5% of patients required simple analgesia only. The commonest intraoperative complication was bladder injury (2.5%), resulting in no long-term morbidity. Bleeding requiring laparotomy/laparoscopy and conversion to laparotomy both occurred in 2% of patients. UTI was the commonest short-term complication (4%). 97% of patients reported no long term complications.

This study of BiClamp® BVSS is, to our knowledge, the largest conducted by a single surgeon, in a single institution. We note an improvement in operator performance with time, with only one intraoperative complication (conversion to laparotomy due to bleeding and difficult access in a patient with a BMI of 47kg/m$^2$) occurring in the last 16 months of data collection. One strength of our study is that high BMI wasn't an exclusion criterion, with 23% of patients having a known BMI >35kg/m$^2$. Intraoperative complication rate in patients with BMI <35kg/m$^2$ compared to BMI >35kg/m$^2$ was 5.4% and 11% respectively. This result is limited as BMI data was obtained for only 60.5% of the cohort. Caesarean section also wasn't a contra-indication, with 7% of patients having had at least one previous caesarean. This did not increase the intraoperative complication rate.

Our study was a retrospective, single surgeon, single institution study so it is difficult to know how this will translate into wider clinical practice. Data collection was based on review of medical records and may not have been complete. Peri-operative blood loss data, for example, was based upon 44% of the cohort, mainly because post-operative Hb measurements are not routine. In our institution, intraoperative surgical protocol dictates that all patients have a pre-operative Hb measurement. If this is low or estimated blood loss is significant, a post-operative Hb is measured. Prospective data collection would allow blood loss estimation through counting and weighing of surgical swabs. Furthermore, weight and size of uterine specimens was unobtainable. Secondly, post-operative pain was determined by analgesia consumption, however prospective

data collection may have permitted the use of pain intensity scores. Thirdly, as a control group was not included, this study is not a direct comparison to conventional methods of VH. A prospective randomised control trial (RCT) however, would allow for direct comparison. Our results have therefore, been compared with other published evidence, as detailed below.

A recent meta-analysis, incorporating eight RCTs, on electrosurgical bipolar vessel sealing (EBVS) for VH included 772 patients, with 2 studies, pooling 118 cases, reporting BiClamp® usage[19-21]. Main outcomes included operative duration, intraoperative blood loss, complication rate and hospital stay[19]. We report similar results to those outlined. A shorter operating time with EBVS over suture ligation is reported by all studies. Estimated blood loss in our study wasn't comparable as blood loss wasn't calculated in millilitres, however Pergialiotis et al. conclude that the mean difference in blood loss between EBVS and suture ligation was statistically significant ($p<0.001$)[19]. Ghirardini et al. report similar findings to our results with ΔHb of 1.4g/dl in their 500-case BiClamp® VH study[22]. They also present similar results regarding surgery duration (mean 48.9 minutes) and hospital stay (mean 3.2 days)[22]

We report an intraoperative complication rate of 3% (6/200) which, whilst not statistically significant, is less than conventional suture ligation (OR = 0.5216 (95% CI – 0.1987-1.3693) p= 0.1863 Z= 1.322) and better than the meta-analysis EBVS / suture ligation comparison (OR = 0.9560 (95% CI – 0.452-2.0222) p= 0.9063 Z= 0.118). (See Figure 2)[19] 19Similar findings are noted in the individual intra-operative complication rates with our data approaching statistical significance and displaying better P values than the EBVS/suture ligation comparison. (See Figure 3) Specifically, our rate is lower than the BiClamp® VH subgroup (3.3%, 1/30) and is over six times the size[20]. We report no labial burns and one case of ureteric injury, a complication not recorded in the meta-analysis.

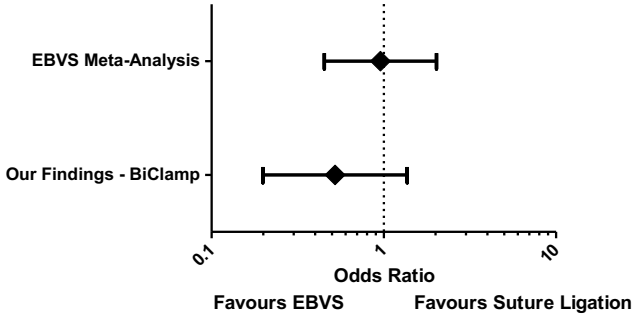


*Fig 2*. Intraoperative complications forest plot: our findings in comparison to the meta-analysis. (Data from Pergialiotis et al. 2014)[20]

A19 2% major post-operative complication rate, which is lower than the meta-analysis suture ligation is close to statistical significance (OR = 0.3697 (95% CI – 0.1226-1.1151) p= 0.0773 Z= 1.767. This is again less than both EBVS and suture ligation (OR = 0.5863 (95% CI – 0.2643-1.3009) p= 0.1892 Z= 1.313). (See Figures 4 and 5)

Pergialiotis et al. conclude that EBVS systems, in comparison to traditional suture ligation, lead to a statistically significant decrease in intraoperative blood loss but don't shorten operative duration or influence complication rate[19]. It is however, important to note that interpretation is limited by small numbers of BiClamp® VH.

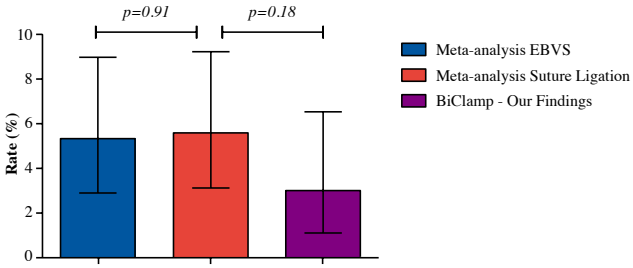


*Fig 3*. Intraoperative complication rates of each group in comparison (Data from Pergialiotis et al. 2014)20 EBVS: 5.364 (2.933-9) Suture Ligation: 5.597 (3.133-9.231) BiClamp: 3 (1.101-6.53) EBVS v Suture p= 0.91 BiClamp vs Suture p= 0.18

We conclude that VH using BiClamp® does not compromise patient safety. Safe surgical technique is paramount, particularly in electro surgery, and can be promoted through training. The technique closely mimics classical VH, making the learning curve achievable. It is a safe, effective, easier alternative to conventional suture ligation; particularly in the absence of uterine descent or a narrow vaginal introitus. Notably, 19.5% of our patients were nulliparous and BMI was >35kg/m$^2$ in 23%. The Northern Ireland population is very stable and highly amenable to follow up, facilitating close monitoring for long-term complications for up to seven years.

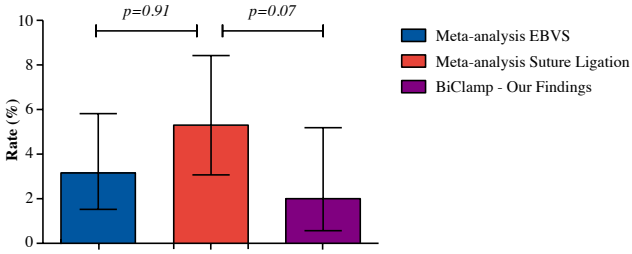


*Fig 4*. Major post-operative complications each group in comparison. (Data from Pergialiotis et al. 2014)20 EBVS: 3.135 (1.503-5.765) Suture: 5.231 (3.047-8.375) BiClamp: 2 (0.545-5.14) EBVS v Suture Sup= 0.19 BiClamp vs Suture p= 0.07

## CONCLUSION

This study, to our knowledge, is the largest conducted in a single institution by a single surgeon. It suggests that ERBE BiClamp® BVSS as a safe, effective alternative to conventional suture ligation in VH, compared with previously published outcomes. The technique affords quicker operative times, less blood loss, minimal intraoperative morbidity and acceptable surgical outcomes. The reduced post-operative pain observed confers more rapid mobilisation and improved recovery. A prospective RCT would be recommended.

Modern medical practice demands clinicians to consider minimally invasive surgical options which are, at the very

least, equal to their conventional counterparts. Our results suggest BiClamp® can achieve this. The procedure closely mimics the classical performance of VH, reducing the learning curve in mastering the technique and allowing the general gynaecologist to perform VH with improved ease and safety. BiClamp® BVSS appears to be an ideal platform to allow the replacement of the trans-abdominal route of hysterectomy with the preferred minimally invasive vaginal approach.

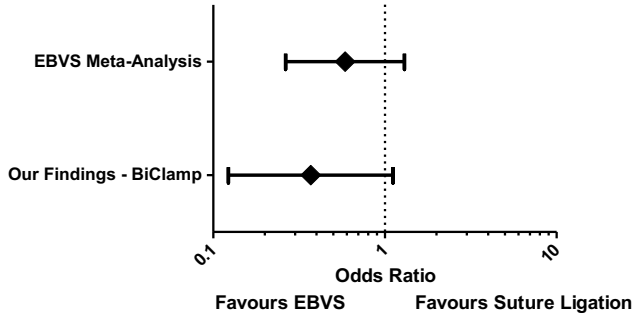


*Fig 5*. Major post-operative forest plot: our findings in comparison to the meta-analysis. (Data from Pergialiotis et al. 2014)[20]

## ACKNOWLEDGEMENTS

We thank Dr Henri Clavé, Clinique St. George, Nice, France, for his expert knowledge and Mr Steve Veck, Eurosurgical Ltd, for his technical support and advice regarding electrosurgery.

Disclosure of Interests, Funding and Contribution to Authorship: We disclose no interests and no funding was obtained. The authors are solely responsible for this paper. GVB, LH and DQ collected the data. GVB and JPB conducted data analysis and the write up. GJD, DQ and JPB participated in the surgery and GJD was the supervising consultant and lead surgeon or surgeon directly supervising trainees.

Ethical Approval: As this project was solely an audit of intra- and post-operative outcomes for the purposes of service evaluation it was not deemed necessary to submit to the Regional Ethics Committee for approval.

Statistics: Statistics analysis was completed using MedCalc Statistical Software version 16.8.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016) and the graphs was devised using GraphPad Prism v5.00 www.graphpad.com GraphPad Software INC. CA, USA.

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*Ulster Med J* 2017;**86(3):**172-176

*Clinical Paper*

# The Effect of Interval From Completion of Short-Course Radiotherapy to Surgery on the Post-Operative Morbidity and Mortality of Patients with Rectal Cancer.

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Accepted: 6th November 2016
Provenance: externally peer-reviewed.

## ABSTRACT

**Aim:** Surgery is the mainstay of treatment for invasive rectal cancer. Advances in surgical technique and radiotherapy over the past few decades have resulted in improved local control and survival.[1-3] Some concern remains regarding the morbidity associated with performing surgery within a short window following radiotherapy. The current study assessed whether the interval between short-course radiotherapy and surgery influences all cause post-operative morbidity and mortality.

Methods: All patients who had undergone short-course radiotherapy for rectal cancer within the Belfast Health and Social Care Trust from 2005 to 2014 held on a prospective database were included (n=102). A retrospective review of patients' clinical records was performed and a comparison made of patients who had undergone surgery less than 4 days with those 4 or more days following completion of radiotherapy. Baseline patient and tumour characteristics, post-operative complications and readmission rates were compared. Statistical analysis was performed using SPSS ®, Version 22 (SPSS, Inc, Chicago, Illinois, USA).

**Results:** There was no significant difference in mortality or overall post-operative complications between groups, however, less serious complications were reduced in patients undergoing surgery less than 4 days following radiotherapy. Perineal wound complications were significantly more common in patients who had undergone surgery 4 or more days following radiotherapy.

Conclusion: Our results support the existing data that post-operative complications may be more common with increasing interval to surgery from completion of radiotherapy. Perineal wound morbidity appears significantly more common in patients who undergo surgery 4 or more days following short-course radiotherapy. A larger study to look particularly at perineal wound morbidity and interval from completion of radiotherapy is warranted.

## INTRODUCTION

The two major developments in the treatment of rectal cancer have been the introduction of total mesorectal excision (TME) and the use of radiotherapy which improved local control and overall survival.[1,4] Prior to TME and radiotherapy, local recurrence was reported in 15-45% of patients with rectal cancers.[5-7] Since the widespread establishment of TME as the gold standard operative technique for rectal cancer, local recurrence rates have dropped to 5-10%.[8,9]

Even before the establishment of TME, preoperative radiotherapy has been shown to reduce local pelvic recurrence and improve survival in the Stockholm I and II trials.[10,11] Results from the Swedish Rectal Cancer Trial then demonstrated that short-course pre-operative radiotherapy reduces local recurrence by more than 50%.[12] Current standard practice for short-course pre-operative radiotherapy (SCRT) involves a standard radiation dose of 25Gy in 5Gy fractions, given over five consecutive weekdays. Surgery is then performed after 3-10 days.

The short interval between SCRT and surgery means that SCRT does not result in any significant tumour shrinkage prior to resection. The radiotherapy in general is well-tolerated although there has been reported post-operative morbidity and mortality.[13-15] Fokstuen and colleagues[16] reported that following short-course radiotherapy, an abnormal leucocyte response following surgery predisposes to an increase risk of sepsis and hence post-operative morbidity. A longer than recommended radiotherapy-surgery interval appeared to be associated with increased post-operative mortality.

The timing of surgery remains controversial. Van de Broek and co-workers[17] suggested that the postoperative mortality from non-cancer related causes is higher with longer intervals to surgery (>3days) in certain subsets of patients following completion of radiotherapy. One might hypothesise that

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post-operative morbidity increases with the interval to surgery following short fractionation radiotherapy. Different intervals from completion of radiotherapy to surgery are seen in all colorectal units due to logistics of theatre availability throughout the working week and individual consultants' job plans.

The aim of this study was to assess whether the interval between SCRT and surgery influences all cause postoperative morbidity and mortality.

## METHODS

The colorectal surgery database is comprised of prospectively collated data relating to colorectal cancer resections performed within the Belfast Health and Social Care Trust. 102 patients who had undergone SCRT for rectal cancer from 2005 to 2014 were identified from the database and included in the study. Patients all underwent appropriate staging investigations and were discussed at the local Multidisciplinary Meeting (MDM) prior to commencement of short-course radiotherapy. Staging investigations were computed tomography (CT) of chest, abdomen and pelvis and pelvic MRI. Two patients could not have an MRI performed due to the presence of a cardiac pacemaker and therefore underwent endoscopic ultrasound.

Patients were all assessed by a colorectal oncologist for radiotherapy planning. A standard radiation dose of 25Gy in 5Gy fractions, given over five consecutive weekdays was used. Surgery was subsequently performed by one of 7 surgeons trained in TME after a delay of 3 to 10 days.

A retrospective review of patients' medical records was performed. A short trial of data collection was conducted to compare the data that could be gleaned from patients' notes (hard copy) compared to electronic sources. These were comparable and so the decision was made to use electronic data sources and only pull patients' charts if there were any data gaps. The main reason for this was difficulty in obtaining charts for the deceased patients.

Data were collected on age, gender, co-morbidities, pre-operative radiological staging (TNM), tumour height, interval to surgery, surgery performed, stoma rates, pathological staging, post-operative complications, mortality, length of stay and 6 week re-admission rates. Post-operative complications were grouped according to the Clavien-Dindo classification of surgical complications.[18] The intention was to group patients into three groups; those who had undergone surgery 0-3 days, 4-7 days and greater than seven days following completion of radiotherapy, in line with previous studies.[17] However, only two patients had undergone surgery with an interval of greater than seven days (10 days) following completion of radiotherapy and so patients were grouped into two groups; those who had undergone surgery less than 4 days and those who had undergone surgery 4 or more days following completion of radiotherapy.

Table 1

*Patient and tumour characteristics for those undergoing surgery <4 days or ≥ 4 days following short-course radiotherapy*

| | **< 4 days** (n=30) n (%) or Mean±SD | **≥ 4 days** (n=65) n (%) or Mean±SD | **P Value** |
|---|---|---|---|
| Age (years) | 67.1 ±8.1 | 63.4 ±13.0 | 0.184 |
| Gender | Male 23 (76.7)<br>Female 7 (23.3) | Male 41 (63.1)<br>Female 24 (36.9) | 0.242 |
| ASA grade | I 9 (30.0)<br>II 12 (40.0)<br>III 8 (26.7)<br>IV 1 (3.3) | I 28 (43.1)<br>II 31 (47.7)<br>III 6 (9.2)<br>IV 0 (0.0) | 0.048 |
| Pre-op Dukes' stage | A 1 (3.3)<br>B 21 (70.0)<br>C 8 (26.7)<br>D 0 (0.0) | A 3 (4.6)<br>B 27 (41.5)<br>C 33 (50.8)<br>D 2 (3.1) | 0.051 |
| Tumour Height (cm) | 5.5 ±3.1 | 5.8 ±2.6 | 0.395 |
| Post-op Dukes' stage | A 2 (6.7)<br>B 12 (40.0)<br>C 14 (46.7)<br>D 2 (6.7) | A 6 (9.2)<br>B 19 (29.2)<br>C 35 (56.9)<br>D 1 (1.5)<br>None 2 (3.1) | 0.365 |

Table 2

*Post-operative course for patients undergoing surgery <4 days or ≥ 4 days following short-course radiotherapy*

| | **< 4 days** (n=30) n (%) or Median (ICR) | **≥ 4 days** (n=65) n (%) or Median (ICR) | **P Value** |
|---|---|---|---|
| Length of stay (days) | 12 (10) | 14 (10) | 0.535 |
| Complications (Clavien-Dindo classification) | Overall 16 (53.3) | Overall 45 (69.2) | 0.169 |
| | I 5 (16.7) | I 7 (10.8) | 0.510 |
| | II 9 (30.0) | II 36 (55.4) | 0.028 |
| | III 7 (23.3) | III 10 (15.4) | 0.394 |
| | IV 0 (0.0) | IV 0 (0.0) | >0.999 |
| | V 0 (0.0) | V 2 (3.1) | >0.999 |
| Perineal wound complications | 0 (0.0) | 9 (26.5) | 0.021 |
| Readmission within 6 weeks | 5 (16.7) | 14 (21.5) | 0.784 |

Statistical analysis of the data was performed using SPSS®Software, Version 22 (SPSS, Inc, Chicago, Illinois, USA). Categorical data were analysed using Fisher's exact test. Continuous data are represented as mean (±SD) and comparisons were made using the Mann-Whitney U-test. A P-value of less than 0.05 was considered statistically significant.

## RESULTS

One hundred and two patients were identified from the colorectal database, having undergone SCRT between 2005 and 2014 within the Belfast Health and Social Care Trust. Of these, 4 patients were seen in the private sector and had all of their work-up performed privately so complete data could not be obtained. These patients were excluded. No notes were available for 2 patients and one patient never underwent surgery as a co-incidental meningioma was diagnosed during SCRT. Therefore, 95 patients were included in the analysis.

There was no significant difference in age, gender and tumour height between patients who had undergone surgery less than 4 days following completion of SCRT and those who had undergone surgery 4 or more days following completion of radiotherapy (Table 1). The ASA grade of patients who had undergone surgery less than 4 days following SCRT was higher than patients who had undergone surgery 4 or more days following completion of radiotherapy (p=0.048). The pre-operative Dukes' stage appeared to be lower in the group of patients operated on less than 4 days post radiotherapy (p=0.051). However, there was no significant difference in post-operative stage between the 2 groups.

The overall complication rate was 64.2%. There appeared to be a lower overall complication rate in those patients who had undergone surgery less than 4 days following completion of radiotherapy (53.3% vs 69.2%), however, this did not reach statistical significance (Table 2). There was a statistically significantly lower rate of grade II Clavien-Dindo complications in patients who had undergone surgery less than 4 days following SCRT (p=0.028). The rate of perineal wound complications was also significantly higher in patients who had undergone surgery 4 or more days following radiotherapy (p=0.021). There was no significant difference in mortality between the groups. Two patients who had undergone surgery 4 or more days following completion of radiotherapy died during admission. Both deaths were related to cardiorespiratory complications in patients with pre-existing cardio-respiratory dysfunction.

There was no significant difference in length of hospital stay (12 days vs 14 days) or readmission rates within 6 weeks (16.7% vs 21.5%) between the two groups. Of note, there were 4 readmissions due to perineal wound complications, each of whom had undergone surgery 4 or more days following completion of radiotherapy.

## DISCUSSION

Pre-operative short-course radiotherapy is widely used in the UK and Northern Europe to reduce local recurrence rates in patients with rectal cancer, treated with TME. In this study, we investigated the effect of interval from completion of SCRT to surgery on overall post-operative morbidity and mortality.

There is a high morbidity associated with rectal surgery following SCRT. The overall morbidity was 62.1% which included any variation from the normal post-operative course. The in-hospital mortality rate was 2.1% (n=2), with both patients being operated on 4 or more days following last fraction of radiotherapy (p=0.99) and not from surgical causes. These figures are comparable with several published clinical trials. Early results from the Dutch TME trial showed a 3% in-hospital mortality. They also reported a 51% post-operative complication rate.[19] Peterson et al. analysed 657 patients from the Stockholm III Trial and found a

post-operative complication rate of 52.5% in patients who underwent short-course radiotherapy and immediate surgery (n=270).[20] In the current study we included any deviation from the normal post-operative course as a complication, for example, prolonged ileus and chest infections. It is not clear if these were included in the studies mentioned above, which may account for our slightly higher post-operative complication rate.

There was no significant difference in overall complications between patients who had undergone surgery less than 4 days following completion of SCRT and those operated on with an interval of 4 or more days (p=0.17). However, on comparing different grades of complications according to the Clavien-Dindo classification, there appeared to be fewer low grade complications in patients who had undergone surgery less than 4 days following completion of SCRT. This reached statistical significance for Clavien-Dindo grade II complications (p=0.027).

When we looked specifically at perineal complications in patients who underwent abdomino-perineal resections, we found that there was a statistically significant difference between the groups. There were no perineal complications in the 17 patients who were operated on less than 4 days following SCRT, however, 26.5% (9/34) of patients who were operated on 4 or more days following radiotherapy developed perineal complications (p=0.021). However, this study was not designed to detect differences in individual post-operative complications and the sample size is relatively small in comparison with other published studies. Therefore, this result should be interpreted with caution. A recent meta-analysis of 32 studies by Musters et al. investigating perineal wound healing after abdomino-perineal resection for rectal cancer, showed a perineal wound complication rate of 15.3% in patients who did not undergo neo-adjuvant radiotherapy.[21] In the patients who underwent neo-adjuvant radiotherapy the perineal wound complication rate rose to 30.2% after conventional surgery.

Perineal wound complications are a significant source of morbidity for patients and are often very slow to heal in the post-radiotherapy setting. Chadwick et al showed that one-half of patients' perineal wounds had not healed by three months post-operatively and one-quarter by one year.[22] In our study, 4 patients were readmitted within 6 weeks post-operatively with perineal wound complications and required negative pressure dressings.

Several theories have been proposed to account for the increased post-operative morbidity following radiotherapy for rectal cancer. The Dutch Colorectal Cancer Group suggest that there is a radiation induced increase in systemic cytokines.[23] Another theory is that bone marrow depression may result in suppression of pre-operative leucocyte counts or the leucocytosis usually seen following abdominal surgery.[20,23,24] However, this does not necessarily explain why patients who undergo surgery within 3 days of completion of SCRT have fewer complications. It may be that the radiotherapy has not reached its maximum potential to cause complication at 0-3 days post completion.

This study looked at different intervals from radiotherapy completion to surgery which were related to consultants' job plans. This inherently meant that different surgeons were being compared as well as the interval to surgery. Only 2 surgeons routinely operated on patients within 3 days of completion of radiotherapy. However, the study was conducted within a colorectal unit in which there is no significant difference between individual surgeon outcomes. The study included both laparoscopic and open surgery and we did not specifically compare this. Laparoscopic resections were however performed in both interval groups. In the data analysis, no specific complications which were attributable to a laparoscopic approach were observed.

## CONCLUSION

Pre-operative radiotherapy in combination with TME has significantly reduced local recurrence rates from rectal cancer. However, its effect on long-term survival has been less impressive. Our study correlates with results from previous studies in terms of complications following SCRT. They also support the suggestion that post-operative complications are more common with increasing interval to surgery from completion of radiotherapy. This needs to be considered when scheduling patients for surgery.

In our results, there was a significant difference in the rates of perineal wound complications in patients who had undergone surgery 4 or more days following completion of radiotherapy. A larger study population in a study specifically designed to look at the differences in perineal wound complications with interval from radiotherapy is warranted.

We have no conflicts of interest to declare.

## ACKNOWLEDGEMENTS

We acknowledge the important role of Dr Robert Hart and Dr Richard Park in the management of these cases.

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*Ulster Med J* 2017;**86(3):**177-180

*Clinical Paper*

# Long Term Follow Up of Male Breast Cancer.

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Accepted: 5th March 2017
Provenance: externally peer-reviewed.

## ABSTRACT

**Introduction:** Male breast cancer accounts for less than 1% of breast cancers with published overall and disease free survival being lower than in females.

**Aims:** To determine treatment and long term outcomes for male breast cancer patients in our unit.

**Methods:** A database has been maintained for all breast cancer patients diagnosed in our unit since 1993. Patients were identified using the database and information was collated on patient demographics, tumour pathology, treatment and outcomes using the database and retrospective chart review. Patients were followed to cause of death.

**Results:** From 1994-2009 twenty-four cancers were diagnosed in twenty-two patients. Mean age at diagnosis was 69. Male breast cancer patients were treated using similar principles to female breast cancer. Twenty patients underwent mastectomy, two patients underwent wide local excision. No patients developed local recurrence. One patient died from their breast cancer with systemic metastases. 10-year overall survival was 22%, 10 year disease-specific survival was 80%. Other causes of death included medical co-morbidity and secondary cancers.

**Discussion:** Disease free survival in our unit is comparable to other published studies. High age at diagnosis and co-morbidity are the most important factors in determining overall outcome. Treatment pathways for male breast cancer should follow guidelines for female disease in order to optimise outcomes. Future research at national or international level is necessary to ensure the most effective treatments are implemented for male breast cancer patients.

**Keywords:** male breast cancer, treatment, outcomes.

## INTRODUCTION

Male breast cancer is an uncommon disease, accounting for less than 1% of malignancies in men, and less than 1% of all breast cancers. Approximately 300 men in the UK are diagnosed with the disease each year[1]. Incidence appears to be increasing, which may be a reflection of increasing longevity in the population or the rising rates of obesity in developed countries[2].

The bimodal age distribution seen in female breast cancer is absent in males, where peak incidence occurs around the age of 70[3].The aetiology is not fully understood, although, as in females, hormonal, environmental and genetic factors have been implicated. Hormonal imbalance occurring endogenously secondary to testicular abnormalities increases risk. Additionally, exogenous oestrogens such as in men treated for prostate cancer increases risk, and individuals with Klinefelter's syndrome (47XXY) have a 20-50 times higher risk of developing the condition[4]. Obesity, a common cause of hyperoestrogenism, has been implicated. Gynaecomastia, physiological male breast tissue, does not increase risk[5]. Genetic factors appear to play more of a role in males than in females with approximately 10% of men with breast cancer carrying *BRCA2* mutations, while mutations in *BRCA1* are exceedingly rare[6]. Recently, the *CHEK2* 1100delC variant has been found to give a 10-fold risk of male breast cancer independent of *BRCA1* or *BRCA2*[7].

Male breast cancer presents at a later age and often more advanced stage with larger tumour size and more frequent nodal involvement than in females. As a consequence, overall survival rates are lower for men and have not improved over the last number of years as female outcomes have[3].

Treatment guidelines are largely based on existing knowledge from treatment of females as no randomised controlled trials exist to support a specific therapeutic approach. Retrospective studies have not suggested different treatment algorithms should be employed. As with females, treatment involves surgery, with simple mastectomy followed by either sentinel node biopsy or formal axillary clearance being the procedure of choice. As the condition is predominantly hormone-receptor-positive, hormonal therapy is an essential component of treatment[8]. Tamoxifen treatment is considered

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the optimum for oestrogen receptor positive disease as several retrospective trials have reported improved disease-free and overall survival rates in those given adjuvant Tamoxifen[9]. Contrastingly, aromatase inhibitors have been linked to a 1.5-fold increase in risk of mortality compared to tamoxifen. Overall survival has been shown to be significantly better in patients given tamoxifen as compared with aromatase inhibitors[10].

The South Eastern Health and Social Care Trust serves a population of approximately 440,000 people in Belfast and North County Down. It provides services for both secondary and tertiary referral and plays an important role in breast screening. Each year approximately 300 new cases of breast cancer are diagnosed, with 1-2 of these being in men. The aim of this study was to determine patient demographics, treatment approaches and outcomes for patients in our unit from 1994-2009.

## PATIENTS AND METHODS

A database has been maintained for all breast cancer patients diagnosed in our unit since 1993. Patients diagnosed with the condition from 1994 to 2009 were identified and data was collected from the database and retrospective chart review with review of histopathological reports. Patients were followed to cause of death by reference to the database and this was confirmed using Northern Ireland Electronic Care Record (NIECR). All patients with the condition were included for analysis. No patients were excluded. Information collated included patient demographics, tumour pathology, treatment and outcomes. Due to the fact that not all tumours were examined for hormone receptor status in the mid-nineties, no information was available on human epidermal growth factor (HER-2) status for 16 tumours. Furthermore 7 tumours were not examined for oestrogen receptor (ER) status and 15 tumours not examined for progesterone receptor (PR) status. Unfortunately, no histological grading was stated on the histopathology reports for 2 tumours. All other data was complete. Unit policy has been to treat male breast cancer on the basis of tumour biology, staging and comorbidity as would be best practice with females. Data were collected on Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and then analysed using SPSS (Version 12, SPSS Inc, Chicago, Il, USA). Age, tumour size and Nottingham Prognostic Index (NPI) were expressed as mean and standard deviation.

## RESULTS

From 1994-2009, 24 breast cancers were diagnosed in 22 patients. One patient had synchronous and one patient metachronous breast cancer. Mean age at diagnosis was 69 years (SD 8.84). The patient with metachronous breast cancer had Klinefelter's syndrome.

Twenty patients underwent simple mastectomy with nipple removal, with 2 patients having bilateral mastectomy, one concurrently and the other a second mastectomy 4 years after his initial surgery. The remaining 2 patients underwent wide local excision with nipple preservation, with one of these individuals requiring mastectomy due to proximity of tumour to surgical margins. 2 patients had sentinel node biopsy and 22 had an axillary node clearance. One patient, with synchronous cancer underwent bilateral axillary node clearance. One patient, with metachronous breast cancer underwent axillary clearance at his first operation and sentinel node biopsy at his second. Mean tumour size was 19mm (SD=/-13.9) and Mean Nottingham Prognostic Index (NPI) was 3.38 (SD+/- 1.36). Tumour characteristics are summarised in Table 1. Adjuvant therapy is summarised in Table 2.

Table 1

*Characteristics of Tumours (Total n =24)*

| | |
|---|---|
| **Histological Type** | |
| Infiltrating ductal | 20 |
| Papillary | 1 |
| Mixed ductal and lobular | 1 |
| Ductal Carcinoma in situ | 2 |
| **Tumour Grade** | |
| 1 | 4 |
| 2 | 14 |
| 3 | 4 |
| No data available | 2 |
| **Hormone Receptor Status** | |
| ER status examined | 17 |
| ER +ve | 17 |
| ER-ve | 0 |
| ER status not examined | 7 |
| PR status examined | 9 |
| PR +ve | 9 |
| PR – ve | 0 |
| PR status not examined | 15 |
| HER2 status examined | 8 |
| HER2 +ve | 0 |
| HER2 -ve | 8 |
| HER2 status not examined | 16 |
| **Nodal disease** | |
| Nodes +ve | 6 |
| Nodes -ve | 18 |
| **Stage (TNM)** | |
| 1 | 11 |
| 2a | 6 |
| 2b | 3 |
| 3a | 1 |
| 3b | 1 |
| 3c | 1 |
| 4 | 0 |

* One patient, who had bilateral metachronous disease, developed deep vein thrombosis on Tamoxifen and treatment was stopped.

TABLE 2

*Adjuvant therapy*

| | |
|---|---|
| Hormonal treatment | 21 (95%) |
| Chemotherapy | 1 (5%) |
| Radiotherapy | 11 (50%) |

No patient had distant metastases at presentation. Only 6 patients had node positive disease. No patients developed local recurrence. As only one patient has had metastases after treatment, no prognostic factors have been correlated. One patient developed systemic relapse 9 years after his initial diagnosis, with lung metastases. He underwent a successful lobectomy, but developed intracerebral metastases and despite chemotherapy died 48 months after his diagnosis of metastatic cancer. No patients have died as a result of their treatment. Fourteen patients have died in total, with causes of death including cardiac failure, stroke, myocardial infarction, lymphoma and primary lung cancer. Four patients have been followed up for less than 10 years (Table 3).

TABLE 3

| | |
|---|---|
| Median follow up (months) | 115 |
| 5 year overall survival | 67% |
| 5 year disease specific survival | 90% |
| 10 year overall survival | 22% |
| 10 year disease specific survival | 80% |

## DISCUSSION

This retrospective case series is limited by its small size as is often the case with male breast cancer studies worldwide. Our results show similar demographics to other studies, with a high mean age at diagnosis and a comparable frequency of histopathological type of disease. The rate of nodal involvement is lower than other studies published[3,5,11].

Surgery has been the mainstay of our treatment protocols, with the most commonly performed operation being mastectomy and axillary node clearance. In recent years' sentinel node biopsy has been more common, and as patients were selected carefully based on tumour size, no patients have required further axillary surgery. We have performed wide local excision with nipple preservation in 2 patients, one of which required mastectomy due to close proximity of surgical margins.

All patients were started on Tamoxifen and completed a duration of treatment of 5 years with the exception of one patient who required cessation of therapy due to deep vein thrombosis. Although not all patients were tested for hormone receptor status in the mid-nineties, our results suggest that all the patients in our unit tested for hormone receptor status had oestrogen receptor positive breast cancer. Oestrogen receptor status was however unknown in 7 cases. HER2 status was negative when tested however results were unavailable for 16 tumours. No patients received Trastuzumab.

Retrospective studies investigating the benefit of radiotherapy have suggested better local control with radiotherapy and improved overall survival for stage 1 disease but no association with improved cause-specific survival[12]. The role for adjuvant chemotherapy is not well established [13].

Eleven patients had radiotherapy and no patient, either in the radiotherapy or no radiotherapy groups developed local or regional recurrence. One patient who did have radiotherapy developed distant metastases. It is impossible to ascertain if this means our selection process for radiotherapy is effective and accurate or if there is no difference resulting from radiotherapy.

Only one patient developed systemic disease and had chemotherapy and so we are unable comment on its benefit. Other studies have reported an uptake of chemotherapy in the region of 33%[13]. Despite only one patient in this study receiving chemotherapy, outcomes have been excellent with regard to disease free survival. This may suggest chemotherapy is not particularly useful unless systemic disease exists.

Historically, overall survival and disease free survival for male breast cancer have been lower than that of female breast cancer[3]. Contributory causes include a lack of awareness in the population, later stage at diagnosis and reduced uptake of adjuvant treatment. In more recent years overall and disease specific survival have been shown to comparable with females when matched for age and stage [14]. Our study shows ten-year disease free survival (80%) in our unit is comparable to other published studies [5,14]. Only one patient has died from their breast cancer. Ten-year overall survival is consistent with other reported studies at 22%, showing that the high age at diagnosis is the most important factors in determining outcome. In particular, comorbidity and development of second cancers appears to be more important than in females.

## CONCLUSIONS

In this small retrospective case series, treatment of male breast cancer has been based on principles similar to those for females, namely pathology, tumour biology, and patient co-morbidity. It is likely that age at diagnosis and medical co-morbidity were the most important prognostic factors in determining ten-year overall survival. Mastectomy and Tamoxifen would appear to be the most effective treatments. We suggest that males should be treated proactively and no differently from females.

Outcomes for male breast cancer would appear to be consistent with that described in the literature [5,14]. However, given the fact that numbers are limited, the question of whether the prognosis for breast cancer is worse in males than in the female population remains unanswered.

It is difficult, if not impossible to carry out adequately powered randomised controlled trials as they would necessarily involve multiple centres and a long study period. Due to speed of progress in the treatment of female breast cancer, where large randomised controlled trials are feasible, it may be most appropriate to concentrate on providing males with comparable treatment to females, specifically best treatment practices for post-menopausal breast cancer. Future research must be at national or international level to ensure the most effective treatments are implemented for these patients. An ongoing international retrospective male breast cancer programme with prospective study by The European Organisation for Research and Treatment of Cancer (EORTC) may provide additional understanding of optimal treatment approaches and long term outcomes for male breast cancer patients.

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*Ulster Med J* 2017;**86(3):**181-184

*Clinical Paper*

# Minimally Invasive management of delayed recognition iatrogenic ureteric injury

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Accepted: 3rd April 2017
Provenance: externally peer-reviewed.

## ABSTRACT

**Introduction:** Iatrogenic ureteric injuries are a rare but serious complication of abdomino-pelvic surgery which can be associated with significant morbidity. 65-80% of ureteric trauma is only identified in the postoperative period. Current guidelines recommend stent insertion or urinary diversion via percutaneous nephrostomy. Good quality evidence on success and outcomes remains scant and the optimum treatment pathway unknown.

**Methods:** A retrospective review of all delayed presentation ureteric injuries treated in our unit between 2005 and 2013 was performed. Clinical, treatment and outcome data were collected in a custom proforma.

**Results:** 19 patients with 21 injured ureters met inclusion criteria. 16/19 (84.2%) injuries were sustained during gynaecological procedures with 10 (52.6%) of these during total abdominal hysterectomy. Suspected mechanisms from diagnostic studies was defined as partial transection in 9/21 (42.9%), complete transection in 3/21 (14.3%) and perforation in 1/21 (4.8%).

Median time from injury to presentation was 16 days (IQR 7-25). 11/21 (52.4%) had successful stenting with a median time to stent placement of 25 days (IQR 18.5-42). Those with failed stenting had a median time to attempted stenting of 65 days (IQR 10-91.3). Those with successful stenting 3/11 (27.3%) had resolution requiring no further intervention. 6/11 (54.5%) required open reconstruction, with the remaining two patients unfit for reconstruction and managed with long term stents. With successful stenting median time to definitive surgery was 413 days (IQR 156-476).

**Conclusion:** Success rates for stenting are similar to those reported in the literature (55% vs. 44-59%), but resolution rates are significantly lower (15% vs. 44-80%). Data for an endourological approach as a possible long-term solution is limited by heterogeneity, and a further well conducted multicentre prospective study is required

## INTRODUCTION

Iatrogenic ureteric injuries are a rare but serious complication of abdomino-pelvic surgery which can be associated with significant morbidity.

Reported intraoperative injuries to the ureter include ligation, transection, electrocautery and avulsion, with 80-90% of damage occurring in the distal third. Iatrogenic ureteric injuries may occur during open, laparoscopic or endoscopic surgery and are a potential complication of any intra-abdominal or pelvic procedure. Colorectal, vascular and urological surgery are all implicated but gynaecological procedures account for more than 50% of ureteric injuries, occurring in 0.5-10% of all hysterectomies. [1-4]

The incidence of ureteric trauma ranges from 0.05-30% in all pelvic surgery, and is higher in patients with recognised risk factors. [1,5-6] When identified intra-operatively, immediate repair and secured drainage affords fewer complications and superior outcomes. [7-9] However, 65-80% of ureteric trauma is only identified in the postoperative period, current guidelines recommend stent insertion or urinary diversion via percutaneous nephrostomy. [1] Unrecognised ureteric trauma may be associated with significant morbidity including fistula formation, sepsis and renal impairment, often requiring additional treatment and prolonged hospital stays. [2, 10]

Traditionally, delayed and early open reconstructive repair was practiced, but with the advance of minimally invasive procedures, novel techniques have been described with variable outcomes. [5, 9, 11-15] Good quality evidence on success and outcomes remains scant and the optimum treatment pathway unknown. [16] Previous studies have been limited by heterogeneous injury type and severity as well as short follow-up periods.

The purpose of this study was to review the management of

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delayed intervention in ureteric injury at our institution over an eight-year period, comparing interventions and outcomes with those of similar studies.

## MATERIALS AND METHODS

Cases of delayed presentation ureteric injury managed at our institution between 2005 and 2013 were identified from coding records. Exclusion criteria were: injuries sustained due to external trauma; minor injuries (American Association of Surgical Trauma grade <2 [Table 1]) and injuries undergoing immediate repair. Nineteen patients (21 ureteric injuries) met inclusion criteria.

Table 1.

*Adapted from Moore et al.*[17]

| **Ureter injury scale** | | |
|---|---|---|
| Grade* | Type of injury | Description of injury |
| I | Hematoma | Contusion or hematoma without devascularisation |
| II | Laceration | < 50% transection |
| III | Laceration | ≥ 50% transection |
| IV | Laceration | Complete transection with < 2cm devascularisation |
| V | Laceration | Avulsion with > 2cm of devascularisation |

*Advance one grade for bilateral up to grade III.

A retrospective review of case notes and radiology electronic systems was performed and data collected on a pre-designed proforma. Demographic data, risk factors, operative details, subsequent management (attempted and successful) and outcomes were all recorded.

Statistical analysis was performed using Prism® (GraphPad Software Inc, San Diego, California) software. Fishers exact test was used for categorical variables and Mann-Whitney U for continuous variables.

## RESULTS

Nineteen patients with 21 injured ureters were treated at our institution, referred from 8 different centres.

18/19 (94.7%) patients were female with a mean age at time of presentation of 46.7 years (range 29-63). Pre-disposing risk factors were identified in 12/19 (63.2%) with malignancy accounting for eight (42.1%) of these, previous surgery for two (10.5%) and major haemorrhage a further two (10.5%).

16/19 (84.2%) injuries were sustained during gynaecological procedures with 10 (52.6%) of these during total abdominal hysterectomy. The non-gynaecological cases were flexible ureterorenoscopy, completion proctatectomy and sigmoid colectomy, all for benign conditions.

12/21 (57.1%) were encountered on the left side, 9/21 (42.9%) on the right. In two patients, the injuries were bilateral. The most common site encountered was lower third with 19/21 (90.5%) of injuries seen here.

Due to the retrospective nature of the study and delayed presentation of cases, the mechanism of injury was difficult to accurately determine in the majority of cases. 3 cases presented with uretero-vaginal fistulae. Documented suspected mechanisms from diagnostic studies was defined as partial transection in 9/21 (42.9%), complete transection in 3/21 (14.3%) and perforation in 1/21 (4.8%). The remainder were unknown.

Median time from injury to presentation was 16 days (IQR 7-25). 19/21 (90.5%) had attempted ureteric stenting (retrograde and/or antegrade). The remaining two patients had percutaneous nephrostomy (PCN) drainage and contrast studies, the injuries were deemed too severe for successful bridging of the defect. They both proceeded to delayed reconstruction. In 12/21 stenting was attempted at presentation, in a further seven PCN was inserted with delayed attempted stenting.

Overall 11/21 (52.4%) had successful stenting (7 retrograde, 4 antegrade) with a median time to stent placement of 25 days (IQR 18.5-42). Those with failed stenting had a median time to attempted stenting of 65 days (IQR 10-91.3). Whilst failed stenting group had a longer median time to presentation, these results did not reach statistical significance (p=0.19) due to small numbers involved (Fig 1.)

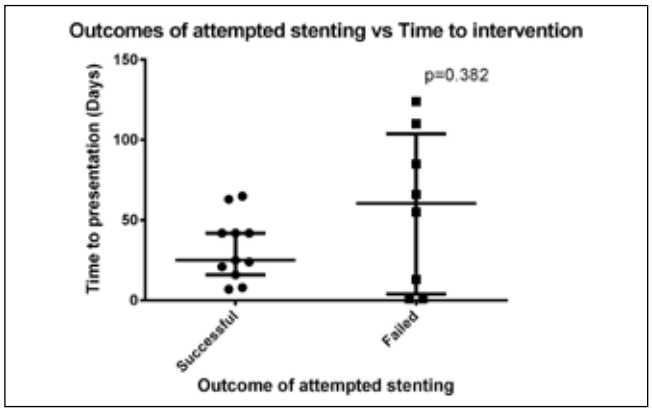


*Fig 1.*

Seven patients with failed stenting, and 2 in which it was deemed not possible, proceeded to delayed open reconstruction, with a median time to definitive surgery of 240 days (IQR 86.8-291). Of those with successful stenting 3/11 (27.3%) had resolution requiring no further intervention. 6/11 (54.5%) required open reconstruction, with the remaining two patients unfit for reconstruction and managed with long term stents. With successful stenting median time to definitive surgery was 413 days (IQR 156-476).

TABLE 2.

*Previously published Iatrogenic Ureteric Injury Series'*

| **Previous Literature** | | | | | |
|---|---|---|---|---|---|
| Lead Author | Year | Cohort | Sucessfully Stented | Resolution | Follow Up (mo) |
| Dowling RA [5] | 1986 | 23 | 11 (48%) | 8 (35%) | n.r |
| Cormio L [13] | 1993 | 30 | 16 (53%) | 16 (53%) | 23 |
| Ku JH [20] | 2003 | 17 | 10 (59%) | 11 (64%) | n.r |
| Park JH [17] | 2012 | 18 | 8 (44%) | 6 (33%) | 6 |
| **Our Series** | | **21** | **11 (52%)** | **3 (14%)** | **23** |

For all patients with ureteric injury the mean number of invasive procedures required until definitive repair was 3 (Range 2-6). Two patients managed with long-term stents have required repeated procedures to renew stents.

## DISCUSSION

Iatrogenic ureteric injuries are a rare but potentially serious risk of abdomino-pelvic surgery, when they do occur, prompt recognition and management is vital to prevent significant and long-term morbidity. The majority of significant injuries occur during non-urological surgery, often with a delay in recognition. Selzman et al. demonstrated that most injuries sustained during non-urological procedures were detected post-operatively, were more complicated and required more complex repair. In comparison, injuries obtained during urological procedures are more commonly identified intraoperatively and managed with insertion of a ureteric stent. [10] In our study, the presence of just 1 major delayed recognition ureteric injury resulting from urological surgery adds weight to this statement, compared with 20/21 (95.2%) occurring during non-urological procedures.

Conditions increasing the risk of ureteric injury include any existing pathology which disrupts the normal anatomy of the ureters. Examples include endometriosis, pelvic inflammatory disease, malignancy and previous pelvic surgery or radiotherapy. [18] Such risk factors were identified in 12/19 (63.2%) of the patients in our study.

The established management of delayed recognition ureteric injuries involves delayed repair 3-6 months following the initial injury, to allow resolution of inflammatory processes and re-establish tissue planes. More recently, primary management by endourological intervention has been shown to significantly decrease morbidity, reduce re-operation rates and aid spontaneous recovery. [10, 18-19] Lask et al. demonstrated placement of a percutaneous nephrostomy (PCN) alone allowing up to 80% of the injured ureters to recover patency.[20] These resolution rates have not been successfully replicated in other studies. In our series 10/21 were treated with PCN drainage (after failed stenting), all subsequently required open reconstructive procedures. Further studies have attempted management with ureteric stenting, successful stenting has been demonstrated in 44-59%, with resolution rates between 33-64% (Table 2). [5, 13, 18, 21]

11/21 underwent successful retrograde or antegrade stenting. Three cases of spontaneous resolution without stricture were seen. The remainder were either reliant on long-term stents (n=2) or proceeded to reconstruction (n=6).

Our findings suggest that PCN alone does not yield spontaneous resolution of injuries. Successful stenting rate was similar to previous studies. Resolution rate was however considerably lower (14%).

There are several reasons why resolution rates in our study may be significantly lower than with other published work. Firstly, our inclusion criteria were strict with only moderate-severe ureteric injuries included (American Association of Surgical Trauma grade ≥3). Similar studies by Park and Ku may have yielded better results partly due to the fact ureteric injuries were not excluded on the basis of severity. [18, 21] Secondly, many of these studies included both intra- and postoperatively detected ureteric injuries, whereas our series only included those identified postoperatively, a factor predisposing to lower resolution rates. [5,13,21] Finally, it must also be considered that our series included a long follow up time of 23 months compared to much shorter periods documented in other studies.

Our results suggest that regardless of approach, multiple interventions are required to restore ureteric patency. Successful stenting led to resolution in 14% of patients, we therefore suggest a minimally invasive approach in the first instance, to secure renal drainage and reduce sepsis. This can be with nephrostomy or stent drainage, but patients should be counseled regarding the likelihood of requiring further surgery.

Our study is limited by small number of participants, heterogeneous injury mechanisms and the retrospective nature of data collection.

## CONCLUSION

The incidence of delayed, post-operative recognition ureteric injuries was significantly higher in non-urological procedures. Extra care should be taken in all types of abdominal/pelvic surgery in patients with known risk factors as the likelihood of ureteric damage is increased. Success rates for stenting are similar to those reported in the literature (55% vs. 44-59%), but resolution rates are significantly lower (14% vs.

44-80%). Data for an endourological approach as a possible long-term solution is limited by heterogeneity but successful initial ureteric stent placement will lead to resolution in some cases. A further well conducted multicentre prospective study is required to define patient selection.

Conflict of Interest: None


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*Ulster Med J* 2017;**86(3):**185-188

*Case Report*

# Dystrophin Exon 29 Nonsense Mutations Cause a Variably Mild Phenotype

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Accepted: 2nd of March 2017
Provenance: externally peer-reviewed

## ABSTRACT

**Background:** Nonsense mutations in the dystrophin gene usually result in a severe Duchenne muscular dystrophy phenotype.

**Findings:** We describe a 7-year-old boy with a rare pathogenic mutation in exon 29 c.3940C>T p.(Arg1314Ter) resulting in exon skipping, in turn rescuing the phenotype from a severe Duchenne type to a milder Becker muscular dystrophy type. No adults have been described with this mutation to date.

**Conclusions:** Exon skipping of exon 29 results in a higher level of functional dystrophin. Some cases of muscular dystrophy may still require muscle biopsy to determine optimal management and pharmaceutical treatment options.

**Key Words:** Dystrophin, Exon 29, Nonsense mutation, Becker muscular dystrophy, Exon skipping

## INTRODUCTION

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are allelic X-linked disorders of the dystrophin gene at the Xp21 locus. The dystrophin gene is the largest gene known and contains 79 exons[1]. The prevalence of DMD in Ireland is around 3 per 100,000 cases[2].

DMD is usually evident from infancy/early childhood and is characterised by delayed motor milestones, a waddling gait, Gower's sign and later calf hypertrophy. Muscle disease is rapidly progressive and many boys with DMD are wheelchair bound as young teenagers. Approximately 30% of patients will have learning difficulties and as many as 80% will develop cardiomyopathy; although only 10% of affected boys will die from heart failure[3]. At a cellular level the dystrophin gene is responsible for producing the protein dystrophin which acts to couple the sarcolemmal cytoskeleton with the extracellular matrix via the dystrophin glycoprotein complex. Loss of this stability makes the muscle more susceptible to damage when exposed to mechanical stress. As muscle damage progresses there is secondary hypertrophy due to infiltration with adipose tissue[4]. Dystrophin is virtually absent from all muscle cells (>98%) in DMD[5].

In contrast, the muscle seen in BMD patients has a variable amount of dystrophin present and constitutes a milder skeletal muscle phenotype. The mean age of onset is 11 years. Loss of the ability to walk may not occur until 40 or 50 years. Often cramping on exercise is the presenting complaint, followed by difficulties in running and climbing stairs.

Antisense-mediated exon skipping therapy is a promising therapeutic approach to skip over the mutated exon, restoring the open reading frame and producing a partially functional dystrophin. Essentially exon skipping converts what would be a severe DMD phenotype into a milder BMD phenotype. Exon 51 skipping has been the target of clinical trials but this will only be directly applicable to about 13% of all DMD individuals[6]. Knowledge of other potential skipping targets is critical to the development of antisense oligonucleotides (AONs) for many other DMD patients. Multiple AON 'cocktail' therapies have recently been used in the mouse model, as a way of expanding the coverage for deletion mutations in exons 45-55 that can be restored[7]. The drug Etiplirsen has recently been approved by the FDA to allow exon 51 skipping[8]. With the advent of treatments, databases of mutations are now being compiled to collect information about the type and frequency of DMD mutations – such as TREAT NMD DMD[9].

## PRESENTATION

We present a 7-year-old boy with a mild BMD phenotype

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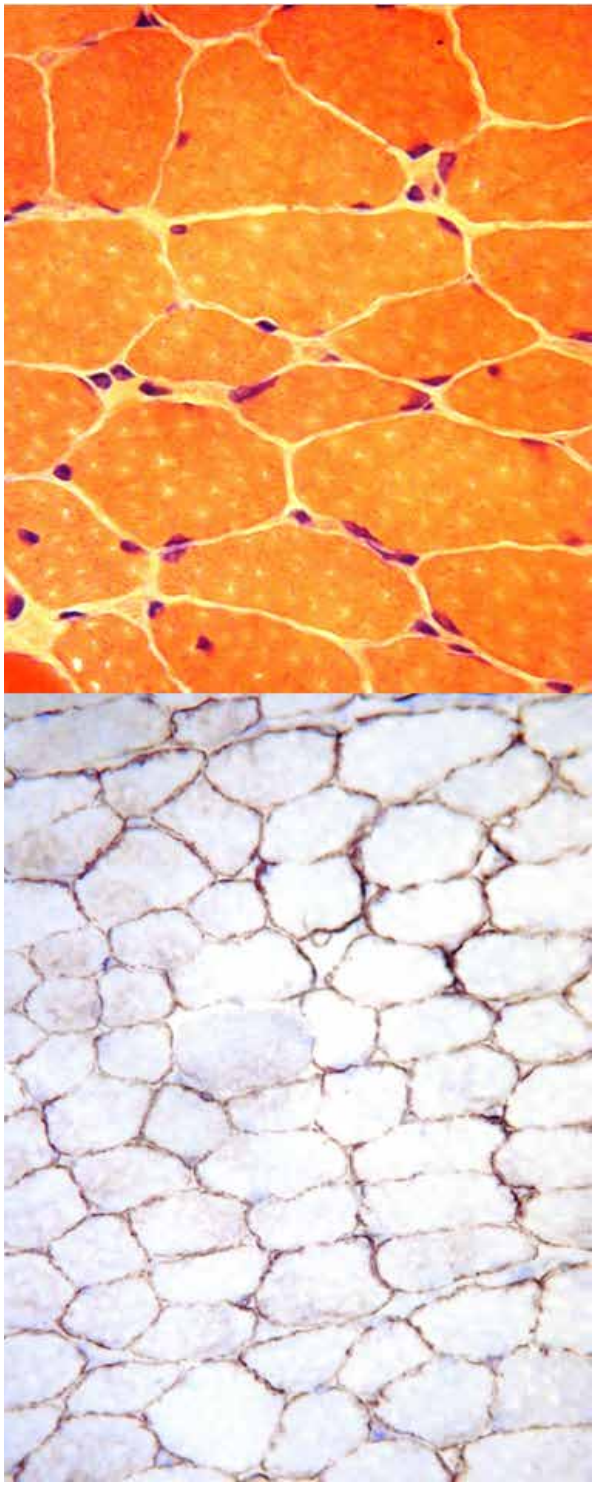

*Fig 1*. H&E image (top)

H&E shows mild variation in the fibre shape and size. Occasional internal nuclei are present but the typical features of a dystrophy are not seen. There are no split fibres; there is no fibrosis or fibre necrosis.

*Dystrophin 1 immunohistochemistry (bottom)*

Dystrophin 1 immunohistochemistry shows generally good circumferential staining with areas of partial loss including one completely negative fibre.

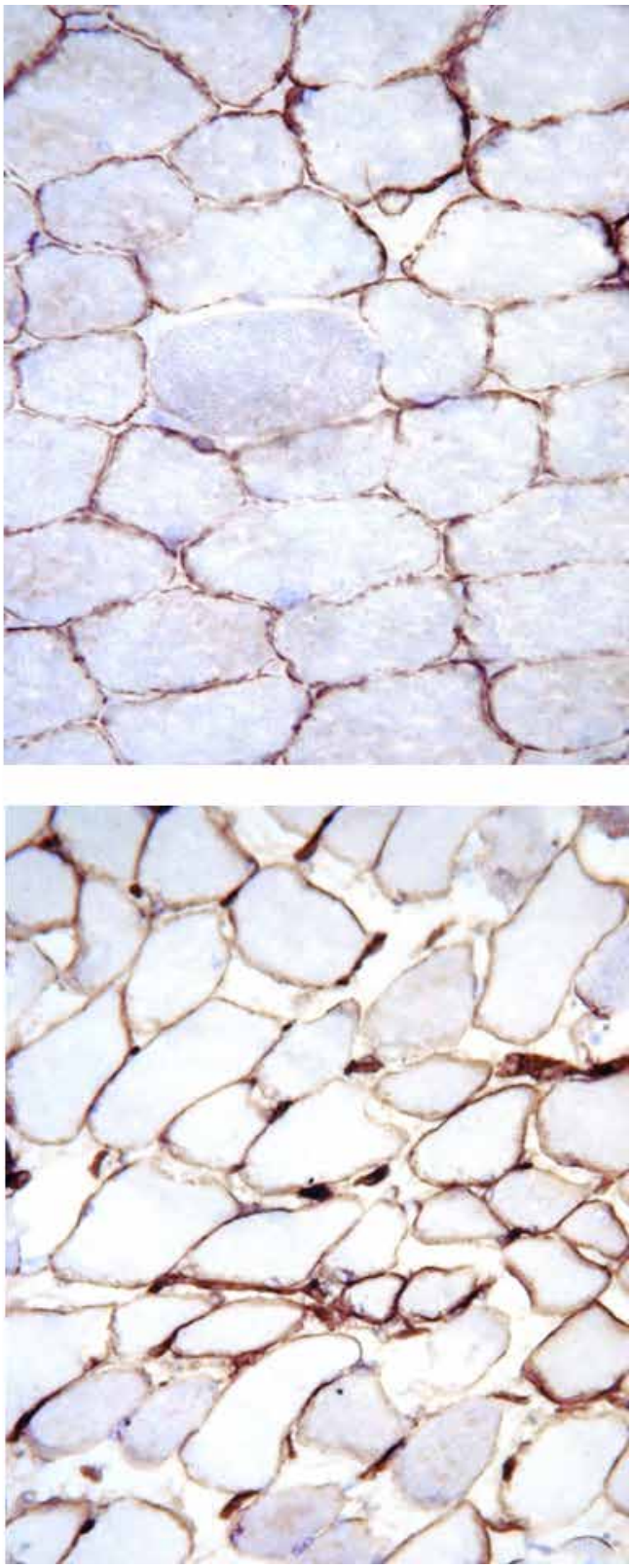

*Fig 2*. Dystrophin 2 (top)

Dystrophin 2 staining is similar to dystrophin 1.

*Utrophin (bottom)*

Utrophin immunohistochemistry shows diffuse circumferential upregulation.

and a pathogenic mutation in exon 29 c.3940C>T p.(Arg1314Ter).

He presented to paediatric services at the age of 5 years with developmental delay. He was born at 34 weeks gestation with a birth weight of 4lbs. His neonatal course was unremarkable. His motor milestones were delayed and he had severe speech delay with only a few words at 5 years old. Upon presentation, he could walk upstairs and run. He had some difficulties coming down stairs and could not jump or pedal a bicycle, but could climb and perform Gower's manoeuvre without difficulty.

## RESULTS

Initial investigations included a creatine kinase level of 10,000 U/L. His initial genetic screening was negative for DMD and hence a muscle biopsy was performed. This was suggestive of a mild dystrophy but the typical features of Duchenne or Becker dystrophy were not present and only showed mild changes in dystrophin (Figures 1 and 2). His muscle strength in all groups of muscles at age seven was at least 4/5. He had a MRI of his brain which was entirely normal. His echocardiogram and array cytogenetic testing analysis were completely normal. Testing of muscle DNA confirmed an exon 29 mutation c.3940C>T p.(Arg1314Ter) which was then identified in blood DNA, allowing carrier testing in family members.

## DISCUSSION

There have been only a few case reports of exon 29 nonsense mutations in the literature and each of them describe an encouraging milder phenotype (Table 1). The variant in our patient is extremely rare and is predicted to produce a truncated dystrophin leading to a severe phenotype. We were unable to take this further with RT-PCR analysis due to hospital funding restrictions, however, evidence in the literature from a 5-year-old male with the same mutation as our patient showed that exon 29 was aberrantly spliced out of dystrophin mRNA transcripts resulting in an in-frame deletion at the RNA level[10]. As a result, there is a higher level of functional dystrophin and a milder phenotype. [A nonsense mutation in exon 27 has previously been reported as promoting exon skipping[11] which may support a similar mechanism for the exon 29 skipping].

Another paper describes 3 patients within the same family as having a mild phenotype (Exon 29 4148C>T). The first, a 58-year-old man, who is wheelchair bound for longer distances and has kyphoscoliosis and cardiomyopathy. His 23-year-old nephew has mild symptoms only and his 26-year-old nephew has a raised CK only[12].

The paper describing the 5-year-old patient with the same exon 29 mutation as our patient (c.3940C>T) notes he had a raised CK level only and doesn't report the developmental delay or speech impairment present in our case[10]. This patient formed part of a database of 229 DMD/BMD patients in East China. He was one of the only two patients with BMD to have a point mutation. All other point mutations resulted in DMD. Our patient had a normal array test and no other causes were identified for the developmental delay and we cannot be certain these features are definitely due to the DMD but such features are recognised in other boys with the condition with other mutations.

Canine models have also been used to explore a mild muscular dystrophy phenotype. Ringo was the most notable dog; a Brazilian Golden Retriever born with complete absence of dystrophin and a clinically mild phenotype and normal lifespan[13]. Vieira et al recently described a 3-generation family of Labrador retriever dogs with no signs of muscle weakness in the setting of markedly increased creatine kinase activity and absent dystrophin[14]. There are parallels with this case and canine models may be helpful in elucidating further therapeutic intervention in boys with DMD as it is useful to know that exon 29 skipping results in a higher level of functional dystrophin.

This case report consolidates a small cohort of patients demonstrating skipping of exon 29. We would hope to continue to observe a mild phenotype in this patient. Expanding knowledge of exon skipping is critical to the on-going research of this mechanism as a possible therapy. It

TABLE 1.

*Published patients with exon 29 mutations*

| Patient | Phenotype | Exon | Mutation | Ref. |
|---|---|---|---|---|
| | | | | |
| 58 yr old male | Wheelchair long distances, kyphoscoliosis, cardiomyopathy | 29 | c.4148C>T | 12 |
| 26 yr old male | Raised CK only | 29 | c.4148C>T | 12 |
| 23 yr old male | Mild symptoms | 29 | c.4148C>T | 12 |
| | | | | |
| 5 yr old male | Raised CK only | 29 | c.3940C>T | 10 |
| | | | | |
| 7 yr old male | Mild skeletal muscle weakness, raised CK and learning difficulties | 29 | c.3940C>T | Our patient |
| Family of male patients | Early onset dilated cardiomyopathy | 29 | c.4148C>T | 16 |

is also invaluable in reassuring patients and parents that the clinical course of this genotype is a seemingly milder one.

Given that our patient's clinical phenotype and muscle dystrophin confer a diagnosis of Becker Muscular dystrophy, although muscle biopsy is not routinely recommended in general diagnostic work-up of cases, this case illustrates that in a small number of cases, muscle biopsy may be helpful in determining the exact phenotype classification. In this case, treatment with approved small molecule compounds such as Ataluren, an oral medication that suppresses nonsense mutations[15] (ameliorating the effect of nonsense mutations within the Dystrophin gene), may not be necessary as our patient would therefore not fit the criteria for treatment on closer examination, thus saving costs and unnecessary side effects. Of note, the ACT DMD trial (48-week randomised placebo controlled phase III trial) demonstrated no statistically significant differences in a 6 minute walk test against placebo. Even etiplirsen the exon 51 skipping drug whilst showing an elevation of 11-21% in dystrophin, did not provide substantial evidence of clinical effectiveness[8]. Further studies using western blotting may help in quantifying the dystrophin expression, and RNA analysis may explain a clearer mechanism for the exon skipping. Identification of adults with this particular mutation will shed light on the evolving phenotype of this mutation, and follow-up of these childhood cases will shed further light on the natural history and progression of the disorder and the effectiveness of treatments.

## ACKNOWLEDGEMENTS

The authors would like to thank the patient and his family for kindly consenting to this publication.

## COMPETING INTERESTS

None

## AUTHOR CONTRIBUTIONS

**Conception:** Rebecca Moore, Sandya Tirupathi, Patrick J. Morrison

**Manuscript writing:** Rebecca Moore, Patrick J. Morrison

**Provision of Histopathology and descriptions**: Brian Herron

**Echocardiography**: Andrew Sands

**Final approval of manuscript:** Rebecca Moore, Sandya Tirupathi, Brian Herron, Andrew Sands, Patrick J. Morrison

There are no sources of funding and no medical writers were used in the preparation of this manuscript.

All authors have seen and approved the final manuscript and none have any competing interests. All authors have agreed to the submission to the journal and the manuscript is not currently under submission in any other journal.

This research was carried out according to our institution's guidelines. Permission was granted to access all relevant patient data.

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*Ulster Med J* 2017;**86(3):**189-195

*Medical History*

# Dr Elizabeth Gould Bell (1862 – 1934) - The First Woman to Graduate In Medicine And Practice In Ulster.

Shelagh-Mary Rea

Accepted: 12th February 2017.
Provenance: Internally reviewed.

## SUMMARY

On 11 October 2016, the Ulster History Circle unveiled a blue plaque in commemoration of Dr Elizabeth Gould Bell MB BCh BAO (Royal University of Ireland) at the entrance of Daisyhill Hospital, Newry, Co Down, Northern Ireland. As one of the first female doctors to qualify in medicine in Ulster in 1893, against all the odds, she entered general practice in Belfast. She became a leading member of the suffrage movement in Ulster and then went on to answer a call for women doctors to volunteer service in the Royal Army Medical Corps in 1916. She was in the first group of such women to be sent to Malta during the First World War. In 1896, she married Dr Hugh Fisher, my great uncle, who was also a general practitioner. He died in 1901 of typhoid fever. Her only son, Lieutenant Hugh Bell Fisher, who had enrolled at Queen's University, Belfast, as a medical student, joined the 2nd Royal Munster Fusiliers and died from wounds he received at the Battle of Passchendaele on 23 November 1917. Dr Bell lived at 4 College Gardens, Belfast from 1925 and died there in 1934.

Dr Bell was a member of the Ulster Medical Society from 1893; Dr Fisher was a member from 1895.

## FAMILY BACKGROUND

Dr Elizabeth Gould Bell[1] was born on 24 December 1862 at Spring Hill House, close to the Newry Workhouse. She was the daughter of Joseph Bell, Clerk of the Newry Poor Law Union, whose family were from Killeavy Castle and Spring Hill, Newry, Co Armagh. Her mother, Margaret Bell, was the daughter of a farmer from the nearby townland of Carnegat. There were three daughters and two sons of the marriage: her sister, Margaret[1,2] became one of the first female general practitioners in Manchester. One of her brothers followed in his father's footsteps and was also Clerk of the Newry Poor Law Union.

## EDUCATION

There is no record of where Dr Bell went to school. However, there is a record that in 1889 she and her sister, Margaret, completed one year's study in the Arts Faculty of Queen's College, Belfast. This was possible due to the movement to allow women in Ulster to enter university education which began in 1867 with the establishment of the Belfast Ladies Institute. Its objective was "to provide advanced classes for ladies of a higher class than hitherto attempted". In 1870 the question of women attending the College came before the Council of Queen's College, Belfast. Thomas Andrews, Vice-President, proposed that they should be permitted to attend particular courses of lectures, "if the Professors considered it expedient and were satisfied the discipline and instruction of the classes would not suffer". They would not be eligible for scholarships or prizes or enjoy the same privileges as the male students. Professor Redfern, President of the Biology

*Fig 1.*

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Section, objected to these restrictions and wanted women to be admitted on equal terms with men, if the charter permitted. However, the matter was deferred indefinitely[3].

The Belfast Ladies Institute approached the Senate of Queen's University of Ireland in 1873 and again in 1882. The Royal University of Ireland (RUI), which had now replaced the Queen's University of Ireland, was open to women and the President of Queen's College, Belfast, J L Porter, supported the women's application to Queen's College. It was perhaps relevant that he had three clever daughters. So it transpired that in 1882-83 women were admitted to Arts Classes only but it was not until 1889 that women were admitted to the Medical Faculty of Queen's College, Belfast for the first time[3].

Elizabeth and Margaret Bell entered the Faculty of Medicine along with 3 other female medical students for the 1889-90 session. They attended the Belfast Royal Hospital, in Frederick Street, which became the Royal Victoria Hospital and the Belfast Union Hospital which became the Belfast City Hospital for clinical sessions. There was no opposition from the staff of these hospitals to the attendance of these female medical students[3]. Of the five female medical students, only Elizabeth Bell and Henrietta Rosetta Neill proceeded to the more prestigious university degree, the rest were satisfied with diplomas from licensing bodies. Dr Bell graduated MB BCh BAO from the Queen's College, Royal University of Ireland on 27 October 1893. Her name was included in the Medical Directory of Ireland on 25 November, 1893. Figure 1 shows a photograph of Dr Bell.

## MARGARET SMITH BELL

Margaret[1,2] who was the second daughter in the family, was not as academically gifted or strong-willed as her elder sister. She opted to take the Licence of the Royal College of Physicians of Ireland (LRCPI) and of the Royal College of Surgeons of Ireland (LRCSI), along with the Licence in Midwifery (LM) in 1894. After attending the Ulster Hospital for Children and that for Eye, Ear and Throat conditions, Margaret entered general practice in Manchester and built up a considerable practice mainly among women. She was appointed medical officer of the influential Ancoats Day Industrial School of the Grove Retreat, Fallowfield and other cognate organisations. On 9 October 1901, she married Dr Joseph Douglas Boyd, also a general practitioner. In the summer of 1906 they had been staying at sister Elizabeth's home in 4 College Gardens and for spells in Portrush seeking benefit for a refractory throat problem. After two surgical operations Margaret died in nearby Claremont Street Hospital. She had one son who became a distinguished radiologist, Dr Douglas Priestly Bill Boyd (MB, QUB, 1931).

## MARRIAGE

On 2 March 1896 Dr Elizabeth Bell married Dr Hugh Fisher[1] in Fitzroy Presbyterian Church, Belfast. The son of Hugh Cumming Fisher, bank clerk, of Lennoxvale Street, he was born on 9 April 1870. He was educated at Methodist College, Belfast from 1885. He studied medicine at Queen's College, Belfast from 1887, qualifying in 1893 with MB BCh (RUI). He became a general practitioner and was based at 75 Great Victoria Street. They had one son, Hugh Bell Fisher, known as Hugo by his family and friends. Sadly, Dr Hugh Fisher died on 18 October 1901 from typhoid fever after only five years of marriage.

## GENERAL PRACTICE IN BELFAST

Dr Bell became a general practitioner and worked from 41 and later 83 Great Victoria Street, Belfast. Her patients were mostly women and young children. She was Honorary Physician[4] to the Women's Maternity Home in Belfast, the Belfast Babies Home and Training School at The Grove, Belfast. She was also medical officer[5] to the Malone Place Hospital. This establishment was set up by some "Belfast ladies" who were concerned about women and girls who frequented public houses in Belfast. The ladies went out at midnight and invited the women to spend the night at the "Belfast Midnight Mission" at the Malone Place Hospital. The homeless and strangers were helped to find homes and jobs. Later, around the turn of the century, the plight of unmarried mothers and their babies was met by setting aside a room for confinements and a trained nurse and mid-wife were appointed.

In February 1919 Dr Bell was appointed as Medical Officer to Riddel Hall[6] which was founded and endowed by The Misses Eliza (1831 – 1924) and Isabella (1836 – 1918) Riddel. They donated a substantial sum of money (£35,000.00) to build Riddel Hall as an independent hall of residence for female protestant students and teachers of Queen's University in 1913. Miss Duffin, first Warden of Riddel Hall said of Dr Bell, "she proved a firm friend and a rock of common-sense in her frank and friendly dealings with students' ailments and I much appreciated the way in which she told me what to note in various illnesses or note a student's general "type" or constitution". Later, Dr Bell became a Governor of the permanent committee of Riddel Hall. It is now home to Queen's University Management School, the William J Clinton Leadership Institute, the Institute of Directors (IOD) and the Northern Ireland Centre for Pharmacy, Learning and Development (NICPLD).

From 1922 to 1926 she assisted the Babies' Clubs welfare scheme, run by the Belfast Corporation, which provided subsidised milk for impoverished mothers.

## OTHER INTERESTS

Dr Bell was medical advisor for the Slainte Health Insurance Scheme. She taught students in the Presbyterian Deaconesses' Home. She was also interested in temperance and supported the Ulster Women's Christian Temperance Association.

## PUBLICATION

Dr Bell published[3] *A Curious Condition of Placenta and Membranes* in the annual report of the Northern Ireland branch of the British Medical Association, for 1895- 1896.

## POLITICAL ACTIVIST

Dr Bell was noted for her involvement in the suffrage movement in the years before the First World War. Although the first suffrage society to be established in Belfast was in 1870 it was not until the early years of the 20th Century that it gained momentum in Ulster. In 1909, the North of Ireland Women's Suffrage Society changed its name to the Irish Women's Suffrage Society (IWSS) which was based in Belfast but had branches outside the city. It was the educated, middle class women who formed the kernel of the suffrage movement. "These women saw their campaign within the context of democracy, claiming that the absence of women from the governing institutions of the state were responsible for a dearth of thoughtful attention directed to matters which concern women more intimately than they can possibly concern men. In essence, the vote came to symbolise women's emancipation from social drudgery, virtuous convention and economical and political subservience. Suffragists aimed to make women feel responsible for their own destinies and those of their children and for their sex as a whole"[7].

The suffragists and suffragettes[8] were members of two very different movements. Suffragist was the broader term referring to the supporters of suffrage for women, more specifically the members of the National Union of Women's Suffrage Societies (NUWSS), formed in 1897 and led for over twenty years by Millicent Garrett Fawcett. NUWSS aimed to achieve enfranchisement for women by peaceful and legal means, such as bringing petitions and Bills to parliament, and distributing literature for their Cause.

In 1903 Emmeline Pankhurst, frustrated at the lack of progress towards getting women the vote, along with her daughters Sylvia, Christabel and Adela, established the Women's Social and Political Union (WSPU), the members of which became known as the suffragettes (around 1906, after a Daily Mail article coined the phrase). Dora Montefiore noted that the WSPU[7] "revolted against the inertia and conventionalism which seemed to have fastened upon... the NUWSS", and certainly its aims were to employ more militant, public, and illegal tactics, although more so after 1905 when it was clear media interest in the fight for suffrage was waning. Their motto was 'Deeds not Words', and, unlike the majority of other groups in support of women's suffrage, they refused to join NUWSS[8].

Dr Bell became a friend and ally of Mrs Emmeline Pankhurst and Lady Balfour, who was also a prominent feminist figure of the time. In 1911, Dr Bell and Miss Margaret Robinson took part in WSPU activities in London[9]. On 21 November 1911[10] they were participating in a demonstration and were arrested for throwing stones through Swan and Edgar's London Department[9] store windows. Dr Bell was subsequently imprisoned in Holloway Women's Prison for this behaviour. There is no evidence that she engaged in any more violent or illegal acts which characterised the tactics of some suffragettes.

The suffragists in Belfast, when imprisoned, refused food in protest at the lack of recognition of their political status. The authorities were worried that if the suffragists died in prison public support for them would gain ground and so they began to release the women prisoners when their health deteriorated. Soon all suffragists took up hunger strikes in prison and the prison authorities started to force feed the women instead of releasing them. This involved inserting a feeding tube down the throat or nose of the prisoner and then introducing liquid into the tube. The procedure was very violent and often caused extreme pain and violent sickness. This practice of force feeding brought about public outcry and in 1913 the Cat and Mouse Act was introduced by the British Government to try and prevent suffragists from getting public support for their hunger strikes. The act allowed the prison authorities to release suffragettes on hunger strike who became ill, and then re-imprison them once they had recovered. The Cat and Mouse Act (officially, the Prisoners Temporary Discharge for Ill Health Act) was supposed to break the spirit of the suffragettes but it failed on every level. Suffragettes released under the Act often went into hiding to recuperate and then carried out more militant acts, but the support from the general public increased fourfold[9].

Dr Bell acted as doctor for the suffragette prisoners in the Crumlin Road Jail. In recognition of her service to the suffrage movement she received this certificate in or around 1912.

*"To Elizabeth Bell*

*On behalf of all women who will win freedom by the bondage which you have endured for their sake, and dignity by the humiliation which you have gladly suffered for the uplifting of our sex, We, the members of the Women's Social and Political Union, herewith express our deep sense of admiration for your courage in enduring a long period of privation and solitary confinement in prison for the Votes for Women Cause, also our thanks to you for the great service that you have thereby rendered to the Woman's Movement. Inspired by your passion for freedom and right may we and the women who come after us be ever ready to follow your example of self-forgetfulness and self-conquest, ever ready to obey the call of duty and to answer to the appeal of the oppressed.*

*Signed on behalf of the Women's Social and Political Union,*

*E. Pankhurst E.Pethick Lawrence"*

The public controversy surrounding the suffrage campaign ensured that no more than a minority of women were prepared to breach the social taboos. It is claimed that approximately one thousand women were actively involved in the Ulster movement by 1914[7]. However, most suffrage activity ceased with the outbreak of the First World War and it was not until 1928 that the Equal Franchise Act was passed giving women in Ulster equal voting rights with men, allowing all women aged over 21 to vote in elections[9].

## SERVICE IN THE ROYAL ARMY MEDICAL CORPS

In May 1916, Dr Louisa Aldrich-Blake, Surgeon at the Elizabeth Garrett Anderson Hospital and Dean of the London School of Medicine for Women, approached all the women on the Medical Register at the time asking them to say if they would be willing to serve with the Royal Army Medical Corps (RAMC). In July of that year Dr Bell was in the first group of women to join the Women's Medical Unit of the RAMC and on 2 August she embarked for Malta along with twenty-one others[10].

The Director General Army Medical Services, Sir Alfred Keogh, was responsible for employing medical doctors. They were referred to as "lady doctors" and were classed as civilian surgeons attached to the RAMC. Women serving as full time doctors in the Army and doing precisely the same work as their male colleagues had neither military rank nor status, but did receive the same pay, rations, travelling allowances and gratuity as temporary commissioned male officers of the RAMC. Dr Bell, according to her service record[11], was contracted to work for twelve months as a Civilian Surgeon in the RAMC. Her salary was 24 shillings a day, including allowances, but excluding duty transport. A gratuity of £60 was awarded at the end of the contract. Dr Bell requested to work in Irish Command but as no vacancies were available she was assigned to St Andrew's Military Hospital.

In August 1915, Malta hospitals had accommodation for 7044 patients. In March 1916, when the needs of the Gallipoli campaign had been met the number of beds had risen to 13,500. In July 1916, an outbreak of malaria among the troops in Macedonia brought weekly convoys of ships carrying the sick increasing from 718 to 2,587 in successive weeks. To accommodate them the beds in the hospitals and convalescent depot were increased to 25,570. The highest figures were reached in October 1916 when the demands of the Salonica Force made it necessary to increase the number of beds. To the end of August 1917, the total number of men treated in Malta was 125,000[12].

In 1915, it was decided to convert St Andrew's Barracks into a hospital. It was taken over by the RAMC on 4 May 1915 and provided 845 beds expanding to 1,158 beds using verandahs and tentage. Dr Bell was one of five lady doctors to work there. The type of cases managed in Malta depended on the phase of the war. During the time that she served in St Andrew's Hospital there were a large number of medical casualties mostly suffering from malaria, predominantly Plasmodium vivax type with a few Plasmodium falciparum. In addition to the malaria cases there were dysentery cases, some of which required drainage of liver amoebic abscesses. In April 1917, German submarine attacks on hospital ships made it unsafe to continue evacuating casualties to Malta from Salonica and five General Hospitals were mobilised at Malta for duty in Salonica. Thereafter, casualties arriving in Malta were greatly reduced[12]. Dr Bell left Malta in July 1917 and returned to Ireland.

## LIEUTENANT HUGO BELL FISHER

Dr Bell and Dr Fisher's son, Hugh Bell Fisher, was born on 5 April 1898 and educated at the Newry Intermediate School and the Royal Belfast Academical Institution, Belfast. In 1914 at the age of sixteen years he entered Queen's University, Belfast, Medical Faculty and had passed his first medical examination when he joined the Officer Training Corps of the University[13]. In November 1915, he was appointed to the 7th Battalion of the Royal Munster Fusiliers and served in various battalions of the regiment including the 1st Battalion. In July 1916, he was appointed to the 2nd Battalion and served overseas (Figure 2).


*Fig 2.*

It is known that Lieutenant Hugh Fisher fought in the Battle of Passchendaele, officially known as the Third **Battle** of Ypres, which was a major campaign of the First World War. The battle took place on the Western Front, from July to November 1917, for control of the ridges south and east of Ypres as part of a strategy decided by the Allies at Conferences in November 1916 and May 1917. Sir Douglas Haig ordered nine British divisions, led by Sir Hubert Gough's army, to advance on the German lines near the village of Passchendaele on 31 July. Passchendaele lay on the last ridge east of Ypres. By 6 November, Canadian and British troops had captured the village. The final battle came on 10 November. At 06.45 the 1st Canadian Division set off to push the Germans a little further north of the ridge.

Meanwhile the British II Corps was attacking the crest at Goudberg with two battalions leading. The battalion on the right lost direction and veered to the right causing a gap to appear. The Germans promptly counter-attacked and penetrated into this gap cutting off most of the battalion on the left, the 2nd Royal Munster Fusiliers. Of seventeen officers in the action only four returned and four hundred other ranks were killed, missing or wounded[14].

*Fig 3.*

A collection of biographical details[15] of old boys of Royal Belfast Academical Institution who served in the First World War and did not return compiled by Alan Curragh records the following:

*"Hugo was reported as being missing on 10th November 1917, the last day of the Passchendaele campaign, and later discovered to have been taken prisoner. The 2nd Royal Muster Fusiliers were taking part in the 1st Division attack on the Goudberg Ridge. They lost over 400 men that day, in which, for a time, they withheld a German counterattack on a position called Void Farm by throwing mudballs at them. The Germans mistook them for bombs and fell back.*

*Private Kennedy of the 2nd Royal Munster Fusiliers reported -*

*"I am in "C" Company, No 11 Platoon. Soon after passing the first German lines of trenches right down in the valley, I saw 2nd Lt Fisher lying on the ground on his face with his hands spread out. I passed him and went on."*

*Lance Corporal Milos wrote -*

*"I saw Lt Fisher being hit in the stomach. He fell in his face in the mud and did not stir again."*

*Hugo's mother received a letter from her son on 21st November, sent from Limburg, a clearing station for the wounded. She reported that "he writes very badly that he is feverish and wounded in the left foot."*

Hugo died on 23rd November 1917, at the age of 20, in a German field hospital in Beveren, Belgium, from a shell splinter wound to his left thigh. He was originally buried in the Military Cemetery at Beveren, but was re-interred at Harlebeke New British Cemetery (ref. XI A 8), Flanders, Belgium".

On 20 November Sir Douglas Haig decided to close down the Flanders campaign and claimed victory. However, the Passchendaele ridge was never used as a springboard for attacks on Bruges or Ghent nor had it exhausted the German Forces. The losses on both sides were enormous but never exactly known: it is estimated that British, French, Canadian, Australian and New Zealand forces suffered approximately 310,000 casualties[15], as opposed to 260,000 on the German side during the battle for Passchendaele. On the Allies side 90,000[16]soldiers were reported as "missing" and thousands upon thousands were never identified[14].

## RESIDENCES

Dr Bell's address in the Medical Register of 1910 was recorded as 83 Great Victoria Street, Belfast. From 1925 she lived at 4 College Gardens, which became the site of the Queen's Common Room[3]. She died at home on 9 July 1934, at the age of 71. Her obituary[4] is recorded in the British Medical Journal.

## HEIRLOOMS

When I qualified in medicine from Queen's University, Belfast, in 1974, my uncle, James Taylor Rea CMG MA gave me the chair that Dr Bell occupied in her surgery in Great Victoria Street. My father, Dr Martin Alexander Rea, MB RAMC OBE bequeathed to me her certificate denoting her support of the suffrage movement (Figure 3) and her (Figure 4) and her husband's graduation certificates.

I also possess a copy of a letter dated 15 November 1917 and headed "BEF, France and signed by 2nd Lieutenant John Doorley, 2nd Royal Munster Fusiliers informing Dr Bell unofficially, as a friend of Hugo, that he was wounded and a prisoner. According to his enquiry from the men he led into action, he was last seen lying in a shell-hole with a wound in the head. Expressing his deepest sympathy of all in the battalion, he stated that Hugo was "very popular in the battalion".

The official letter confirming that Hugo was "missing believed to be killed" was dated 13 November 1917 and signed by Herbert P.K. Ireland, Lieutenant Colonel, Commander, 2nd Royal Munster Fusiliers. It states, "He led

his men into action on the morning of the 10th November with great gallantry and arrived at his objective. While there he was seen to fall believed instantaneously killed. At that time we were subjected to intense shelling at that point and some counter-attacks and we lost some of our ground including that where your son was and therefore I cannot definitely assure you of his fate. But no doubt whatsoever remains in my mind after sifting the accounts that he was shot dead and suffered no pain. I enclose a slip showing the disposition made of his personal effects. If I can be of any use to you in the matter please command me". I do not have the letter Hugo gave to Lieutenant Doorly to give to his mother just before he went into action, should anything happen to him.


*Fig 4.*

A letter written by Hugo in reply to a letter written by my father, was postmarked 1 October 1917. My father was aged fourteen at the time. It is obvious from the letter that Hugo was unable to say much about his whereabouts or the conditions of warfare. He refers to moving every three days. However, Hugo's sense of humour is reflected in his writing: about the battlefield he writes "there are little bits of lead flying about and they don't seem particular as to what they run into. But there is always some nasty medicine in every spoonful of jam n'estce pas?" His letter ends with the words, "Thanks for your good wishes. I'll do my best to avoid running into one of those things. See and have a good time yourself. Cheery O, Your cousin, Hugo".

Dr Bell was known in the family as "Aunt Betty". It is noted in family records that she was quite a formidable lady but very hard-working and kind. Living close to the University, she was visited often by her nephews and nieces and at times provided them with accommodation while they were studying at University.

## THE ULSTER HISTORY CIRCLE BLUE PLAQUE

The Ulster History Circle is a small voluntary, non-profit, organisation that places commemorative plaques in public places in towns and villages all over the Province in commemoration of men and women who have contributed to its culture, industry and history. When Dr Bell was awarded the Blue Plaque (Figure 5) it was decided to place it at Daisyhill Hospital because it occupies the site of the Newry Workhouse close to where Dr Bell was brought up and where her father worked. The Workhouse was built in 1841 and functioned until 1948. It is quite possible that Dr Bell and her sister were inspired by the plight of the destitute inmates of the workhouse to devote their lives to the service of others.


*Fig 5.*

It was my privilege to be present at the unveiling of the Blue Plaque and to speak, as a relative, about Dr Bell's life history and achievements. Her husband, Dr Hugh Fisher, was a brother of my paternal grandmother. Dr Bell was a truly remarkable woman, intelligent and courageous, whose life was marred by immense tragedy with the death of her husband and the loss of her son. She succeeded in medicine despite discrimination on the grounds of gender. Joining the profession in the first place was a major challenge and she, along with other women doctors during the First World War, were found to be competent, effective and resourceful. She was also a pioneer of the feminist movement in Ireland.

Dame Beulah Bewley[16], in her article about the careers of early women doctors, concluded; "In the early twentieth century a successful woman doctor described her position in the profession as being 'on the inside sitting alone'. One hundred years later, women are prominent in all branches of medicine in Ireland, as elsewhere, and owe their success in large part to these early pioneers".

**ACKNOWLEDGEMENTS**

I would like to thank Alan Curragh for his kind permission to quote his biographical details of Lieutenant Hugh Bell Fisher and Maud Hamill, Ulster History Circle, for her photograph of the Blue Plaque and for her helpful advice.

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*Ulster Med J* 2017;**86(3):**196-197

*Medical History*

# Dr Robert Stephenson's Address to the Belfast Medical Society on 2nd December 1850

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Accepted: 21st February 2017
Provenance: Internally peer-reviewed.

## SUMMARY

Dr Robert Stephenson's presidential address for the 1850–51 session is available online. It offers a more detailed explanation for the failure of the first Belfast Medical Society than do other accounts. It also discusses the revival of the Society in 1822.

## INTRODUCTION

A list of presidents for the current society and its two main predecessors has been placed on the Ulster Medical Society's website. It contains links to all available presidential addresses before 1980, the earliest and most interesting historically being Dr Robert Stephenson's which was delivered to the Belfast Medical Society on 2nd December 1850.[1] He had been asked to speak on the revival of the Society in 1822 and was uniquely placed to do so as he was the only survivor of those who had attended the first meeting and had been Secretary to the Society for its first sixteen years. The importance of his address, however, lies not so much in the revival, although that is of interest, as in what he had to say about the failure of the first Belfast Medical Society. This was founded in 1806 as a medical library, ran into trouble about 1814 and ceased to exist in 1818. Its books, chiefly comprising valuable donations from Dr William Drennan and Dr William Halliday, were kept in 'the hospital' which in 1806 would have been the 'Belfast Dispensary and Fever Hospital' in West Street, established in 1799. This charitable institute had been founded in Factory Row in 1797 under the pressure that year of unusually prevalent fever but closed within months when its limited funds were exhausted. An even greater outbreak of fever in 1816 and 1817 lead to the accelerated completion of a new 'Fever Hospital' in Frederick Street in 1817, which, in 1845, and under new trustees, became the 'Belfast General Hospital'. (This in turn became the 'Belfast Royal Hospital' and then the 'Royal Victoria Hospital'.)

In 1851, Dr Andrew George Malcolm published his *History of the General Hospital, and the Other Medical Institutions of the Town* from which much of the history above is taken.[2] Malcolm had been present at Dr Stephenson's address but in his book he chose to be discreet about the Society's trouble saying only that there were 'serious difficulties of opinion among the Hospital attendants' and that the 'demon of discord invaded its ranks.' Stephenson's knowledge of the difficulties must have come indirectly from others as he could not have experienced them personally (he qualified from Edinburgh in 1817), and it is unlikely that they were recorded in the minutes. (Malcolm said that those up to 1814 were extant in 1851 although they have since been lost.)

## THE TROUBLE

Stephenson did not go into details and did not name names but it is clear that the unpleasantness had been building up for some time before erupting. He said that the Society 'became exclusive, chary of its admissions, centralized until nothing remained except the governing authorities.' The ordinary members had left, 'weary of the views, and of the measures of those active in the management.' The authorities (president, officials and council) then fell out among themselves over the medical care of the poor, whether it should be 'by gratuitous attendance, or by officers appointed, and paid by salaries.' As funds were limited and as the cases of sickness claiming relief were 'numerous and pressing' (perhaps related to the fever of 1816–17), the views of the former prevailed. Stephenson said 'That was indeed the season of faction, and party-spirit among the profession in Belfast.' The terms 'faction' and 'party-spirit' could imply the involvement of religion or politics but he offers no other evidence for this and one hopes that he meant only that the argument was hotly contested by both sides. In any event, much bitterness resulted and those holding the second view seceded from the Hospital and 'scattered the books connected with the library' before clearing the library of its contents altogether. Their first thought was to divide the books by lot; the second was to sell them by auction and divide the proceeds among themselves. Legally this might have been permissible but morally it was questionable and after 'strong remonstrance' the books were returned to the donors. This must have been during or after 1820 as Dr Drennan died in that year[3] and his books were received by his family. Robert Stephenson said that 'the late Dr Stephenson'—presumably his father, Dr Samuel Martin Stephenson, who died in 1833[3]—then persuaded Dr Halliday and Dr Drennan's family to return the books to the Hospital, taking responsibility for their safety. It is reasonable to

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suppose that eventually the responsibility for the books was transferred back to the Belfast Medical Society (that is 'the library').

## THE REVIVAL

In 1822, Robert Stephenson took the first step towards the revival of the Belfast Medical Society by summoning 'the attending and consulting staff' to meet in the Hospital on the 8th of May but he said that 'only four answered to the call.' Those founders were Drs McDonnell, Forcade, R Stephenson and Mr Moore.[4] Given the previous difficulties it is not surprising that the revived Society had no council or president, the arrangement being that the fifth person to enter the room at each meeting fulfilled the quorum and acted as the chairman. The first five also constituted a Standing Committee during the ensuing month 'to look after [the Society's] business in any case of emergency, or to give council to the Treasurer, or Secretary in any case of doubt.'

## TREASURER AND SECRETARY

Dr Forcade was the first Treasurer and Dr Stephenson the first Secretary and they continued to be re-elected annually until 1835 in the case of Dr Forcade (who died) and 1838 in the case of Dr Stephenson (who retired). Stephenson was highly regarded and his retirement as Secretary was marked by a public breakfast in the Temperance Hotel in Waring Street[5] and a presentation of the Bridgewater Treatises specially bound and containing the autographs of the members. He in turn had high regard for Dr Forcade saying that he 'would work with the diligence of a clerk on every detail, that could in any way tend to the perfection, and stability of a Society so essentially connected with the mutual improvement, and intelligence of his professional brethren.' The chances of potential troublemakers succeeding must have been considerably reduced with those two holding the only permanent offices.

## DR STEPHENSON ELECTED PRESIDENT

In 1850, after twenty-eight years of stability, the Society decided that the existing system of governance was no longer adequate and on 7th October it was recorded: 'Seeing the necessity there is for some recognised head in this body, it is resolved that a member be annually elected by ballot to act for the year as President of the Medical Society.'[4] The following month Dr Stephenson was elected to that position and Drs McGee and Malcolm were elected Vice-Presidents. It was further agreed that 'in addition to the President and Vice-presidents six members be annually elected, who shall constitute the Council of the Society….' Dr Stephenson was negative in places in his presidential address, ironically not favouring the changes in the Society which had led to his presidency, and calling its Pathological Museum a 'morbid excrescence'. He later had the address printed by Marcus Ward & Co., Belfast, and every member of the Society was presented with a copy. Very few of these are now known to exist and the Ulster Medical Society is indebted to Dun's Library, Royal College of Physicians of Ireland, Dublin, for providing a scan of their copy with permission for it to be transcribed and placed online.

## AFTERTHOUGHT

Malcolm, quite rightly, said of the troubles of 1814 that they were 'a blot upon our medical annals' but every cloud has a silver lining and it is possible that today the Ulster Medical Society is the better for them. William Whitla joined the Ulster Medical Society in 1874 and it is likely that he was aware of the contents of the address Robert Stephenson had given twenty-four years previously. Might the account of the greed displayed have influenced the terms of the trust deed of the (Whitla) Medical Institute of 1902 such that the Ulster Medical Society would not benefit from its sale should it come to that? It is not impossible—in which case we owe our present rooms[6] to our quarrelsome predecessors of 1814.

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*Ulster Med J* 2017;**86(3):**198-200

*Medical Education*

# Adaptive Learning in Medical Education: The Final Piece of Technology Enhanced Learning?

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Accepted date: 2nd May 2016
Provenance: externally peer-reviewed

## ABSTRACT

Technology enhanced learning (TEL) is now common practice in the field of medical education. One of the primary examples of its use is that of high fidelity simulation and computerised mannequins. Further examples include online learning modules, electronic portfolios, virtual patient interactions, massive open online courses and the flipped classroom movement. The rise of TEL has occurred primarily due to the ease of internet access enabling the retrieval and sharing of information in an instant. Furthermore, the compact nature of internet ready devices such as smartphones and laptops has meant that access to information can occur anytime and anywhere. From an educational perspective however, the current utilisation of TEL has been hindered by its lack of understanding of learners' needs. This is concerning, particularly as evidence highlights that during medical training, each individual learner has their own learning requirements and often achieves competency at different rates. In view of this, there has been interest in ensuring TEL is more learner aware and that the learning process should be more personalised. Adaptive learning can aim to achieve this by ensuring content is delivered according to the needs of the learner. This commentary highlights the move towards adaptive learning and the benefits of such an intervention.

## BACKGROUND

Technology enhanced learning (TEL) now plays a significant role in the field of medical education. Examples being the flipped classroom approach where video based information is delivered to learners prior to class with class time spent problem solving[1], Problem or Team Based Learning sessions where portable devices allow for the instant retrieval and sharing of information among peers and faculty[2]; high fidelity simulation and computerised mannequins[3]; and in assessment practices where exams are delivered via computer based instruction[4].

Easy access to the internet via portable connected devices allows doctors to gain clinical information instantly, either in the ward or clinic environment. Platforms such as UpToDate (http://www.uptodate.com/) and eMedicine (http://emedicine.medscape.com/) can provide expert knowledge and there is increasing use of app based access to medical journals. Doctors also rely on technology to further their learning through the use of online knowledge based modules[5]. This concept takes the learning process further with the inclusion of assessment, providing learners with instant feedback. This is particularly beneficial as feedback from more formal examinations is often limited[6].

Technology based high fidelity simulation has allowed learners to take part in clinical scenarios in a safe learning environment and gain knowledge and skills to better equip them when dealing with real life patients. Simulation can help to provide instant feedback and allow for the repetition of clinical situations in order to better ensure competency is reached[3].

Technology has also allowed for documentation of a learner's progress during training courtesy of online portfolios[7]. Here, trainees and specialists can capture their competency across the domain of knowledge, skills and attitudes in relation to a particular area. They can also take part in reflective based writing of cases which were managed well and those more difficult to manage situations. The introduction of revalidation in the UK and the American Board of Medical Specialties (ABMS) Portfolio Program in the US means that demonstrating competency is now a formal requirement and electronic portfolios are an obvious choice for record keeping as well as distribution of an individual's performance to date[8].

## ADAPTIVE LEARNING (AL)

Whilst the use of technology has been positive in many aspects of medical education, one of the primary concerns from a learning point of view is its current lack of recognition of a learner's needs. At present TEL is delivered in a standard fashion to reach a large cohort of learners regardless of individual knowledge, understanding or skills. This is problematic as it is well recognised that learners during training have different levels of understanding and subsequent knowledge gaps. Whilst some may achieve competency

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relatively quickly, others may struggle to do so. Variation in rates of competency achievement is well recognised but is not easily solved when teaching materials are delivered on a mass scale. From a teacher perspective, engaging with learners one on one and recognising each individual's strengths and weaknesses is simply not possible during large scale lectures and seminars where often due to time constraints, information is delivered in a passive fashion[9]. It is important to appreciate that more needs to be done to achieve the true potential of technology enhanced learning. In our view, TEL should be leveraged to address real life teaching and learning problems such as learner diversity and engagement. With these points in mind, TEL can be conceived as a means to enhance faculty-learner interactions, as well as learner-content interactions[10]. By ensuring that content is learner specific, a personalised and adaptive learning environment can help individuals better meet their competency requirements.

At the most basic level, adaptive learning is a process that provides an individualised learning experience with technologies designed to determine a learner's strengths and weaknesses. Once an individual's strengths are recognised, the computer based technology can modify the learning material to ensure that there is greater focus on an individual's limitations. One example comes from The University of New South Wales, which offered a massive open online course (MOOC), "Learning to Teach Online". In this course, there were thousands of learners with just two core teachers and hence educational support on an individual basis was impossible. This situation was addressed by having learners engage with assessment and reflective activities that generated personalized learning content based on their responses and self-reflection information. From an exam and course participation perspective, research by the Educational Growth Advisors on the use of AL has demonstrated an 18 percent increase in pass rates and 47 percent decrease in withdrawal from educational courses[11].

Adaptation is however not just limited to the content for learners based on their particular learning requirements. Other forms of adaptation include: an adaptive system interface where learner preferences are met with respect to navigation and structure of the course content, the discovery and assembly of content from multiple sources – such as learning repositories available via the web and discussion forums to connect peers and faculty with each other, based on a specific understanding of each individual learner and their requirements[12].

In the medical field, there has been little in the way of formal research into adaptive learning uses, yet this is likely to change as time progresses. Elsevier currently utilises an adaptive learning platform powered by Cerego to assist health science users. Dr Jan Plass at NYU, commented that "Cerego ensures a continuous update on research theories allied to learning and information processing. Performance is predicted per user to determine what they already know and what they need to know, helping to ensure an understanding of higher level tasks[13]". McGraw Hill Education has also entered the AL domain and partnered with technology company Area9, founded by Dr Ulrik Christensen, one of the pioneers in this area[14] . More recently, the NEJM launched an adaptive learning process, in recognition of the fact that frequent updates in the medical field conflict with clinicians' limited time. The resource focuses on clinical scenarios which aim to mirror real life occurrences with the knowledge + learning system designed to aid preparation for internal medicine exams[15].

Published work by Kellman in relation to AL, centres on the repeat delivery of specific knowledge items or categories if mistakes are made. There is also use of "interleaving", where information is delivered in an alternating or mixed fashion to better ensure learning gains whilst "mastery criteria" ensure specific learning objectives are reached before a learner can be deemed competent[16]. These techniques have been trialled during delivery of the dermatology histopathology curriculum at UCLA with significant improvements in pre and post-test scoring ($P < 0.0001$). In the future, there is also hope for the utilisation of AL in relation to more procedural and high fidelity simulation based tasks. Figure 1 illustrates 2 examples of Adaptive Learning.

- **Preparation for examinations** - > attempts gastroenterology specific questions - > AL system recognises optimum knowledge of extra manifestations of inflammatory bowel disease but poor knowledge of treatment escalation - > computerised delivery of treatment escalation occurs to ensure an understanding of this poorly understood aspect

- **Preparation for real life working** - > attempts module on management of acute conditions as part of continuing professional development (CPD) - > AL system recognises optimum knowledge of the features of sepsis but poor knowledge of antibiotic prescribing in relation to infection - > computerised delivery of information on antibiotic prescribing occurs to ensure an understanding of this poorly understood aspect

*Fig 1*. Medical student or doctor in training potential AL examples

## CLOSING REMARKS

In this commentary, we have sought to show that TEL has failed to an extent to deliver value added learning and that the adoption of more learner specific, adaptive learning systems could address this issue by solving real life teaching and learning problems specific to knowledge deficiencies and user engagement. Adaptive learning could generate personalized learning content to improve mastery of learning and connect learners and faculty to one another based on educational needs. Faculty could then engage with their learners at a much deeper level recognising learner deficiencies and facilitating

the learning process[17].

No conflicts of interest

Funding NA

All authors contributed equally to this article and agreed the final version following re edits. No previous work by ourselves has been published on this aspect.

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# Letters

## PARAMILITARY SHOOTINGS AND ASSAULTS

Editor,

Few doctors working in Northern Ireland will be surprised by the findings of McGarry K et al[1] that 20 years after the IRA and UVF/ UDA 'ceasefires' in 1994 there were MORE patients admitted to the RVH after paramilitary shootings and beatings than before the 'ceasefires'.

The accompanying paper by Napier et al[2] noted that since the 'ceasefires' across Northern Ireland there have been 3691 patients requiring orthopaedic expertise after loyalist and republican attacks. Truly an Irish ceasefire!

My only criticism of these most valuable papers is in their use of the term 'punishment attacks'. This shameful but all too often used term trivialises, sanitises and in essence colludes with what are unjustified, vicious and occasionally murderous crimes.

Shockingly- but not surprisingly- 500 victims were under 18 years old, with some just 12. This is, of course, child abuse.

I can't conceive of any other society where the victims of child abuse would have their abuse described as 'punishment'!

Orwell[3] said: 'political language makes murder respectable and lies sound truthful'.

Doctors must be careful not to fall for the euphemisms and mistruths of propagandists.

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## AUTHOR'S RESPONSE: PARAMILITARY SHOOTINGS AND ASSAULTS

Editor,

Dr. McGarry makes a valid point that the use of the term, "Punishment," implies fault on the victim's behalf. There was no documented evidence that any of the cases included in our study were involved in criminal behaviour.

It is however important to differentiate these assaults from random acts of violence. Considering the significant financial, social and cultural impact of such attacks on our local communities it is time that critical awareness is raised about their ongoing frequency. Perhaps it is indeed time the euphemism of, "Punishment Attack," is replaced with a dysphemism that better reflects the grim reality of the event.

Dr. Kevin McGarry

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## INAPPROPRIATE ED ATTENDANCES IN NORTHERN IRELAND: COMMENT FROM RCGP NORTHERN IRELAND.

Editor,

We wish to comment on a letter published in the January 2017 edition of Ulster Medical Journal which discusses inappropriate attendance at emergency departments (ED) in two ED departments in Belfast Trust which were largely self-referrals [1].

We feel this retrospective observational survey had many methodical flaws. The most obvious of these was the author's definition of an inappropriate attendance at an emergency department.

This subject has been researched extensively and an internationally recognised definition of appropriate attendance at ED has not yet been made. It is unsurprising then that the range of values of inappropriate attendance in different studies varies from 6% to 80% [2].

The authors define "inappropriate attendance" by "no change in patient management, addition to the patient care or …add to the patient journey." They were however all triaged by a clinician who accepted responsibility for this. Thus, we feel this definition of inappropriateness is subjective and does not take into account the fact that the investigators were relying solely on the accuracy of the information provided on the ED notes and patient's history.

We share the author's frustration at patients accessing services inappropriately however we feel the need to work together to ensure the best care for our patients. We were surprised that 16 cases referred by GPs were deemed inappropriate.

A robust, prospective study on factors influencing ED attendance would be welcome as it could help identify the real issues of attendance – such as social, environmental and professional – and inform future investment in the best solutions.

We feel recent proposals by NHS England of placing a GP in every ED department would be counterproductive. It would destabilise our workforce further and would encourage more patients with primary care problems to attend ED.

Dr Laurence Dorman

RCGPNI Deputy Chair for Policy

On behalf of RCGPNI Executive Team

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1. Todd A, Johnston PC. Uptake of the use of patient-doctor e-mail in an endocrinology outpatient setting. *Ulster Med J*. 2017;86(1):42-9.

2. Murphy AW. Inappropriate' attenders at accident and emergency departments I: definition, incidence and reasons for attendance. *Fam Pract*. 1998;15(1): 23-32.

## AUTHORS' RESPONSE: INAPPROPRIATE ED ATTENDANCES IN NORTHERN IRELAND: COMMENT FROM RCGP NORTHERN IRELAND.

Editor,

We thank Dr Dorman and the RCGPNI Executive Team for their interest in our work and we are pleased to reply.

Dr Dorman rightly acknowledges that there is no internationally recognised definition of an Emergency Department (ED) inappropriate attendance. A recent survey of ED nurses, doctors and paramedics in three Irish hospitals identified a variety of definitions of inappropriate attendance, with variation within the different professional groups.[1] It is possible that other healthcare practitioners may have disagreed with some of the assessments made by the small group undertaking our analysis of attendances.

We recognise the limitations associated with our review, including its small size and its retrospective nature, which, as we acknowledge in our paper, means that our analysis was limited by the comprehensiveness of the ED notes.

We would welcome further, larger studies into the appropriateness of ED attendances and the characteristics associated with ED attendance. Studies undertaken in other areas have provided some analysis of the determinants of ED use.[2,3]However, despite the limitations which we have noted in our own analysis, we believe that it has given us some useful information on the proportions of attendees to EDs, within one Trust in Northern Ireland, who may have the potential to be seen safely in alternative settings.

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## COMPLETE TRANSECTION OF THE RADIAL NERVE ASSOCIATED WITH A CLOSED HUMERAL SHAFT FRACTURE

Editor,

A 29-year-old female sustained a closed, comminuted fracture of her left midshaft humerus (**Figure 1**) with an associated radial nerve palsy, disruption of her right sacro-iliac joint with an associated fracture of the right superior pubic ramus and a stable first cervical vertebral fracture as the result of a high-speed road traffic accident. The pelvic injury was stabilised using two sacro-iliac screws and a halo-vest applied in order to manage her cervical spine fracture. A decision was taken to proceed with operative fixation of her left humeral shaft fracture to assist with postoperative mobilisation.

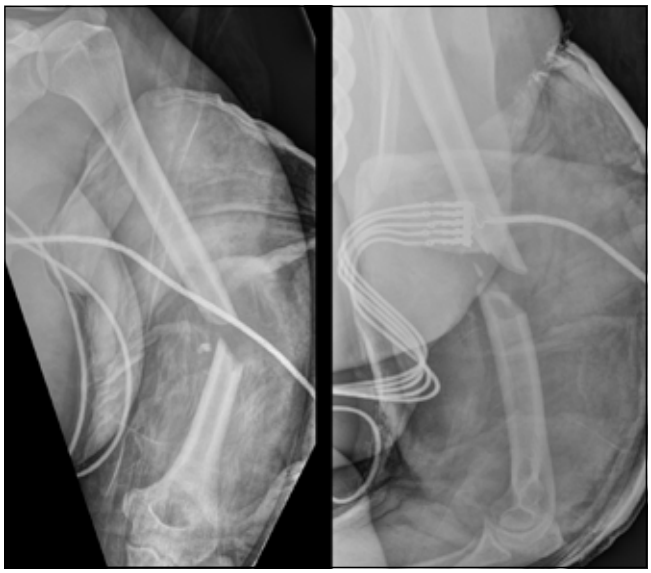

*Fig 1*. Preoperative anteroposterior and lateral radiographs of left humerus.

The humeral shaft fracture was exposed via an anterolateral approach. The fracture fragments were noted to be widely separated with significant periosteal stripping and soft tissue disruption. The radial nerve was found to be completely transected just proximal to the level of the fracture. The humeral fracture was stabilised using a narrow dynamic compression plate (**Figure 2**). A direct end-to-end nerve repair was performed once fracture stability had been achieved. Postoperatively she was referred for splinting and upper limb rehabilitation. The pelvic and cervical spine injuries healed without complication and the left humeral shaft fracture proceeded satisfactorily to bony union. Approximately 11 months post-injury, the patient regained full recovery of her left radial nerve motor and sensory functions (**Figure 3**).

Approximately 11% of patients with a closed humeral shaft fracture develop a radial nerve palsy with spontaneous recovery of nerve function occurring in approximately 70% of cases and hence the presence of a radial nerve palsy at the time of a closed humeral shaft fracture is not an absolute indication for surgical exploration.[1] Middle third humeral fractures have the highest incidence of nerve injury because

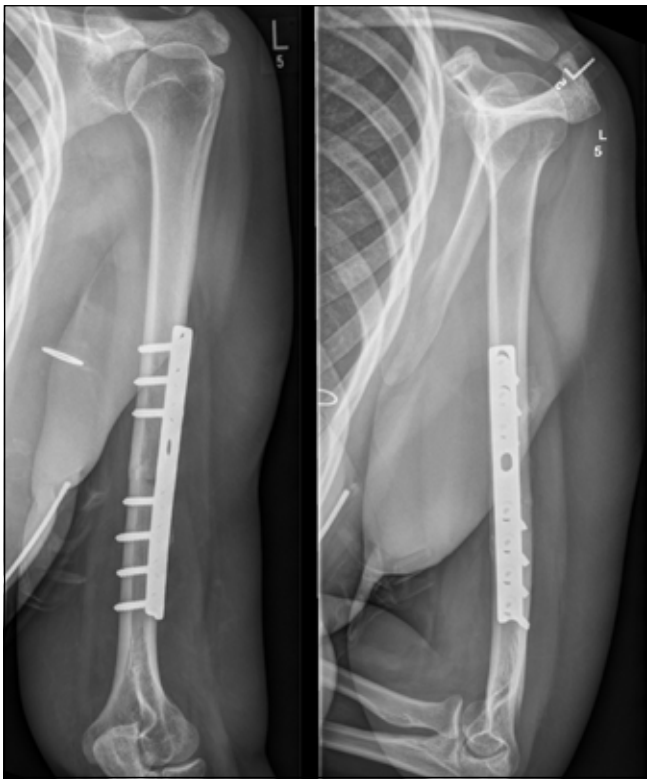

*Fig 2*. Postoperative anteroposterior and lateral radiographs of left humerus.

the nerve lies immediately adjacent to the periosteum in this region [2]. Closed fractures are more commonly associated with a neurapraxia, whereas neurotemesis is more common in open fractures [3,4].

Leucht et al. [5] reported two cases of radial nerve transection associated with a closed humeral shaft fracture. Both patients underwent operative fixation of their humeral fracture due to their associated injuries and at the time of surgery transection of the radial nerve was noted. The authors concluded that without the additional injuries the two patients would have been candidates for functional bracing with the result that the radial nerve transection would have been missed.

Non-operative treatment of closed humeral shaft fractures usually leads to a satisfactory outcome even in the presence of a radial nerve palsy. However, some patients may have a radial nerve transection which will be missed if their fracture is treated conservatively. We suggest that the possibility of radial nerve transection should be considered in closed humeral shaft fractures with an associated radial nerve palsy which occur as a result of high-energy trauma or those fractures where there is marked displacement of the bone fragments.

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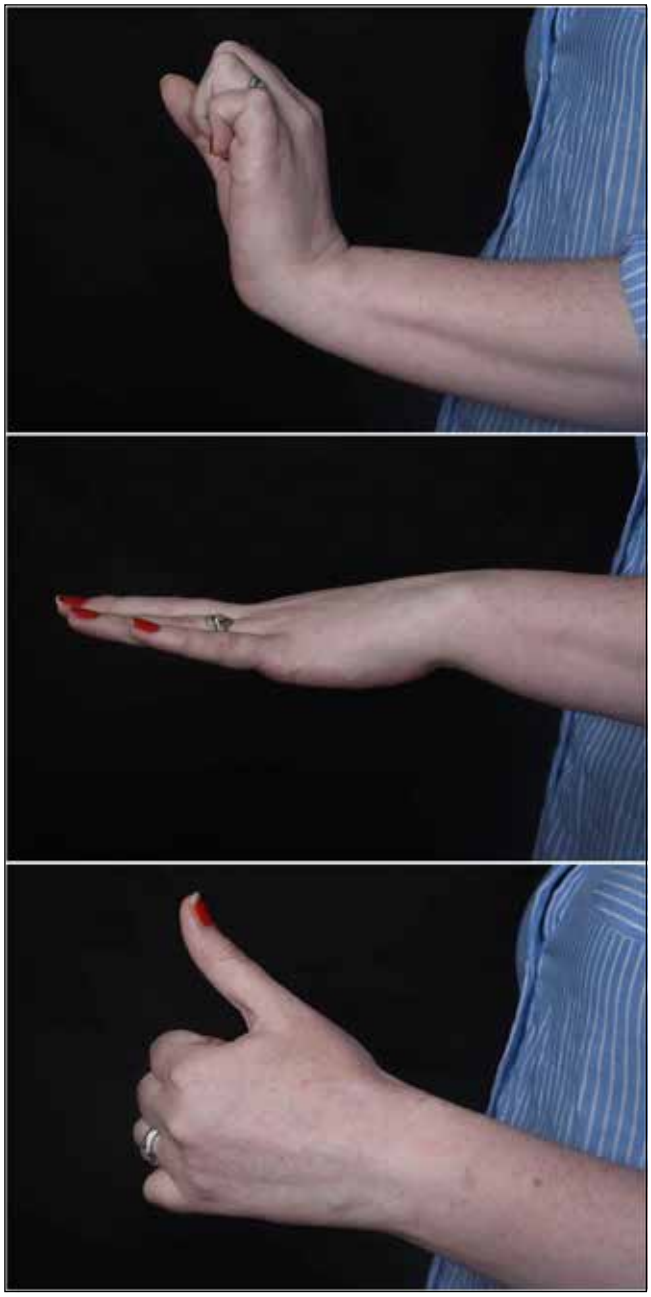

*Fig 3*. Clinical pictures demonstrating active left wrist extension and active extension of the fingers and thumb left hand.

## ATYPICAL PRESENTATION OF SOFT TISSUE SARCOMA

Editor,

Soft-tissue sarcomas are rare malignancies of mesodermal origin and constitute <1% of new malignancies. There are multiple histological sub-types and only about 10% of all sarcomas are synovial. They usually present as a painless limb mass. Metastases can be as common as 40% with high-grade tumours and occur most commonly in the lung, but may also affect liver, brain and bone [1].

A 27 year old man presenting with left sided chest pain was found to have multiple soft tissue lung lesions on chest x-ray (Figure1). A CT guided biopsy was unsuccessful and referral for VATS (video assisted thoracoscopic surgery) was made to obtain tissue samples.

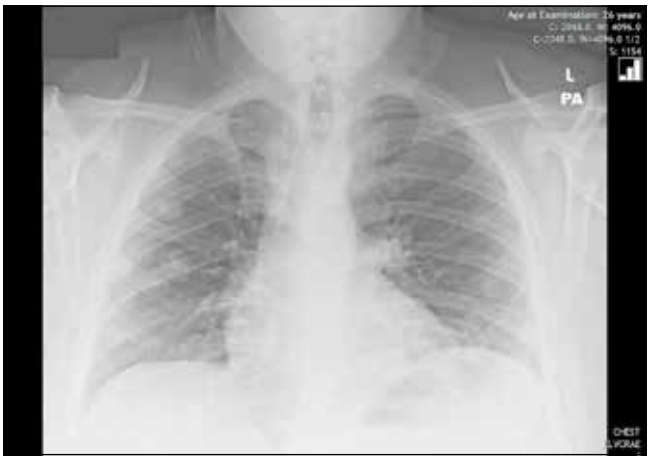


*Fig 1 Chest X-ray showing multiple lung nodules*

At review 1 month after the initial chest X-ray, the presence of long-standing inflammation of the right foot became evident. The right foot had been inflamed for 6 months and was significantly larger than the left with mild erythema (Figure2). MRI of the foot revealed a large lesion at the medial aspect with bony erosion consistent with a malignant tumour.

VATS identified large abnormal lung nodules (Figure3) confirmed to be malignant on frozen section. The histology was not typical of lung carcinoma, melanoma or common pleural/lung lesions. Immunohistochemistry showed positive staining of biphasic spindle cells with CD99, EMA and bcl-2, as well as focal staining with Cam 5.2 and AE1/3 in the epithelioid areas. This favoured a diagnosis of synovial sarcoma confirmed with the presence of t(X;18) translocation identified by molecular studies. No further biopsy of the primary lesion was deemed necessary to confirm the diagnosis of metastatic synovial sarcoma.

The t(X;18) chromosomal translocation identified in the sample sent for molecular pathology is typical for synovial sarcoma and essentially describes a fusion between SSX on chromosome X and SS18 on chromosome 18 [2,3]. This translocation is virtually pathognomonic for human synovial sarcoma [3]. The fusion process is similar to the oncogenesis of certain leukaemias [2].

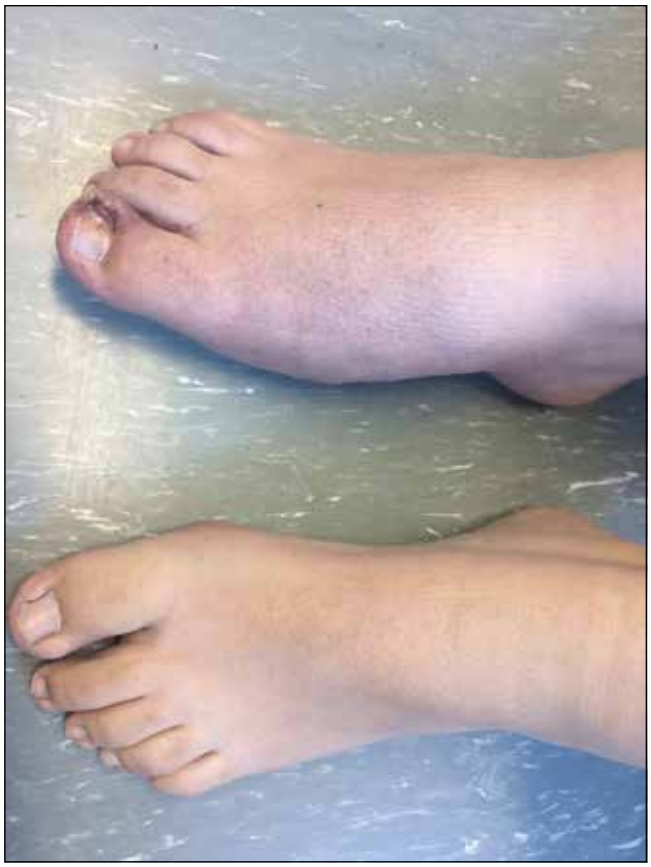

*Fig 2 Swollen right foot as compared to left foot, initially thought to be unrelated*

The stable SS18-SSX fusion protein created as a result of the translocation is subsequently incorporated into the BAF complex. This prevents the BAF47 subunit, usually part of the complex, from inclusion. BAF47 is a tumour suppressor gene and its absence may play a significant role in the development of synovial sarcoma [2]. Interestingly, proliferation of synovial sarcoma may be potentially reversible if normal complexes are reassembled. This may guide the development of future therapeutic agents [3].

This case highlights the importance of a thorough patient review. This was an atypical presentation of synovial sarcoma with the pulmonary metastases identified prior to the primary

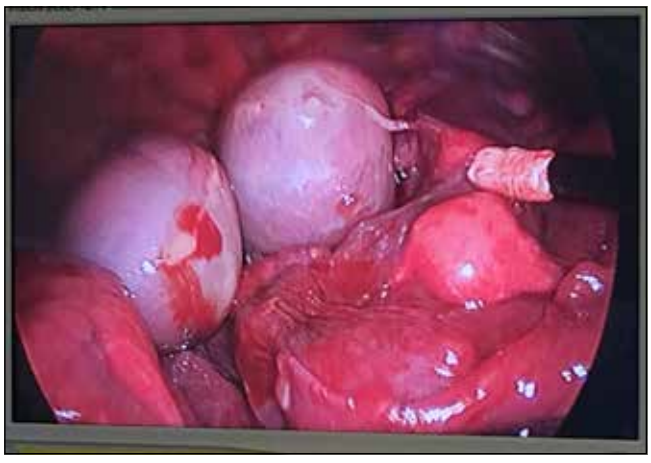

*Fig 3 Macroscopic images of lung nodules during VATS procedure*

malignancy. It is unusual for synovial sarcoma to be identified from incidental findings of lung metastases. The patient was treated with trabectadin instead of doxorubicin in view of compromised left ventricular ejection fraction. Trabectadin is at least as efficacious as doxorubicin for the treatment of translocation-related sarcomas [4]. One year after initial diagnosis he is receiving palliative chemotherapy, with metastases mostly stable in size. The mass in the right foot has continued to grow in size, as have some of the pulmonary nodules.

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## NO BABY BOOM OR SEX RATIO CHANGES FOLLOWING *FIFTY SHADES OF GREY* IN ENGLAND AND WALES

Editor,

*Fifty Shades of Grey* (FSOG) was a 7/2011 erotic romance that traces the deepening and complex relationship between a college graduate and a young business magnate, with soft porn elements that include bondage/discipline, dominance/submission, and sadism/masochism. The media hyped this, claiming FSOG "sparked a "mommy porn" revolution".[1] The second and third volumes of FSOG were published in 4/2012. A film adaptation of the first book was released on 13 February 2015.

FSOG was touted as inciting increased coital activity, thereby potentially resulting in a baby boom. "It's one of the hottest and best-selling book series of all time. It has made millions of readers swoon".[1] August authorities were cited as confirming this effect. Robin Milhausen, an Associate Professor of Family Relations and Human Sexuality at the University of Guelph, was quoted: "the material is arousing… Many women respond to the book and don't even know it. It's leading to more sex".[2]

The male to female ratio at birth (male divided by total births: M/T) approximates 0.515 (slight males excess). Numerous factors may affect M/T.[3] Increased coital activity may not only increase the birth rate but also increases M/T as sex ratio at conception follows a U-shaped regression curve on cycle day of insemination. Thus, increased coital activity will increase the likelihood of conception early in the cycle, increasing male conceptions.[4]

This study sought spikes in total births or M/T in England and Wales circa nine months following FSOG books.

## METHODS

Monthly male and female births for England and Wales were obtained from the Office for National Statistics for 1/99-8/99 (Ms. Athena Ray – personal communication). The null hypothesis was that FSOG releases in 7/2011 and 4/ 2012 did not influence total births and M/T circa nine months later, i.e. 4/2012 and 1/ 2013.

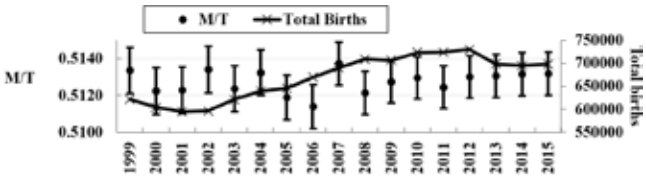


*Fig 1*. Annual births and M/T for England and Wales, 1999-2015

## RESULTS

This study analysed 11831728 live births (M/T 0.5128, 95% CI 0.5125-0.5130). Annual births and M/T shows no discernible spikes (figure 1). A monthly breakdown for 1/2010-8/2016 shows no discernible spikes in total births or M/T at/around 4/2012 and 1/ 2013 (figure 2).

## DISCUSSION

Linda Murray, Global Editor-in-Chief of BabyCenter.com stated that "reading '50 Shades of Grey' is acting like an aphrodisiac for women…It's putting them in the mood more frequently and they're having more sex and they're ultimately getting pregnant faster".[1] And the Daily Mail averred that "the meteoric rise of Fifty Shades of Grey is set to spark a new wave of births, according to pregnancy and parenting websites".[5] FSOG was therefore anticipated to result in a "revolution … coming to the delivery room, where a baby boom sparked by the "Fifty Shades of Grey" phenomenon is predicted".[1]

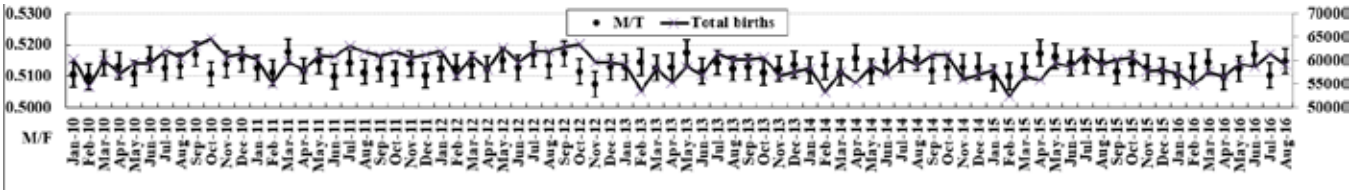


*Fig 2*. Monthly births and M/T for England and Wales, January 2010-August 2016

This paper thus highlights the importance of measurement of cause and effect since expected effects may not always ensue from events. It also highlights the importance of the availability of M/T data by month since analyses as carried out in this study are impossible without data at this level of detail.

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## IS IT TIME TO REVISIT THE RED FLAG REFERRAL SYSTEM?

Editor,

The 'red flag referral' system is currently under stress due to the huge number of suspected cancer referrals. There are guidelines from both the Northern Ireland Cancer Network (NICaN)[1] and the National Institute of Clinical Excellence (NICE)[2] regarding specific criteria for what constituents a red flag referral.

The red flag referral pathway is centred on two groups of patients:

1. 95% of patients identified with cancer should begin their definitive treatment within 62 days of referral (typically General Practice referrals)
2. 'In-hospital' referrals should begin definitive treatment within 31 days of consulting with a specialist and a treatment plan initiated

All upper and lower GI suspected cancer referrals were assessed over a 1-year period (October 2015 – September 2016) in a district general hospital. Both 62- and 31-day referral pathways were analysed. Data were obtained from cancer trackers and checked for accuracy.

For suspected upper GI cancers, there were 2629 referrals over the 1-year period, divided into 1520 62-day referrals and 1109 31-day referrals. There were 164 (6.24%) confirmed cancers. 57 (3.75%) of these cancers were 62-day referrals and 107 (9.64%) cancers were 31-day.

There were 3951 referrals for suspected lower GI cancers over the 1-year period, with 2652 62-day referrals and 1299 31-day referrals. There were 188 (4.76%) confirmed cancers. 63 (2.38%) of these cancers were 62-day referrals and 125 (9.62%) cancers were 31-day.

There was very low progression from suspected to confirmed cancer from red flag referrals for both upper and lower GI symptoms. 62-day referrals for suspected cancer were particularly low (3.75% and 2.38% for upper and lower GI referrals respectively).

In the current environment of increasing demands on the NHS – is it time for current red flag referral criteria to be revisited? We should have a true partnership between secondary care and general practice - setting up a working group between general surgeons, gastroenterologists, and general practitioners to revisit guidelines to determine what is realistic and deliverable in the current financial constrained environment. Perhaps such 'red flag' patients should be referred to community assessment centres for direct access endoscopy. These trained endoscopists may be nurses, associate specialists, or staff grade doctors. It would be especially important for a number of these endoscopists to be sessional family doctors, who are JAG (Joint Advisory Group in Endoscopy) accredited. This would encourage collaboration between general practice and secondary care, allowing for validation and audit of the red flag referral pathway.

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*Ulster Med J* 2017;**86(3):**207-208

*Abstracts*

# Proceedings of the fourth annual Queen's University Belfast Student Research Symposium

## Wednesday 29th March 2017, Wellcome-Wolfson Institute for Experimental Medicine

### OVERVIEW

QUB Scrubs hosted their first annual Student Research Symposium on 29th March 2017 at the Wellcome-Wolfson Institute for Experimental Medicine. Queen's University Academic Medicine Society (QUAMS) had previously hosted three Student Research Symposia, and QUB Scrubs were pleased to be able to pick up where they left off, sharing their goal of providing a forum for medical and dental students across all year groups to develop research experience.

Professor Stuart Elborn opened the symposium as the keynote speaker, using his career to illustrate the value of research and outlining emerging areas of note. This was followed by talks from academic leads and students alike on summer studentships, intercalated degrees, the INSPIRE mentoring programme and clinical academic training.

Ten students submitted abstracts from a variety of research centres, on topics ranging from the provision of HIV services in developing countries to the identification of molecular targets in colorectal cancer. Abstracts were screened by a senior medical student against predetermined eligibility criteria; all were deemed suitable and accepted for poster presentation. Posters were then independently double marked by a team of postgraduate research students, to award a first, second and third prize.

The symposium was organised in collaboration with staff from the School of Medicine, Dentistry and Biomedical Sciences and was made possible by the INSPIRE grant from the Academy of Medical Sciences, as well as donations from the Medical Defence Union and Blackwell's Bookshop. QUB Scrubs are extremely grateful for the support received and look forward to welcoming many more students for future events.

### FIRST PRIZE

*"Systematic evaluation of multiple breath washout quality in bronchiectasis."*

Gokul R. Lakshmipathy, Katherine O'Neill, Judy Bradley, Bronch-UK Partnership

Bronch-UK, Northern Ireland Clinical Research Facility, Queen's University Belfast

Background: Lung clearance index (LCI) is highly sensitive to early bronchiectasis compared to forced expiratory volume (FEV1). Quality checks are done for the accurate estimation of LCI, however very little evidence is available on the impact of over-reading on such multiple breath washout (MBW) variables. The aims of the study were to;

1. Determine the impact of over-reading on LCI, LCI coefficient of variation (LCICV) and tidal volume (VTCV)
2. Identify time taken to accomplish LCI training
3. Calculate costs involved in setting up a MBW study

Methods: MBW data from first 110 tests of the Bronch-UK study were analysed. P-value less than 0.05 was considered significant. Dates of training and testing were needed to determine training duration. Costs were calculated from purchase receipts and salary bandings.

Results: Of the 110 tests, 18% were excluded from LCI analysis. 55% of tests were rejected due to technical unacceptability and 20% were removed for not having relaxed breathing pattern. In the remaining tests, LCI and VTCV did not change significantly after over-reading (mean difference: LCI - 0.03, p = 0.97; VTCV - 0.29%, p = 0.21). Conversely, LCICV was significantly reduced after over-reading (mean difference: LCICV - 0.45%, p = 0.03). On average, operators took 6 months to complete training. Setting up an LCI trial costs around £40,719.35.

Conclusions: Following removal of tests for technical and qualitative reasons, LCI and VTCV scores did not change after over-reading. This finding highlights that some aspects of over-reading may not be required. LCICV reduced significantly after quality control, which could have implications on overall variability of LCI in the study. Setting up an LCI trial is expensive, thus trained personnel should perform these tests.

Patrick Hickland, Gokul R. Lakshmipathy, Kirsten McCollum, Kathryn Mullan

Contact Details: Patrick Hickland phickland01@qub.ac.uk

## SECOND PRIZE

*"Investigating the expression of the A20 repressor DREAM in cystic fibrosis lung disease."*

Kirsten McCollum Bettina Schock, Madeleine Ennis

Centre for Infection and Immunity, Queen's University Belfast

Background: Cystic fibrosis (CF) is an autosomal recessive condition characterised by chronic inflammation. A defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) leads to dysfunctional ion transport across the epithelial cell membrane. The epithelial surface becomes dehydrated, airway secretions become highly viscous, leading to impaired mucociliary clearance, entrapment of bacteria, and chronic infection. Previous work demonstrated persistent activation of the transcription factor NF-ÎºB contributes to a pro-inflammatory state. The enzyme A20 has a central function in terminating NF-ÎºB signalling. CF primary nasal epithelial cells show reduced baseline expression of A20. Transcription of the A20 gene is normally repressed by the protein DREAM. Therefore, it is hypothesised that the reduction in A20 is due to the increased expression of DREAM.

Methods: Quantitative PCR and immunocytochemistry techniques to determine mRNA and protein levels of the A20 repressor DREAM in CFBE41o- and 16HBE14o- cell lines, basally and after stimulation by LPS.

Results: Basal expression of DREAM mRNA and protein is significantly higher in CFBE41o- cell lines compared to 16HBE14o-. Upon stimulation with LPS, the induction of DREAM mRNA is significantly enhanced in CFBE41o- cell lines. In CFBE41o- DREAM protein is located mostly within the cell nucleus, but in the cytoplasm in 16HBE14o-.

Conclusions: The objective of this project was to gain an understanding of the mechanisms behind the lack of A20 and the subsequent inflammation seen in CF. Subject to further experimentation; modulation of DREAM expression may prove to be a new therapeutic target in CF inflammatory airways disease.

## THIRD PRIZE

*"Preliminary analysis of plasma antioxidant status in patients with Alzheimer's disease: A meta-analysis."*

Kathryn Mullan, Chris R. Cardwell, Bernadette McGuinness, Jayne V. Woodside, Gareth J. McKay

Centre for Public Health, Queen's University Belfast

Background: Serum antioxidants may afford neuroprotective effects against Alzheimer's disease (AD) via correction of the pro-oxidative imbalance. Observational studies have investigated plasma antioxidant status in AD patients, but to date, results have been inconsistent and findings have not been consistently replicated in trials of antioxidant supplements in AD populations. The objective was to determine the current best estimate of the mean difference in serum levels of ten dietary antioxidants between patients with AD and cognitively intact controls.

Methods: Electronic searches of four databases were conducted up to December 2016 according to PRISMA guidelines. Case-control studies in which plasma levels of dietary antioxidants were reported in individuals with AD and non-demented control participants were eligible for inclusion. Meta-analyses were performed and the pooled weighted mean difference (WMD) for each antioxidant was reported.

Results: We identified 51 studies, which collectively reported data on the ten antioxidants under investigation. Compared to control subjects, pooled effects found participants with AD had significantly lower plasma levels of alpha-carotene, beta-carotene, lycopene, vitamin A, C and E, and UA ($p < 0.05$). No significant difference was observed for plasma levels of beta-cryptoxanthin, lutein and zeaxanthin.

Conclusions: The lower serum levels of dietary antioxidants from the carotene and vitamin subclasses indicate that individuals with AD have impaired systemic availability of these subclasses. To our knowledge, these are the first meta-analyses showing lower blood lycopene levels and unaltered beta-cryptoxanthin, lutein and zeaxanthin levels in AD. We propose the evidence is used to inform trial design of novel dietary antioxidant therapies in a condition of major public health importance.

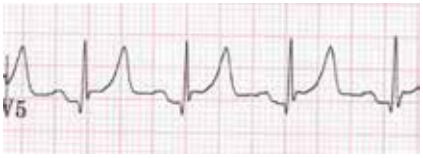
*Ulster Med J* 2017;**86(3):**209-210

# Curiositas (Cardiology)

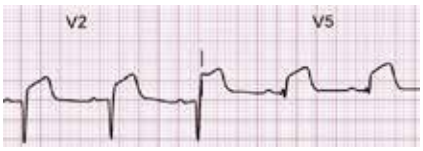
## UNDERGRADUATE QUIZ

Anterior ST-segment elevation myocardial infarction (STEMI) can be a life-threatening condition. Prompt recognition of the typical ECG findings and rapid transfer to a primary percutaneous coronary intervention centre are critical. Although the ECG appearances of anterior STEMI are quite characteristic, confusion sometimes arises with 3 other ECG morphologies. Can you identify the genuine anterior STEMI and name the 3 imposters?

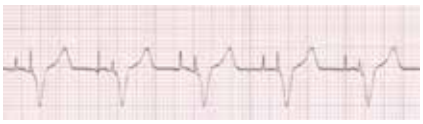
1. A 17 year old man presented with chest pain. He had a flu-like illness one week ago.



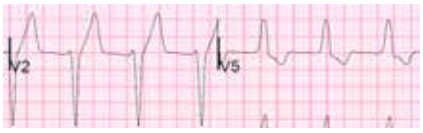

2. A 54 year old woman with diabetes complained of chest pain following a large meal. She is known to have hypercholesterolaemia and hypertension.




3. A 78 year old woman presented with chest pain. She attended a cardiology clinic with dizzy spells in the past, and had a procedure which helped.



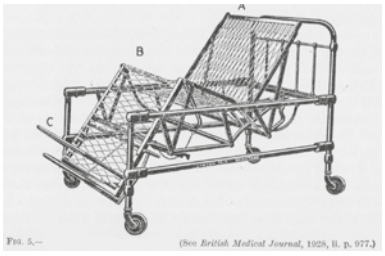
4. A 60 year old man with several previous myocardial infarctions attended the Emergency Department with chest pain.




*Dr John Purvis (Consultant Cardiologist, Western Health & Social Care Trust) & Ms Sandra Messiha (Medical Student, Queen's University Belfast).*

## HISTORICAL QUIZ

The image below is taken from Sir Thomas Lewis's classic cardiology textbook *Diseases of the Heart* 4th Edition (MacMillan and Co. Ltd., 1946). It demonstrates an item of equipment designed by the author in 1928 to help with the management of which cardiac condition?

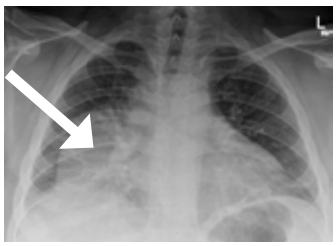


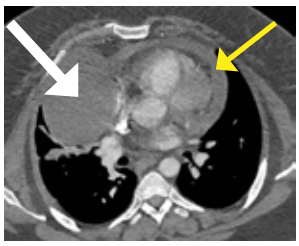

*Dr John Purvis (Consultant Cardiologist, Western Health & Social Care Trust)*

## POSTGRADUATE QUIZ 1

A 28 year old man presented to the emergency department with a 2 week history of intermittent sharp chest pain and progressive breathlessness. He was apyrexial. The white cell count was $12x10^9$/L and CRP 60 mg/L. Troponin T <3 ng/L. His blood pressure was 130/76 mmHg and heart rate 113 beats/min. Sinus tachycardia was demonstrated on an ECG.

His chest radiograph and CT aortogram images are shown.



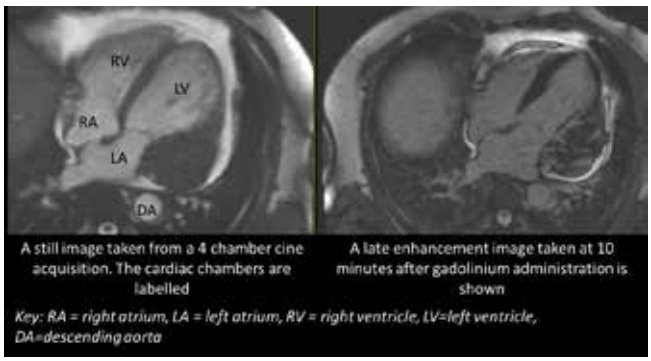


1. What are the most striking abnormalities on the images?
2. What would your acute and long term management priorities be for this man?

*Drs Alison Smyth & John Purvis (Cardiology Unit, Western Health & Social Care Trust)*

## POSTGRADUATE QUIZ 2

A 50 year old man presented with flu-like symptoms and chest pain together with a small elevation in serum troponin concentration. He was provisionally diagnosed with myocarditis. He subsequently developed non-sustained ventricular tachycardia (VT) and frequent ventricular ectopy. Coronary angiography did not demonstrate any significant coronary artery disease. Echocardiography revealed severely reduced left ventricular function and a suspicious abnormality around the lateral aspect of the left ventricle. Cardiovascular magnetic resonance (CMR) imaging was performed in order to delineate this abnormality further.




1. Describe the most abnormal feature present on CMR.
2. What is the differential diagnosis?
3. What next investigation would be most useful?

*Dr Caroline Bleakley, Prof Theresa McDonagh & Dr Dan Sado (Department of Cardiology, Kings College Hospital, London)*

**ANSWERS** See overleaf

**CONSIDER CONTRIBUTING TO CURIOSITAS?**
Please refer to *'Curiositas: Guidelines for contributors'* http://www.ums.ac.uk/curiositas.html and email *umj@qub.ac.uk* with your ideas and submissions.

## CURIOSITAS: ANSWERS

### UNDERGRADUATE QUIZ

1. Acute Pericarditis. There is concave ST segment elevation in the ECG shown, and slurred depression from the P wave to the QRS complex (PR depression). These changes are characteristic of acute pericarditis and will affect all 12 ECG leads as the viral inflammation affects the whole pericardium. In contrast, anterior ST segment elevation changes are seen predominantly in the territory of the left anterior descending artery (V2 – V4).

2. Anterolateral STEMI. There is convex-upward ST segment elevation. This will be seen primarily in leads V2-V4 in an anterior STEMI, but may extend into the lateral territory (V5, V6, I and aVL) as is seen here.

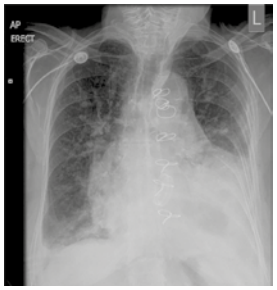
3. Paced ECG. This rhythm strip shows two electronic "spikes" with each heart beat – one before each P wave and one before each QRS complex. This patient has a dual-chamber pacemaker. The tip of the ventricular lead initiates ventricular contraction from the right ventricle. There is then slow conduction from cell to cell towards the left ventricle. This leads to a broad QRS complex (>3 small squares; >120 ms), and the pattern resembles left bundle branch block.

4. Left bundle branch block. The QRS complex is broad (>3 small squares; >120 ms), with a predominantly negative QRS axis in V1-V2 and a positive axis in V5-V6. Generally speaking, the axis of the QRS complex is opposite to that of the T wave in the same lead. In this case, damage from previous infarction has destroyed the conducting tissue in the left bundle branches so that ventricular activation occurs via the right bundle and then by slow neighbour-to-neighbour conduction through the left ventricle. This prolongs the QRS duration and affects the ST segments. The appearance is similar to a paced ECG but without the spikes!

*Dr John Purvis (Consultant Cardiologist, Western Health & Social Care Trust) & Ms Sandra Messiha (Medical Student, Queen's University Belfast).*

## HISTORICAL QUIZ

This is an image of a "cardiac bedstead" used to prop patients upright when they were suffering from what Sir Thomas called heart "failure with congestion." Normally, most pulmonary vascular flow to the lungs is directed to the lower dependent lung segments, but in heart failure, there is proportionally greater flow to the upper segments. This can be seen in classical chest radiograph appearances of pulmonary vascular congestion. The redistribution becomes even more marked when the patient lies supine, so keeping the patient propped up can indeed be helpful.

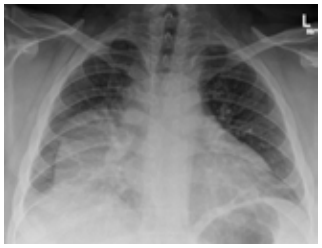


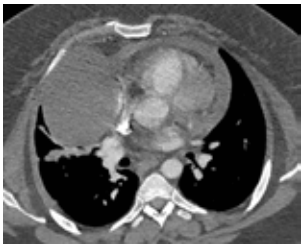
*45 year old male with previous coronary artery bypass grafting and a left ventricular ejection fraction of 20%, admitted acutely 10 days after forgetting to renew his prescription for loop diuretics. The image shows evidence of previous sternotomy, gross cardiomegaly, small pleural effusions and upper lobe pulmonary vascular congestion.*

The advent of powerful pharmacotherapy (such as potent diuretics) from the 1950s onwards reduced the need for the cardiac bedstead. The physiology remains sound and keeping a patient upright can be of symptomatic benefit.

*Dr John Purvis (Consultant Cardiologist, Western Health & Social Care Trust)*

## POSTGRADUATE QUIZ 1





1. The chest radiograph demonstrates cardiomegaly and an opacity projected over the right hemithorax (white arrow). The right heart border is separately identified. The CT aortogram demonstrates a small pericardial effusion (orange arrow), most likely in keeping with pericarditis given the acute clinical history. A large pericardial cyst (white arrow) is noted extending from the right atrial border into the lower right hemithorax.
2. Acutely, pericarditis should be managed in accordance with current guidelines[1]. First-line therapy is non-steroidal anti-inflammatory drugs, with colchicine used as needed, and steroids or steroid-sparing agents reserved for resistant or recurrent cases. The pericardial effusion, although small, should be evaluated by serial echocardiography. The pericardial cyst is incidental, but is large and is causing some compression of lung tissue. Long term surveillance with chest imaging will be required. Pericardial cysts are uncommon congenital anomalies that occur more commonly on the right side. They are benign lesions, and generally do not require surgical resection unless they are symptomatic.

1. Adler Y, Charron P, Imazio M et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2015; 36: 2921-2964.

*Drs Alison Smyth & John Purvis (Cardiology Unit, Western Health & Social Care Trust)*

## POSTGRADUATE QUIZ 2

1. CMR shows a large mass within the myocardium measuring approximately 7cm at the posterolateral wall of the left ventricle. On late enhancement imaging, the mass shows heterogeneous uptake of gadolinium contrast.
2. Lymphoma or other cardiac tumour, thrombus or haematoma.
3. Biopsy.

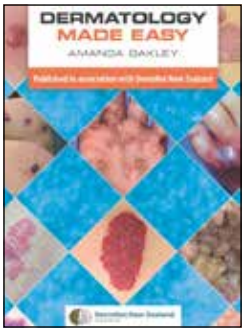
The differential diagnosis of a cardiac mass includes cardiac tumours (lymphoma, primaries or metastases), thrombus or haematoma. A malignant process was felt to be the most likely cause here[1]. However, the diagnosis made from tissue obtained from surgical endoscopic biopsy, was of a calcified thrombotic haematoma. Intramyocardial haematoma is extremely rare in the absence of preceding chest wall trauma (not present in this case). Only one similar case has been reported[2]. Intracardiac cavity thrombosis is much more common in areas of slow blood flow such as the left atrial appendage or at an akinetic left ventricular apex following, for example, a myocardial infarction. A calcified intramural haematoma in the left ventricle is rarely reported, and as such, there is no standardised approach to management. After discussion with the cardiothoracic surgical team, it was felt that, in this case, excision would carry significant risk to surrounding structures including the left coronary arteries. The patient had a radiofrequency ablation for his VT (the focus of which was the area around the haematoma), and remains under surveillance.

1. Fussen S, De Boeck BW, Zellweger MJ et al. Cardiovascular magnetic resonance imaging for diagnosis and clinical management of suspected cardiac masses and tumours. *Eur Heart J* 2011; **32**: 1551-60.
2. Arora A, Sheikh A. Calcified pericardial haematoma causing heart failure. *Br J Hosp Med (Lond)* 2015; **76**: 487.

*Dr Caroline Bleakley, Prof Theresa McDonagh & Dr Dan Sado (Department of Cardiology, Kings College Hospital, London)*

# Book Reviews

## DERMATOLOGY MADE EASY.




Amanda Oakley. Scion Publishing Ltd, 2017. Pp420, £29.99

ISBN 978 1 907904 82 0.

This textbook has been written by the well known Professor Amanda Oakley, who has become immortalised not only in her role as a leading dermatologist but more particularly as the person who established the world famous comprehensive website for the New Zealand Dermatological Society (DermNet NZ) which serves dermatologists and their patients on a global basis. Not a day goes by that I do not direct patients to this website for comprehensive and accurate information on their skin disorders. Armed with the 15,000 images from this website, Amanda Oakley is uniquely able to provide images on virtually any skin condition - undoubtedly this has helped her to produce a very impressive and comprehensive textbook of dermatology which includes more than 700 clinical images. The book format is a high quality paperback and an electronic version is also available.

This is a beautifully produced and illustrated textbook, which would give any medical student or general practitioner the information, knowledge and ability to treat a wide range of medical dermatology. It would also appeal to the increasing numbers of dermatology nurse practitioners. As an "essential fact" book it would not have sufficient detail for trainees in dermatology.

The book begins, as is often the case in introductory textbooks, by going through the terminology used in dermatology (such as papule, pustule or scale) before progressing to chapters based on differential diagnosis by symptoms (for example rash with fever or itch), by morphology (such as rashes with papules and plaques or skinny rashes) or rashes categorized by body sites. These chapters would certainly help guide someone with more limited dermatological knowledge according to the patient's symptoms, signs and rash according to body location.

The chapters on individual categories of dermatological conditions are well organised and deal with all the usual dermatoses including infections, drug eruptions, eczema, hair problems infections drug eruptions eczema hair problems and pigmentary lesions. The text is written in a bullet point format making for easy reading and this, taken in combination with an extensive collection of high quality photographs makes the book easy to read and informative. One cannot emphasise enough the quality and comprehensive nature of the photographic content.

In an era where surgical dermatology is now at least 50% of the work in any dermatology department, a criticism of this book is the lack of any section dealing with the surgical components of the specialty with this topic being compressed to 2 pages in a book of 420 pages. This book makes no attempt to deal in any serious way with the growing subspecialty of surgical dermatology. A chapter on skin surgery would inform those practitioners not wishing to do skin surgery themselves while helping those wishing to embark on the most basic skin surgery. Another deficiency was the lack of a specific section on dermoscopy, which is considered by many to be the "stethoscope" of current dermatology, and which has become routine with many general practitioners. While there is selected dermoscopy in some chapters this is not as extensive as one would expect given the popularity of dermoscopy in dermatology. A second edition of this book would benefit from a chapter dealing specifically with the elements of and common use of dermoscopy.

The last sections of the textbook deal with drugs used in dermatology and include sections on drugs such as hydroxychloroquine, acetretin, isotretinoin and immunosupressants such as azathioprine and ciclosporin. By necessity, the information on many of these drugs is basic and suited more to medical students, general practitioners or the increasing band of general practitioners with a specialised interest. This section would not provide sufficient knowledge for practitioners wishing to prescribe these drugs but serve to give a source of information in monitoring such patients and watching for side effects.

My overall impression of this textbook is one of excellence in dealing with all aspects of medical dermatology. The book is impressive and the photographic illustration second to none for any book dealing with solely medical dermatology. It certainly exceeds in quality and information the contents of similar books written for medical students and general practitioners.

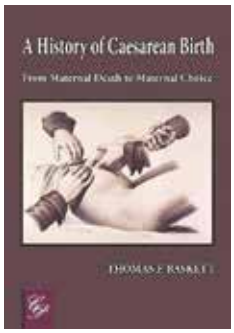
As someone who was interested in dermatology even as a medical student my only regret is that this book was not around when I was a student as it would have very adequately guided me into my beloved subspecialty. At a price of £29.99 it is remarkably good value. The book more than exceeds the requirements of any medical student but I suspect will be mainly useful for general practitioners and nurse practitioners with an interest in medical dermatology. I have little doubt that this will be a highly successful textbook given the popularity of the New Zealand dermatology website and the excellence of the clinical photography.

David Eedy

## A HISTORY OF CAESAREAN BIRTH FROM MATERNAL DEATH TO MATERNAL CHOICE

Thomas F Baskett. Clinical Press Ltd, 2017. Pp 196, £19.00

ISBN 978-1-85457-065-9




What a great title for a book that looks historically, medically, economically and socially at the most common operation carried out on women in the world.

Right at the start, I fully recommend this book to everyone, and not just Obstetricians. Birth fascinates, intrigues, and challenges us all. I have yet to attend a dinner party and meet a woman who had a fully normal delivery, at least of their first baby!

Everyone seems to have had their own very personal experience, is keen to share same, and the stories they relate invariably stimulate participation by everyone at the table, male and female, informed or uninformed, teetotaler or lover of the grape.

Knowledge of the birthing process and the intricacies of same are no bar to having a view on how birth should be performed. Where one should give birth? What analgesia, or none, should be accessed? Who should have a caesarean? Who should make that decision? Who should pay for the operation? The questions are endless.

There is no doubt though that the decision to have or not to have a caesarean is one of the most likely to arouse controversy.

What started as a cultural post mortem procedure and is now considered in many societies to be a matter of choice is expertly and uniquely described in this beautifully researched and written book by Tom Baskett. A world-famous Obstetrician who hales from these shores, and who in the latest of his prolific tomes has produced a book that is entirely readable, non-confrontational and leaves no questions unanswered in a rich series of chapters.

Caesarean sections were performed by doctors on live patients initially to save the mother's life alone. Indeed, the very operation, sadly in the early days, also sometimes hastened the mother's end. Anaesthetics were poor, infection could often not be controlled, haemorrhage could be noted and arrested, but blood could not be replaced.

Nature is a tough Obstetrician who appears to believe in survival of the fittest, whereas the very essence of medicine is to aim for survival of the weakest. Medics always want to work with nature when she's at her best, but there are times when she must be confronted. There is nothing as normal as normal midwifery, and nothing as abnormal as abnormal midwifery, and nothing can go from one to the other so quickly, and often so devastatingly.

Left to nature alone, in the under resourced world up to 1 in 10 babies and 1 in 100 mothers will die. In these countries, there need to be far more caesareans performed, while some will say that in developed counties there should be far fewer.

The World Health Organisation (WHO), represented by a round table meeting of a few big names in the Reproductive world, tried in the 80s to determine once and for all the perfect Caesarean Section rate.

They came down on 15%.

A rate that for decades provided a big stick in many countries for non-obstetricians such as managers, politicians and various members of the caring professions to beat us Obstetricians with.

Unfortunately, that figure didn't take into account the huge number of variables, economic, cultural, medical support and facility access to name but four. There just can't be one rate that covers all.

The WHO recommended rate has now, at last, been withdrawn.

Caesarean section is now one of the safest surgical interventions in the world today. The decision to deliver a baby by this method saves countless lives. In the past decades with an improved clinical environment, increasingly the operation has been used to save the life of the fetus, and not just the mother.

Tom Baskett has left nothing out in his book. He addresses every aspect in a non-confrontational, fair, unbiased, logical and transparent manner. Did I say he came from Ulster? Ah! He left these shores long ago after his medical student and early training days, to take a Chair in Canada. That explains a great deal.

Before reading this book, I may have been aware of about 10-15% of the content, gathered by osmosis over the decades, but the other 85% was news to me and, I'd suggest, to any medic.

If you've gone to the trouble of reading this review, please go the extra metre and buy it for yourself, your partner, or your children you're trying to encourage into medicine. If nothing else, you'll be the star expert witness at the next dinner party!

Prof Jim Dornan

# Game Changers

## AN UPDATE IN AORTIC VALVE INTERVENTION AND EARLY DISCHARGE

Dr H Douglas, Dr M Spence

*Department of Cardiology, Royal Victoria Hospital, Belfast, BT12 6BA*

Severe aortic stenosis is common and carries significant morbidity and mortality in an ever-growing elderly population.

It is now fifteen years since the advent of Transcatheter Aortic Valve Implantation (TAVI). The first ever case was performed in 2002.[1] Since then data from randomised controlled trials supporting favourable outcomes with TAVI for patients in whom surgical aortic valve replacement is considered high risk have led to its inclusion in the latest International guidelines for management of valvular heart disease[2].

The TAVI programme at the Royal Victoria Hospital was commenced in 2008. Over 700 cases have been performed to date. All cases are considered at our regional heart team meeting (comprising a minimum of general cardiologist, interventional cardiologist and cardiac surgeons) and implementation of our early discharge pathway in 2013 has already shown locally that in a cohort of carefully selected patients next day and even same day discharge can be safely facilitated[3]. Currently, cases from Belfast are included in ongoing international registry work around the feasibility and safety of early discharge[4].

The TAVI programme continues to thrive, providing patients evaluated by our heart team with a transcatheter solution with short recovery time, reduced length of stay in hospital and good outcomes.

1. Cribier A et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation*. 2002; **106**: 3006–3008
2. Nishimura RA et al. "2014 AHA/ACC Guideline for the management of patients with valvular heart disease.", *J Am Coll Cardiol*. 2014; **63(22)**: e57-e185.
3. Noad RL et al. Pathway to earlier discharge following TAVI: Assessment of safety and resource utilization. *Catheter Cardiovasc Interv*. 2016; **87(1)**:134-42.
4. https://clinicaltrials.gov/ct2/show/NCT02404467 (Downloaded 05/07/2017).

## SENTINEL BIOPSY IN VULVAL CANCER – ESTABLISHING A REGIONAL SERVICE IN NORTHERN IRELAND

*Dr F McCloskey,Dr T Lynch, Dr H Nagar, Dr E Murtagh*

*Departments of Radiology, Nuclear Medicine and Gynaecology, Belfast City Hospital, BT9 7AB*

Sentinel node biopsy has an established role in the management of breast cancer and an evolving role in melanoma management. It now also plays a key part in the management of selected vulval cancers.[1+2]

It was introduced to Northern Ireland in 2015 and to date 20 patients with vulval cancer, ranging from FIGO stage 1b-3c, have received sentinel node localisation, using a peri-tumoural injection of Tecnetium-99 radiolabelled nanocolloid. The sentinel nodes were identified using a GE SPECT CT gamma camera system. In theatre, nodes are located using a hand-held detector, localising the most proximal draining node (sentinel) from the tumour. 90% of sentinel node biopsies were negative for disease. The 2 biopsy-positive patients were of a higher FIGO stage, they underwent groin node dissection and remain disease free.

The GROINSS-V study found that 1-5 % of vulval cancers will metastasise to non-sentinel lymph nodes. This was reflected in our regional experience, with one biopsy-negative patient presenting with metastatic disease within 1 year.[3] This should be interpreted in the context of a 10-15% recurrence rate in vulval cancer overall.

Careful patient selection in accordance with local guidelines and patient counselling preoperatively is of utmost importance. Implementation of this technique has led to a dramatic reduction in rates of groin node dissection with its associated morbidity.

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## IMMUNOTHERAPY FOR LUNG CANCER – A GAMECHANGER!

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Cancer evades the ability of the immune system by turning on cell surface proteins which turn off immune-surveillance cells such as T-helper cells[1]. Immunotherapy treatments such as the immune checkpoint inhibitors overcome cancer's ability to switch off the immune response to altered cells. Randomised trials studying immunotherapy have demonstrated a patient benefit across a number of disease sites, in both curative and non-curative settings.

Pembrolizumab, a monoclonal antibody for the PD-1 receptor (B cells and T cells), has been NICE-approved in 2017 for the treatment of metastatic non-small-cell lung cancer (NSCLC) in second-line therapy and is available via the

cancer drugs fund in England for first line therapy. Immune checkpoints such as the PD-1 receptor down-modulate the immune response as described above. The KEYNOTE-010 trial showed that pembrolizumab was better than standard second-line chemotherapy in terms of disease progression and toxicity[2]. The particularly impressive outcome from many such immunotherapy studies is controlled or absent disease 5 years after starting treatment in a substantial cohort of patients.

Adverse effects from immune checkpoint inhibitors are largely related to overstimulation of the immune system and include pneumonitis, hepatitis, endocrinopathy, skin rashes and gastrointestinal toxicity[3]. There is growing evidence that radiotherapy delivered before or with immunotherapy, increases the likelihood a clinical response, and further investigations are under way[1].

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# So you want to be an Academic Foundation Programme Doctor?

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Accepted 29th March 2017

## WHAT IS THE ACADEMIC FOUNDATION PROGRAMME?

The Academic Foundation Programme (AFP) provides many opportunities in clinical placements for foundation trainees to develop research, teaching and leadership skills.[1] These AFP posts are integrated within Foundation Year training schemes and may be part of Foundation Year 1 (FY1) or Year 2 (FY2) rotations. The generic academic skills are developed in addition to competencies within the core Foundation Programme Curriculum.

The AFP posts are an integral part of several initiatives to enhance and strengthen career structures for academic medicine to enable AFP doctors to develop research, teaching, leadership and management skills in addition to the competences outlined in the Foundation Programme Curriculum. An influential document (usually known as the "Walport report") was published in 2005 by the UK Clinical Research Collaboration.[1] This highlighted the need for better integration of clinical and academic medicine training and recommend a new and clear structure in order to achieve this.[2] More recently, the "Shape of Training" report has emphasised that doctors in academic training pathways need training structures that are flexible enough to allow them to move in and out of clinical training while still attaining the competencies and standards of that training.[3]

In the UK there are now over 500 AFP posts available within a wide range of individual programmes. These are early stage career posts that allow foundation year trainees to experience first-hand the joys and challenges of clinical academic medicine. Each of the postgraduate deaneries in England, Wales, Scotland and Northern Ireland will have separate applications for AFP posts reflecting the diversity of AFP posts available.

## WHAT IS THE STRUCTURE OF ACADEMIC MEDICINE?

A training path in academic medicine is designed to be flexible with opportunities for trainees to enter at different career stages. It is not necessary to have completed an AFP in order to train as an academic clinician.

An AFP post permits the integration of research projects throughout or during dedicated blocks of "academic time" within the foundation programme. This enables trainees to develop skills at an early stage to improve their success in an academic career. The structure of individual AFP posts varies between postgraduate deaneries in England, Scotland, Wales and Northern Ireland, so it is important to be familiar with the scheme within the local deanery.

In most AFP placements, the trainee will have completed an FY1 rotation and the academic component is undertaken in FY2. This may involve one of the four-month rotations effectively being supernumerary with fewer clinical responsibilities so that the trainee has protected time to complete a research project. In other AFP schemes the trainee may integrate a research theme throughout all of the FY2 rotations.

The type of research project undertaken varies widely reflecting the interests of the AFP trainee, their respective academic supervisor and specialty background. AFP doctors also obtain valuable transferable skills including enhanced understanding of research ethics, presenting at conferences, scientific writing, publishing, and experience of teaching and assessing medical students. Some AFP doctors may also obtain additional clinical or teaching qualifications and occasionally there is funding provided for these[1,3,4].

After completion of Foundation Programme FY1 and FY2 training (including the AFP post) it is usual for the doctors to enter core training posts or "run through" speciality training. There are further opportunities to pursue a clinical academic pathway including applying for an Academic Clinical Fellowship (ACF)[5,6]. The ACF posts typically have 25% of training time protected for research and scholarly activity. ACF postholders are encouraged to pursue further postgraduate research and compete for funding to allow them to go Out-of-Programme for up to 3 years and complete a doctoral thesis (PhD or MD). These various training and research posts act as stepping stones to a longer term clinical academic career (Figure 1)[7].

## HOW DO YOU APPLY TO BECOME AN AFP DOCTOR?

Applications by medical students to be an AFP trainee are included in the NHS' new Oriel online application system (www.foundationprogramme.nhs.uk) and the AFP application is additional to that of the standard Foundation Programme schemes – which must always be completed by all applicants. Applicants may select up to two Academic Units of Application (AUoA) from the 14 available within the UK.

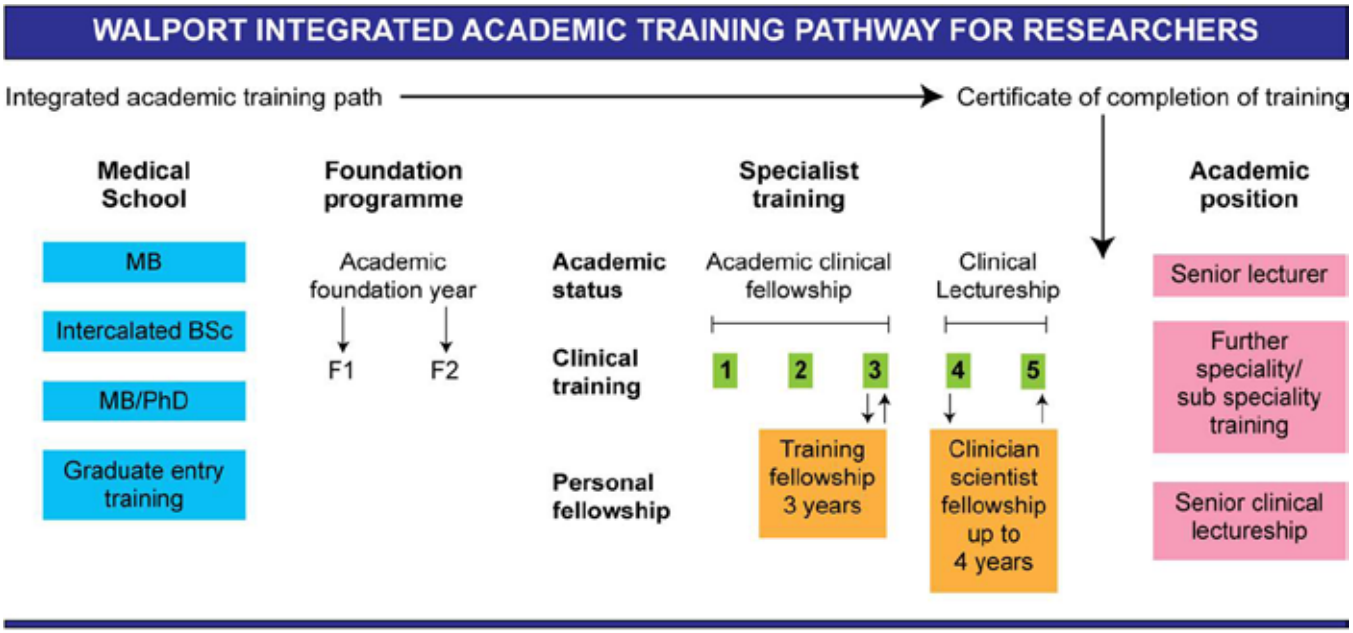


*Fig 1: Integrated pathway of medical and academic training.*
(from http://www.ecat.ed.ac.uk/clinical-academic-careers/uk-training-structures/)

Foundation Programmes are ranked by applicants in order of their preference of UK postgraduate deanery location. Unlike the standard Foundation Programme schemes the AFP posts do not need to be ranked by local deaneries but the individual jobs within an AUoA need to be ranked at the application stage. AFP posts are more competitive than the normal Foundation Programme rotations and, in 2016, there were 2,252 AFP applications for 515 AFP posts across the UK[4].

Applications to Foundation Programmes are ranked on the basis of combined scores from the Situational Judgement Test (SJT) and Educational Performance Measure (EPM)[8]. The SJT and EPM each have a maximum of 50 points. The EPM is a measure of clinical and non-clinical skills, knowledge and performance (up to the point of application). The EPM has three elements; medical school performance to date in deciles, for which 34-43 points are available; additional degrees, which are worth up to 5 points; and publications, for which up to 2 points are available. In addition to the normal points scored during the Foundation Programme, the majority of AUoAs award points to "white space questions", national and international presentations, and undergraduate academic prizes. Some AUoA have a decile cut-off and will not accept applications from students in the lower 50% of their medical school cohort. "White space" questions are typically open-ended and provide candidates with an opportunity to demonstrate attributes and experience that are relevant to a clinical academic career. The answers to these questions in addition to the overall Foundation Programme application score will determine which applicants are called to AFP interviews.

Usually two applicants per available AFP post will be interviewed. The interview process varies between AUoA but will typically involve a personal interview with or without additional interview stations. In the personal interview candidates will usually be asked about their reasons for applying, academic interests and experience, and long-term career plans. In some AUoAs, additional interview stations might involve discussion of a written clinical scenario or a research abstract that candidates will be given a few minutes before the interview. In this time, they will be expected to come up with management plans for the clinical scenarios or critically appraise an abstract.

The interview score will form the majority of the overall AFP application score and those candidates that meet the cut-off score will be offered an AFP position. Highest performing applicants will be more likely to receive their first preference of AFP posts from the ranking process and all candidates above the cut off will be offered positions until the list is exhausted.

## WHAT ARE THE BEST AND WORST ASPECTS OF AN ACADEMIC FOUNDATION PROGRAMME POST?

Applying to, obtaining a place and completing an AFP post is challenging. However, securing an AFP position also comes with many benefits. So, before applying, it's important to consider the pros and cons.

AFP posts are competitive with more than four applicants for each place. Nevertheless, applicants who secure an AFP post can gain valuable experience and skills whilst adding achievements to their CV. Applications for future clinical training posts will be enhanced by research outputs including presentations and publications, formal teaching qualifications, quality improvement projects and leadership experience. For

individuals interested in academic medicine careers – or those that already have additional degrees or research experience – an AFP post may act as a bridge to further academic training positions such as an academic clinical fellowship. Successful AFP applicants are usually able to rank all six posts within the two years of their foundation programme training and this may mean they have rotations based in larger teaching hospitals.

Some individual AFP posts may have lower levels of direct clinical responsibility and less day-to-day involvement in the specialty (compared to a standard FY2 post). This may provide some challenges for AFP doctors with attaining the range of FY2 competencies compared to their FY2 peers in standard rotations. In addition, AFP trainees will typically have more teaching responsibilities than other doctors at their stage of training. The additional teaching experience may actually be a benefit particularly for those trainees with a major career interest in medical education. Overall, AFP trainees may need to work harder to achieve all their targets (academic and clinical) and will learn at this early career stage that it can be challenging maintain a good work-life balance as a clinical academic.

Finally, it is worth noting that some AFP posts may be associated with a lower salary during the placement (reflecting a reduction in on-call clinical work) but this might be offset by the additional time the trainee has to explore the many and varied clinical academic roles.

## I WANT TO KNOW MORE – WHERE SHOULD I GO NEXT?

The AFP guide may be downloaded from the Foundation Programme website (www.foundationprogramme.nhs.uk) . This is updated annually and provides an overview of the Academic Foundation Programme posts in each AUoA. Further details can be found on each AUoA or local deanery's website – often with testimony from current or past AFP doctors.

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**Volume 86 No. 3** **September 2017**
ISSN 0041-6193



*Front cover: Dr Elizabeth Bell, one of the first female doctors to qualify in medicine from Belfast in 1893.*