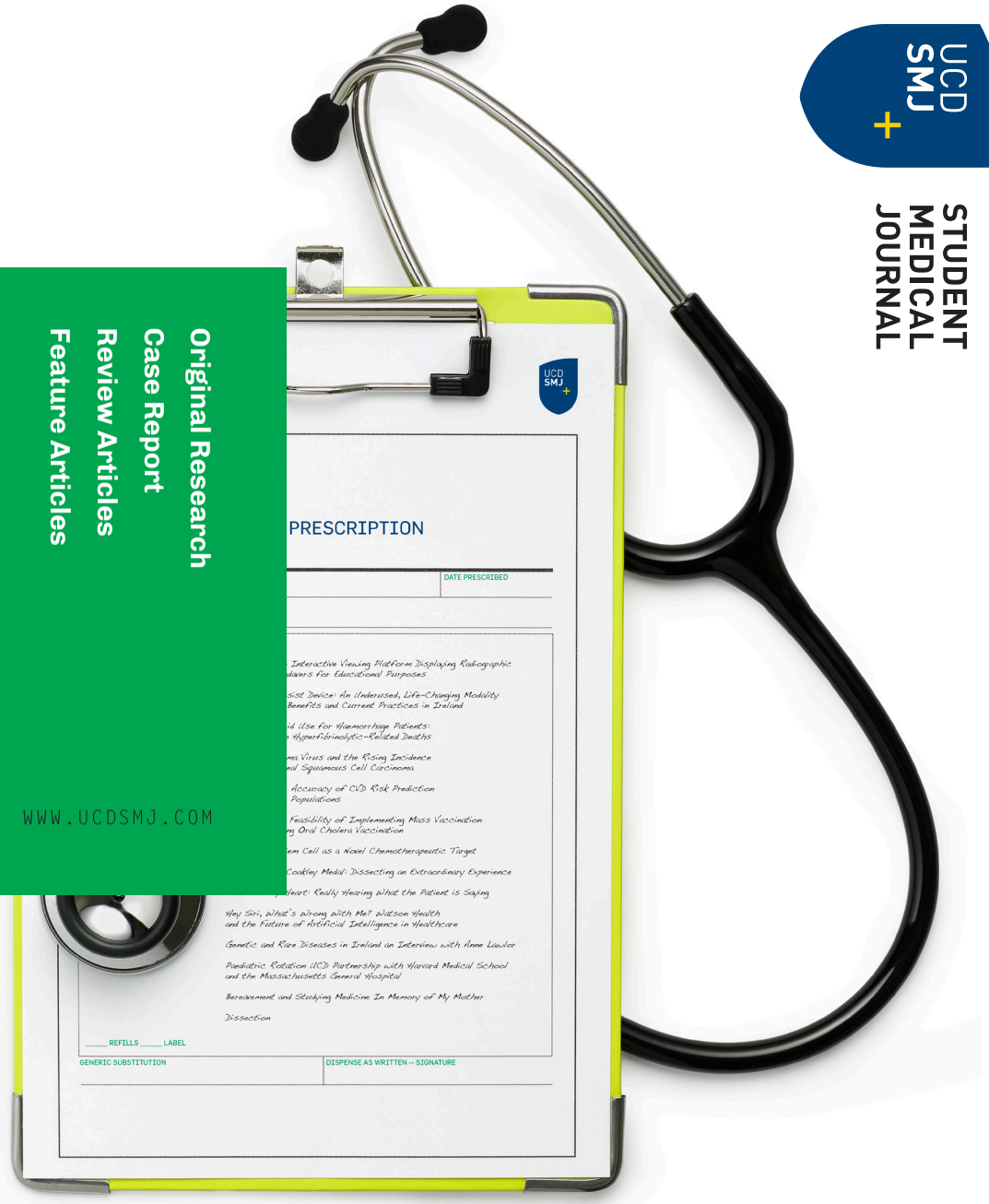
supported by Bank of Ireland, Montrose



UCD SMJ + STUDENT MEDICAL JOURNAL

Original Research
Case Report
Review Articles
Feature Articles

2016 EDITION 03

WWW.UCDSMJ.COM

Published by Anglo Printers,
Toberboice Ln,
Drogheda,
Co. Louth.

ISSN (Print): 2009-4795
ISSN (Online): 2009-4809

Table of Contents

Committee 2015/16

Paddy O'Donohoe
Marketing+Finance Manager

Jack Evans
Editor in Chief, Digital+Design

Kordan Harvey
Editor in Chief, Content

Eithne Nic An Ríogh
Chairperson

Aoife Nechowska
Digital+Design

Enya Fullston
Digital+Design

Jake Kiely
Digital+Design

Nina Esfandiari
Digital+Design

Rajiv Lakhani
Digital+Design

Adam Flaczyk
Editorial Team

Sophie Sharpe
Editorial Team

Aisling Cafferkey
Editorial Team

Aoife Cox
Editorial Team

Caroline Moran
Editorial Team

Claire Egan
Editorial Team

Eimear Flanagan
Editorial Team

Lade Adeusi
Editorial Team

Megan Hanlon
Editorial Team

Olwyn Kelly
Editorial Team

Audrey Ho
Marketing Team

Leslie Saba
Marketing Team

Milly English
Marketing Team

Nataliya Perera
Marketing Team

Ruky Agbahovbe
Marketing Team

Zelda O'Brien
Marketing Team

Acknowledgements

Co-Founders of the UCDsmj and Co-Editors of the First Edition

Aileen Conway
Denise Connolly

UCDsmj 2nd Edition Executive Team

Róisín O'Sullivan
Bebhinn Shine
Maeve Jones-O'Connor
Neasa Conneally

Website Design

Jack Evans

Portrait Photography

Matthew Bechbache

Stock Images

Images Courtesy of UCD School of Medicine

Peer Review & Academic Advisors

Dr Mary Codd
Prof Gerard Bury
Dr Cillian De Gascun
Dr Glen Doherty
Dr Michael Gallagher
Dr Alan Jacobsen
Prof James Jones
Dr John Lambert
Dr Noreen Sheehy
Dr Michelle Smith

UCD Medical Society

Patrick Short, *Auditor*
Sarah Egan, *Treasurer*

Journal Design

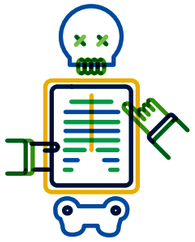
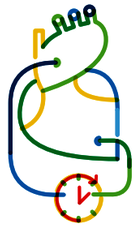
Fay Teo
cargocollective.com/sufuiteo

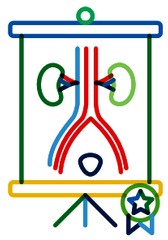
Printer

Anglo Printers
angloprinters.ie

Special thanks to the following individuals for their contributions to the UCDsmj

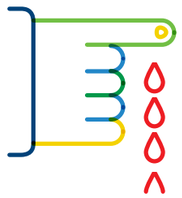
Prof Jason Last
Dr Cliona McGovern
Dr Rhona Mahony
Prof Patrick Murray
Dr Amanda McCann










Executive Commitee




Paddy O'Donohoe
Jack Evans
Kordan Harvey
Eithne Nic An Ríogh

Letter from UCDsmj

Medicine is changing in exciting ways. Advances in biology, biochemistry and medical technology bring incredible, innovative, and expensive new ways to treat illness. An aging and chronically diseased population is putting significant strain on already stretched systems. Meanwhile, the Internet and its easy access to information has allowed a generation of patients to meaningfully question the opinions of care providers.

To meet these challenges medical education must change, and this edition of the UCDsmj provides a glimpse into what the future might hold. Eithne Nic an Riogh demonstrates the utility of technology in anatomy teaching. Meggan Connell and Karen Mulligan uncover what it means to truly listen, and Rory Plant waxes poetic about the dissection room.

This issue also explores how traditional clinical medicine may change as we learn more about genetics and biochemistry. Grace Oon Bee Gan presents a case where a small motor can replace the function of a left-ventricle. Luke O'Brien reviews how biomarkers can aid in diagnosis and prognostication, and Calvin Flynn discuss the prospect of specifically attacking the stem cells that seed and propagate cancer.

We celebrate the achievements and endeavours of our fellow students with a piece by Ning Xuan Ho on the Coakley Dissection Medal and competition, while Nathaniel McHugh gives us a glimpse into his experiences during the UCD facilitated Harvard Paediatric Elective program. We also have, for the first time, contributions from students outside of UCD. Conrad Flaczyk, from McGill University, Montreal, Canada, explores the feasibility of mass vaccination programs following disasters like the one experienced in Haiti.

Finally, we note that it is important to never forget the human side of medicine and look at how this will change with advances in healthcare technology. Anne Lawlor, Information Officer at the Genetics and Rare Diseases Organization discusses the lack of support for children with genetic or rare diseases. Laura Mannion gives us a sobering look at the role of artificial intelligence in diagnosis and treatment. Darren O'Gorman writes about the loss of his mother, and how it has informed his experience studying medicine.

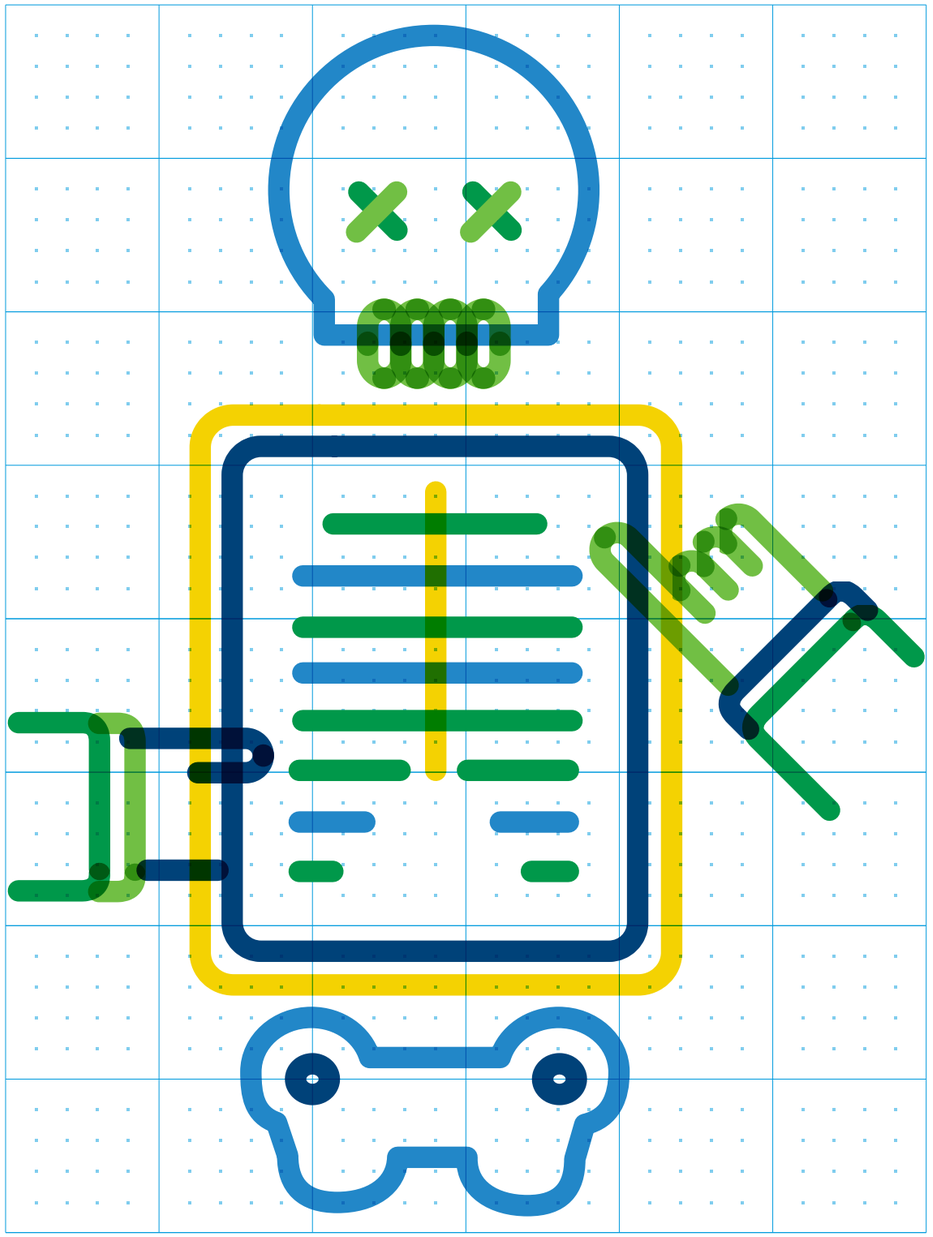
Despite all of the challenges the future of medicine faces, this edition should bring you some excitement. Not only for the education you are receiving, and the world that you are entering, but for the difference you can make. Much of your careers will consist of adapting to a changing landscape, doing old things in new ways. In these pages, your fellow students show that you are ready for the challenge.

It has been our great honour to put together this edition of the Student Medical Journal. Such a high standard of content covering such a wide variety of topics fills us with hope for the future of the healthcare professions. Each of the authors and collaborators involved in making this edition should be proud of their quality work, and the Executive Committee is delighted to bring this work to you, the reader.

X-perience: *An Interactive Viewing Platform Displaying Radiographic Profiles of Cadavers for Educational Purposes*

Written by Eithne Nic an Ríogh[1], Gary F Perry[1], James FX Jones[1], Adam Tattersall[1], Martin Heduan[1], Richard H Stern[2], Peter MacMahon[3], Nicola Giannotti[1] & Michaela Davis[1].

[1] UCD School of Medicine, University College Dublin, Belfield, Dublin 4.
[2] Radiology Department, Mount Sinai Hospital, 1468 Madison Avenue, New York.
[3] Radiology Department, Mater Misericordiae University Hospital, Eccles Street, Dublin 7.



Written by
Eithne Nic an Ríogh
Gary F Perry
James FX Jones
Adam Tattersall
Martin Heduan
Richard H Stern
Peter MacMahon
Nicola Giannotti
Michaela Davis

ABSTRACT

This project presented radiographic profiles of anatomical donors for educational purposes. An interactive viewing platform called *X-perience* was developed to vividly display these images. Comprehensive donor profiles were created by adding medical histories and consultant radiologist reports. These image-based clinical cases enhanced anatomical learning and offered an early introduction to clinical radiography. *X-perience* complemented the dissection process by reinforcing the concept of the donor as the student's first patient.

Full skeletal radiographs were obtained from 13 donors. Radiographic images were produced digitally, then labelled and stored using unique identifiers. Articulate Storyline 2 (Articulate Global Inc., United States) was used to build *X-perience* as an HTML5 interactive interface. To assess the value of *X-perience*, preclinical students in UCD's undergraduate medical programme were surveyed. This cohort had prior traditional anatomical teaching and could compare anatomical learning with and without *X-perience*.

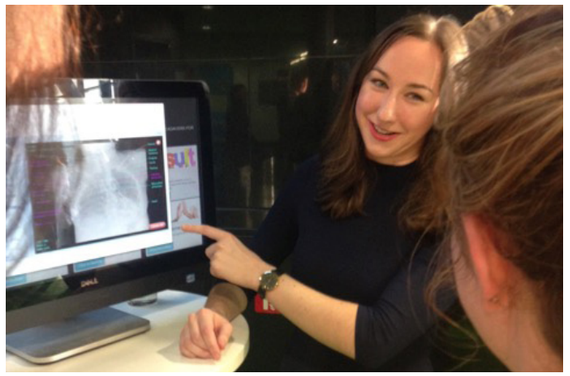
The workflow of profiling cadavers and constructing *X-perience* proved successful. *X-perience* is currently used by students during dissection. A survey of student opinion of the instrument (Kirkpatrick Level-1) produced favourable results. Students agreed that *X-perience* was relevant, easy to use and provided an integrated view of the human body. They appreciated the clinical relevance that *X-perience* offered. A greater understanding of the importance of radiology was acknowledged.

The introduction of similar viewing platforms in other medical schools is recommended. Imaging modalities such as CT and histology could further refine *X-perience*. In addition to providing educational value, *X-perience* strengthens the body donation programme, highlights the individuality and dignity of each donor and generates enthusiasm amongst students.

INTRODUCTION

Traditionally, instruction in human anatomy has involved learning from both cadaveric dissection and formal lectures. The aim of this project was to introduce another dimension to learning anatomy using the medium of radiology. This integrated approach to anatomy learning was previously missing in the dissection lab at University College Dublin (UCD). To fulfil this need, the e-learning tool *X-perience* was created.

Cadaveric radiography as an anatomy teaching aid has been described in the literature as far back as 1983 by McNiesh[1] and 1985 by Pantoja.[2] More recent reports on medical student and anatomy faculty impressions of supplementing cadaver dissection with radiological images have been extremely positive.[3] Pantoja commended this approach to anatomy teaching as an effective, easily implemented learning aid. Both McNiesh and Pantoja commented on increased student enthusiasm and interest in anatomy and radiology.[1,2] Sugand et al. state that multimodal teaching is the basis of future learning and helps combat the issue of limited dissection time.[4] While some medical schools have "abandoned dissection for user friendly multimedia", it has been suggested that the beneficial values of orthodox dissection should not be replaced, but rather enhanced by hybrid teaching modalities.[4] A large body of research suggests that multimedia teaching is most useful in combination with dissection.



The Royal College of Radiologists advocates the inclusion of clinical radiology within the university curriculum.[4] Owing to the importance of radiological imaging in modern medicine, the ability of a student to interpret radiological images is vital.[5] While most medical students will not become radiologists, they must develop a fundamental knowledge of radiological imaging.[6] Anatomy can be made relevant and clinically vibrant through exploration of cadaveric CT images.[3] Radiology also improves the ability to identify anatomical structures in diagnostic radiographs both in the short and long term.[3] The integration of radiographic images in the teaching of anatomy has been proven to reinforce learning and to result in better retention of both radiological and anatomical knowledge.[5]

In exploring the value of examining images specific to the cadaver being dissected, Lufler *et al.* conclude that images need not be cadaver specific. However, cadaver specific imaging generates greater interest among students, encourages them to assume the role of a physician, and promotes respect for donors.[7]

X-perience presents donor specific radiographic profiles of UCD cadavers for educational purposes. This interactive viewing platform displays radiographic images, giving UCD anatomy students the opportunity to explore interesting findings and common pathologies relating to specific donors.

METHODS

Commencing in May 2015 the diagnostic imaging department of UCD obtained full skeletal radiographs from 13 donors (10 Female and 3 Male) aged 58-101 years. Each donor was transferred from the anatomy laboratory to the imaging room where images were captured. Radiographic images consisted of antero-posterior and lateral skull, cervical spine, chest, upper and lower arm, hand, abdomen, pelvis, upper and lower leg. This provided a complete skeletal survey of each donor. The images were produced digitally using Digital and Computed Radiography and stored securely as a DICOM dataset using unique identifiers for each donor. Exposure factors and total radiation dose were recorded.

Using Adobe Photoshop (Adobe, United States) the identity was removed from each image and the images were systemically labelled. Collaborating with consultant radiologists in Mount Sinai Hospital, New York and in the Mater Misercordiae Hospital, Dublin the images were systematically labelled with both anatomical and pathological findings. This made the images clinically relevant for students as well as a valuable study tool for anatomy. Khalil *et al*. stress the importance of clear labelling to empower rather than overwhelm the student.[6] Clinical histories were researched from donor files and presented alongside the images to provide a comprehensive profile on each donor.

The e-learning authoring software Articulate Storyline 2 (Articulate Global Inc., United States) was used to construct *X-perience*. This software allowed for the creation of a web enabled HTML5 interactive interface that students were able to use on the touch screens in the dissection lab. Students were initially presented with a welcome screen on which they were reminded of the sensitive nature of the material they were viewing. Following this, a simple map of the dissection room was displayed from which students could select the donor whose profile they wished to view. An interactive folder displayed the donor history as well as an interactive body outline from which the relevant body region could be selected. The images were grouped according to four body regions: head, trunk, upper limb and lower limb.

The body region of interest could be chosen by clicking on the body outline or by clicking on the tabs.

"Factual information was presented alongside the images of interest, briefly describing topics such as intramembranous and endochondral ossification, fracture classification and treatment options."

On viewing a specific image, students were initially presented with an unlabelled image, which allowed feature discovery by the student. Labels pointing out relevant anatomical structures in green and pathological findings in pink could be turned on as desired. The radiological findings relevant to the specific image could be seen alongside the image in a side bar.

Another valuable feature of *X-perience* was the interactive quiz. This drag and drop quiz allowed students to test their anatomy knowledge. When a correct label was dragged from the bottom of the screen to the relevant region, the label slotted automatically into place. Incorrect answers returned automatically to the bottom of the screen. This easy to use quiz provided instant feedback to students and was a fast and effective method of testing anatomy learning.

To assess the value of *X-perience* preclinical students in UCD's undergraduate medical programme, specifically Stage 3 Locomotor Biology students (n = 50) were surveyed. This cohort had prior traditional anatomical teaching in Stage 2, and thus could effectively compare anatomical learning with and without *X-perience*. Anatomy laboratory demonstrators were also consulted for feedback on *X-perience*. Responses were recorded using a 5 point Likert scale of strongly agree, agree, neutral, disagree and strongly disagree.

The following statements were presented on the survey:

1	I found *X-perience* easy to use.
2	*X-perience* is helpful for learning anatomy.
3	*X-perience* helps me understand why anatomy is the foundation of much of my coursework.
4	*X-perience* gives me a better appreciation of my anatomical donor.
5	I now have a better understanding of the clinical application of radiology.
6	*X-perience* is relevant to medical education.
7	I can identify anatomical structures more accurately after using *X-perience*.
8	*X-perience* helps bring material from numerous modules together, creating an overall picture of the human body.

An open-ended response and comment section was also included where students were encouraged to give feedback.

RESULTS

The workflow of profiling cadavers and constructing *X-perience* proved successful. *X-perience* is currently used by medical students on touch screens during practical classes. The results of the student acceptability survey, Kirkpatrick Level 1, showed extremely positive student feedback. 84% of students agreed that *X-perience* was a relevant, helpful and easy to use learning tool. 84% of students found that *X-perience* provided them with a more integrated, complete view of the human body and brought material from numerous modules together. Students (88%) appreciated the clinical relevance that *X-perience* brought to their learning. A greater understanding of the importance of radiology was acknowledged by 92% of students. 92% of students felt that by using X-perience they gained better appreciation of the anatomical donors and their medical histories. Students' reported comments were: "Absolutely brilliant", "Very cool", "Extremely interesting and useful", "Very impressive software".

CONCLUSIONS

While radiological profiles of donors have been carried out as far back as 1983, many medical schools have yet to adopt this learning tool. Following the successful integration of radiological profiles in UCD anatomy teaching, the introduction of similar viewing platforms at other medical schools can be recommended. The unique benefit of *X-perience* is the interactive, student-friendly display of the clinical profiles. The method of display encourages students to delve more deeply into their anatomy learning and explore the individuality of their donor. Advanced imaging modalities such as CT, as well as histology, could further refine *X-perience* and it is hoped that this will be carried out in future years.

"In addition to its educational value, X-perience strengthens the body donation programme, highlights the individuality and dignity of each donor and generates enthusiasm amongst anatomy students."

Acknowledgements

We would like to acknowledge the generosity of all the anatomical donors to UCD for providing us with the opportunity to learn in such a unique and privileged way.

Exemption from full ethical review was granted by the Human Research Ethics Committee – Sciences in University College Dublin.

References

01 McNiesh LM, Madewell JE, Allman RM. Cadaver radiography in the teaching of gross anatomy. Radiology. 1983 Jul;148(1):73-4.

02 Pantoja E, Nagy F, Zambernard J. Clinical radiographs of the cadaver as a teaching aid in anatomy. Radiology. 1985 Apr;155(1):28.

03 Bohl M, Francois W, Gest T. Self-guided clinical cases for medical students based on postmortem CT scans of cadavers. Clin Anat N Y N. 2011 Jul;24(5):655-63.

04 Sugand K, Abrahams P, Khurana A. The anatomy of anatomy: a review for its modernization. Anat Sci Educ. 2010 Apr;3(2):83-93.

05 Rengier F, Doll S, von Tengg-Kobligk H, Kirsch J, Kauczor H-U, Giesel FL. Integrated teaching of anatomy and radiology using three-dimensional image post-processing. Eur Radiol. 2009 Dec;19(12):2870-7.

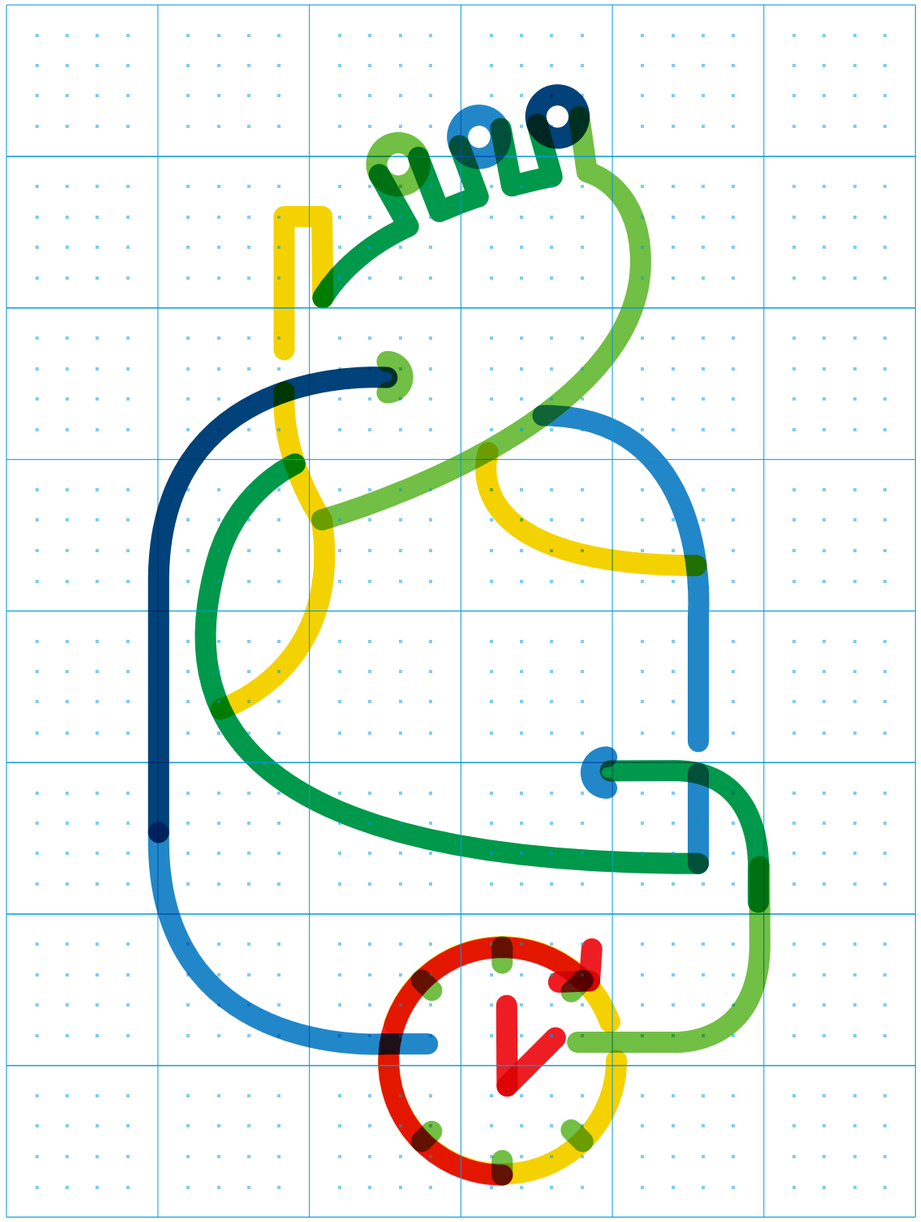
06 Khalil MK, Payer AF, Johnson TE. Effectiveness of using cross-sections in the recognition of anatomical structures in radiological images. Anat Rec B New Anat. 2005 Mar;283(1):9-13.

07 Lufler RS, Zumwalt AC, Romney CA, Hoagland TM. Incorporating radiology into medical gross anatomy: does the use of cadaver CT scans improve students' academic performance in anatomy? Anat Sci Educ. 2010 Apr;3(2):56-63.

Ventricular Assist Device: *An Underused, Life-Changing Modality*

Written by Grace Oon Bee Gan, Dr Alan Jacobsen

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



Written by Grace Oon Bee Gan
Dr Alan Jacobsen

ABSTRACT

Left ventricular assist device (LVAD) is a novel therapy in the treatment of end-stage heart failure. This technology may be used as a bridge to transplant or as destination therapy in patients who are not suitable for heart transplant. This paper presents the case of a gentleman at 11 months post-LVAD implantation who is currently awaiting heart transplant surgery. Over the years, research has shown improved long-term survival rates in ventricular assist device patients.

CASE BACKGROUND

Cardiovascular disease remains the most common cause of death in Ireland, accounting for 30.6% of total deaths in 2014.[1] While heart transplant is the gold standard for treating end stage heart failure, due to the shortage of donors and ineligibility of some patients for transplant surgery, this option is not always available.

"In such patients a LVAD may be used. This device acts as a pump in place of the failing heart. The device consists of an inflow tube from the left ventricle connected to a pump and an outflow tract to the aorta. "

LVADs are powered by an external battery connected to the pump via a driveline. The first generation pulsatile LVADs (HeartMate XVE, Thoratec Corporation, United States) have now been largely replaced by the smaller more durable second generation continuous flow LVAD (HeartMate II, Thoratec Corporation, United States). Canseco *et al*. recently reported that LVADs were underutilized in clinical practice given the improvement in cardiac function associated with its long-term use.[2]

CASE PRESENTATION

This 50-year-old gentleman was seen in clinic 11 months post-LVAD implantation. He had been previously well until August 2014 when he suffered an acute ST elevation myocardial infarction (STEMI) while working in the United Kingdom. He was driving when he suffered acute central chest pain associated with dyspnoea and a sense of impending doom. He denied palpitations, syncope, or nausea and vomiting. He was brought by ambulance to hospital where he was diagnosed with STEMI. An emergency angiogram revealed a left coronary artery thrombus and occlusion of his left anterior descending artery. Following an emergency percutaneous coronary intervention to his left anterior descending artery, he developed cardiogenic shock necessitating utilization of an intra-aortic balloon pump. His ejection fraction continued to deteriorate and he received veno-arterial extra-corporeal membrane oxygenation (ECMO) on day 5 of admission. On day 9 he was transferred from ECMO to an LVAD. His right heart function continued to deteriorate necessitating conversion to a bilateral ventricular assist device (BIVAD) on day 14. His hospital stay was further complicated by acute kidney injury and respiratory failure.

Over the next 3 months he improved sufficiently to be taken off BIVAD. At this stage the patient was on the newer second-generation LVAD and was well enough to be transferred back to Ireland where he spent 1 month as an in-patient in a high dependency unit. Four months after initial admission he received an automatic implantable cardioverter defibrillator for primary prevention of arrhythmias. This is routine for all patients on LVADs as they are unable to receive cardiac compressions due to the high risk of dislodging the device.[3]

OUTCOME AND FOLLOW UP

The patient completed his heart transplant work-up 6 months post-LVAD surgery. Unfortunately, his transplant is likely to be delayed due to the success of the LVAD itself and because donors of his height are scarce. He has adapted well to living with an LVAD and has a positive outlook on life. He has greatly improved his lifestyle, has ceased smoking and does regular exercise. His heart failure is controlled with spironolactone, bisoprolol, furosemide, aspirin, ramipril, atorvastatin and sildenafil. He is anticoagulated with warfarin (currently supratherapeutic) and his target INR is 3.1. At an 11-month follow-up, he denied any complications associated to the LVAD such as infection, thromboembolism or device failure.

DISCUSSION

Since its introduction into clinical practice, VAD technology has significantly improved survival rates among patients with end stage heart failure.[4]

"Patients receiving the second generation LVAD as destination therapy were shown to have almost three times better survival at 2 years compared to those on best medical therapy. "

Moreover, patients on LVAD reported better quality of life than those on medical therapy, calculated based on the Minnesota Living with Heart Failure Questionnaire.[5]

Two major causes of mortality in patients with first generation LVADs were infection and mechanical failure. Patients with LVAD are at high risk of infection as the driveline exiting the skin is a potential sight of bacterial and fungal colonization. The incidence of mechanical failure has been greatly reduced with the more durable second generation LVADs.[5] Nevertheless, it is important to note that the risk of complications is higher in VAD patients than those on medical treatment.

Despite these better survival rates, Miller *et al*. reported an underutilization of LVADs in clinical practice.[6] As a comparison, the number of new VAD implants per year in the U.S. was estimated at 1700, as opposed to only 430 a year in Europe.[7] In Ireland, there are currently only 5 patients with an LVAD. This small number is primarily due to the expense of the device and the low availability of VAD centres. At present there is only one VAD centre in Ireland. Additionally, certain demographic groups have been shown to be less likely to receive an LVADs, including women.[3] This may have previously been due to the large size of first generation pulsatile LVADs relative to the size of the average female body. However, with the introduction of the smaller second generation LVADs it is expected that in the coming years there will be a rise in VAD implantation among women with end-stage heart failure.

Furthermore, difficulty in patient selection for LVAD surgery has been a limiting factor. There are currently no consensus guidelines for the utilization of LVAD. The following are some considerations taken into account:

INDICATIONS	CONTRAINDICATIONS
NYHA Class IV	Potential for recovery from heart failure
Life expectancy less than 2 years without VAD	Other terminal illnesses such as malignant metastases
Patient does not meet transplant criteria	Patients above 65 years of age with both right and left heart failure
Heart failure refractory to medical treatment at least 60/90 days	Impaired ability to care for device (e.g. neurological or psychiatric illnesses)
Left ventricular ejection fraction less than 25%	Active systemic infection
Cardiogenic shock or cardiac failure unresponsive to medical treatment	High risk of renal or hepatic failure
IV inotrope therapy to be discontinued due to systemic failure	Anticoagulation contraindicated (e.g. recent hemorrhagic stroke)

Concrete funding schemes as well as precise guidelines are required before LVAD can be considered an equally viable alternative to heart transplant.

CONCLUSIONS

The use of LVAD in end-stage heart failure patients has been proven to be more effective than conventional medical therapy. Utilization of this modality of treatment is expected to rise in various demographic groups in the coming years either as a bridge-to-transplant or as destination therapy.

PATIENT'S PERSPECTIVE

Initially, the VAD routine was very difficult. The patient was required to connect batteries every morning and was not able to work or to lift heavy loads. Initial aftercare may also have been insufficient. First, the wound site should have been checked more often for infection. Second, the family of the patient should have been more involved in recovery, and had access to councillors and psychiatrists. The patient's outlook for the future is to receive a transplant and to try and lead a normal healthy life as much as possible, both before and after the transplant.

Acknowledgements

The author would like to thank Dr Alan Jacobsen and Dr Aideen Gough who contributed greatly by reviewing this case report. Thanks are also extended to the patient who consented for his case to be used for educational purposes.

References

01 Central Statistics Office. Vital Statistics Yearly Summary [Internet]. Dublin: Central Statistics Office; 2015 [updated 2015 May 29; cited 2015 October 3]. Available from: http://www.cso.ie/en/releasesandpublications/ep/p-vsys/vitalstatisticsyearlysummary2014/

02 Canseco DC, Kimura W, Garg S, Mukherjee S, Bhattacharya S, Abdisalaam S, Das S, Asaithamby A, Mammen P, Sadek H. Human Ventricular Unloading Induces Cardiomyocyte Proliferation. Journal of the American College of Cardiology. 2015 March; 65(9):892-900.

03 Grossman S, Brady W, Brown D, Rosen P. Cardiovascular Problems in Emergency Medicine: A Discussion-Based Review. West Sussex: Wiley-Blackwell; 2011.

04 Rose E, Geljins A, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, OZ MC, Poirier VL. Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure. New England Journal of Medicine. 2001 Nov; 345:1435-1443.

05 Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G, Jaski B, Farrar DJ, Slaughter MS. Predicting Survival in Patients Receiving Continuous Flow Left Ventricular Assist Device. Journal of the American College of Cardiology. 2013 Jan; 61(3):313-321.

06 Miller L. Is Left Ventricular Assist Device Underutilized in the Treatment of Heart Failure? American Heart Association Journal. 2011; 123:1552-1558.

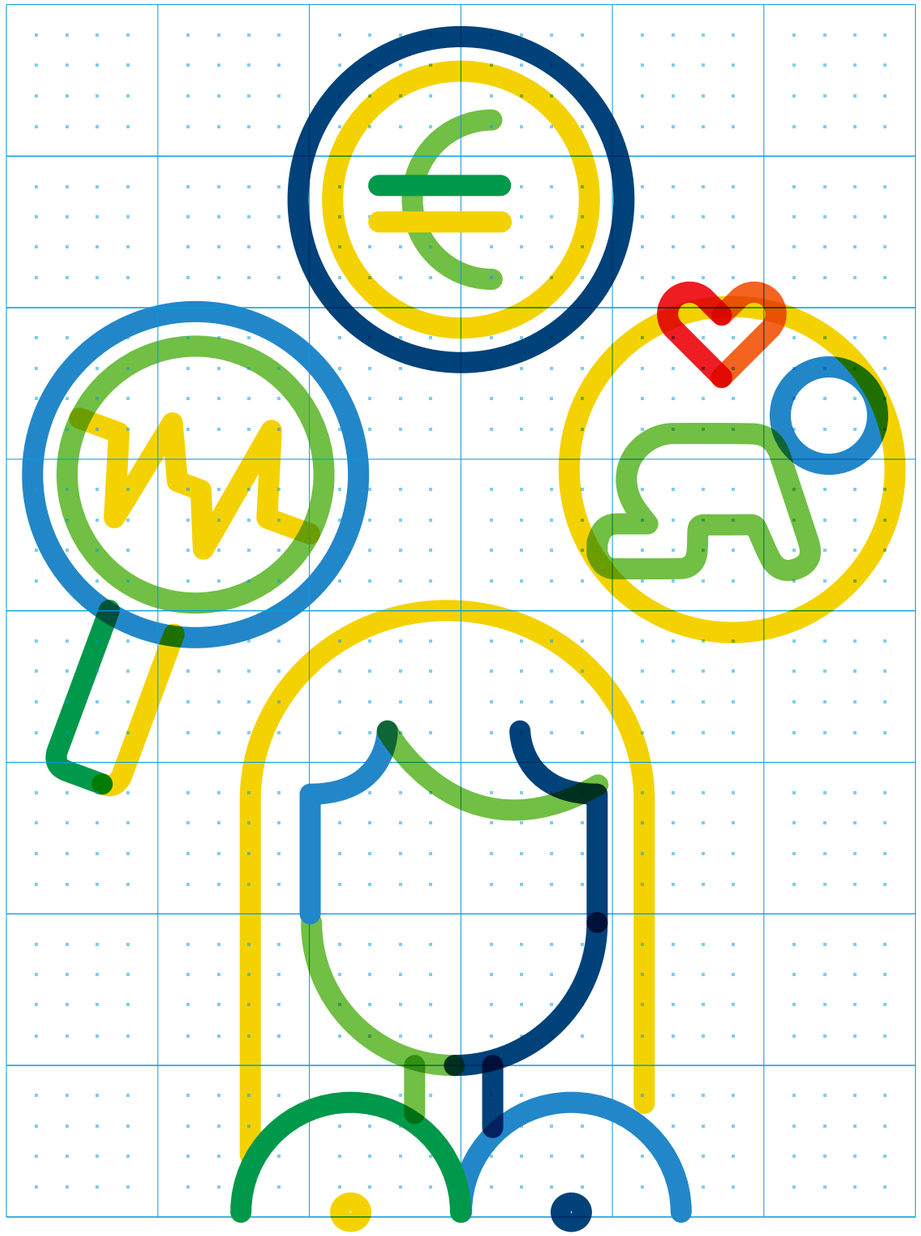
07 Birks E. The Comparative Use of Ventricular Assist Devices. Difference between Europe and the United States. Texas Heart Institute Journal. 2010; 37(5): 565-567.

08 Wilson S, Mudge G, Stewart G, Givertz M. Evaluation for a Ventricular Assist Device. American Heart Association Journal. 2009: 119: 2225-2232.

Breastfeeding:
Benefits and Current Practices in Ireland

Written by Roisin McGinley

UCD School of Public Health, Physiotherapy and Sports Science,
University College Dublin, Belfield, Dublin 4.



ABSTRACT

Breastfeeding can offer significant nutritional and non-nutritional benefits to both infant and mother. The World Health Organisation (WHO) recommends that, whenever possible, infants should be fed exclusively on breast milk until six months of age and that breast milk should continue as part of the diet for at least two years.

During the initial phases of human development nutrition has the potential to positively or negatively affect organ function, and thereby predispose individuals to a later onset of optimal health or disease. The short and long-term breastfeeding supports the optimal development of the immune system, motor control and cognitive ability.

The initial months after birth may also serve as a critical window for the development of obesity, a condition which is of significant concern to public health in Ireland at present. Parental feeding practices during infancy, such as the timing of solid food introduction, may be a key modifiable determinant of childhood obesity.

The promotion of breastfeeding among mothers in Ireland has been a key government health policy since the mid-1990s. However, the prevalence of breastfeeding is still relatively low. Findings from the 2011 Growing Up in Ireland study revealed that just under 50% of babies were being breastfed when they left hospital and 57% had ever received breast milk. Among those who had never breastfed the most frequent reason for not doing so was 'formula feeding preferable' (48%); the next most frequent reason was 'inconvenience/ fatigue (17%). Every effort should be made to ensure mothers are offered support and encouragement to initiate and maintain breastfeeding.

INTRODUCTION

Breastfeeding is a complex and exceptionally adaptive function. It is an intricate process of interaction between mother and child that is more than simply a means of nutrition.[1] While infants will make daily leaps in neurocognitive, motor and social development, they are completely dependent on parents and guardians to feed and nurture them.[2] Thus, it should be no surprise that what occurs in the first months of life may be essential to lifelong nutritional status.[1,3]

The World Health Organisation (WHO) recommends that, whenever possible, infants should be fed exclusively on breast milk until 6 months of age and that breast milk should continue as part of the diet for at least 2 years,[4] yet globally only 38% of infants are breastfed.[5] The concept that nutrition during the initial phases of human development has the potential to alter organ function, and ultimately predispose individuals to a later onset of disease, is an area of great interest within medical science and of significant concern to public health.[6]

THE BENEFITS OF BREASTFEEDING TO THE INFANT

Breastfeeding offers numerous short and long term benefits for infant health. It may protect against morbidity and mortality from infectious diseases.[6] Systematic reviews on the long term effects of breastfeeding have found that participants who were breastfed experienced lower mean blood pressure and total cholesterol. Evidence also suggests that breastfeeding is associated with increased cognitive development in childhood.[7] Furthermore, the evidence suggests that breastfeeding may have a small protective long term effect on the prevalence of obesity.[7] Breastfeeding also correlates with a reduction in a range of infectious and non-infectious illnesses including diarrhoea, respiratory illness, ear infection, type 1 diabetes mellitus, coeliac disease, inflammatory bowel disease, childhood cancer, allergies and asthma.[7]

Breastfeeding also has many positive benefits beyond nutritional status. Colostrum, produced in the first days of breastfeeding, contains over 90 known components, including vitamins, minerals, amino acids and immune and growth factors. In addition, its mild laxative effect encourages the passing of the infants first stool, the meconium.[8] Furthermore, the neonatal period is particularly critical as the newborn is immediately exposed to a large number of microorganisms and foreign proteins, and breastfeeding is important for the provision of immune-modulating factors which may exert a decisive impact on the breastfed baby's developing defence.[9] Human milk is quantitatively different than either soy or bovine formula. Numerous bioactive factors are exclusive to human milk including specific human growth hormones and growth factors. For instance, breast milk reinforces mucosal defences by providing secretory IgA (SIgA) and IgM (SIgM) antibodies, and delivering immune cells, cytokines and high concentrations of oligosaccharides.[8]

THE BENEFITS OF BREASTFEEDING IN MATERNAL HEALTH

Maternal health must also be considered in relation to breastfeeding. A study by Schwarz et al.[10] which examined the data of 139,681 postmenopausal women, found that those who breastfed their children were less likely to have developed hypertension, diabetes, hyperlipidaemia and cardiovascular disease when postmenopausal.[10] Women who had a cumulative lifetime duration of lactation greater than 12 months were approximately 10% less likely to have developed cardiovascular disease than parous women who had never breast-fed at 7.9 years, the median duration of follow-up.[10] Thus, the authors concluded that lactation may play a significant role in reducing risk of cardiovascular disease.[10] Lactation increases a mother's metabolic expenditure by an estimated 480 kcal/ day. Lactating mothers lose more weight in the postpartum period than mothers who do not

Breastfeeding has been proposed to be associated with postpartum depression. However this link has been underexplored in the literature.[1,12,13] A proposed mechanism is that lactation is associated with an attenuated stress response, involving cortisol and the lactogenic hormones oxytocin and prolactin, which appear to have both antidepressant and anxiolytic effects.[12] A bidirectional relationship has been identified between breastfeeding and depression, with prenatal depressive symptomatology predicting less breastfeeding postpartum and early breastfeeding predicting less depressive symptomatology later in the postpartum.[13]

BREASTFEEDING AND OBESITY

The prevalence of obesity is a topical issue in Ireland at present, and indeed a major public health crisis around the world.[14] The initial months after birth may serve as a critical window for the development of obesity.[14,15] Parental feeding practices during infancy, such as the timing of solid food introduction, may be a key modifiable determinant of childhood obesity.[15]

A prospective pre-birth cohort study of 847 children from Project Viva, a longitudinal pre-birth cohort of mother–offspring pairs in Boston, Massachusetts, revealed that the introduction of solids before the age of 4 months was associated with a six-fold increase in the risk of obesity at age 3 years among infants who were never breastfed or who stopped breastfeeding before the age of 4 months.[15] The authors stated that the association was not explained by rapid early growth.[15] One possible explanation for the benefit of breastfeeding might be that breastfed children learn appetite control and that this control remains after the introduction of solid food. This lack of appetite control may lead to overfeeding in bottle-fed infants due to lack of parental responsiveness to infant satiety cues.[2,16]

BREASTFEEDING IN IRELAND

The promotion of breastfeeding among mothers in Ireland has been a key government health policy since the mid-1990s. However, the prevalence of breastfeeding is still relatively low.[17] In 2008 the Health Service Executive (HSE) commissioned a national study to determine the rate and duration of breastfeeding in Ireland. This national study, the first since 1986, measured breastfeeding rates following discharge from hospital. It aimed to assess the rate of exclusive and partial breastfeeding at three critical periods: from birth to 48 hours, at 3 to 4 months, and at 6 to 7 months.[18]

The authors found that 56% of mothers who responded to phase 2 of the survey (3 to 4 months post-natal) had initiated breastfeeding at birth. Amongst mothers who initiated breastfeeding, those who were aged 40 to 44 were the most likely to be exclusively breastfeeding at 3 to 4 months (48%). The length of hospital stay was not found to be a significant factor on rates of breastfeeding. At 6 to 7 months, 18% of the 461 mothers who were breastfeeding at 3 to 4 months remained exclusively breastfeeding. This was just 6% of the 1002 mothers who had breastfed their infants at birth, and only 2.4% of the 2527 mothers who joined the study.

Fundamentally, the study revealed relevant and potentially modifiable factors associated with breastfeeding initiation in Ireland. Peers were found to be influential in a mother's choice of infant feeding method. Professional, managerial and technical workers were more likely to initiate breastfeeding than those in non-manual, semi-skilled, skilled or manual employment. The younger the mother when she gave birth, the less likely she was to initiate breastfeeding.[18]

A WHO Ireland country profile, completed in 2013, examined nationally representative data from 2008 and revealed that the prevalence of exclusive breastfeeding at 6 months of age was 2.5% in Ireland.[19] Taking these findings into consideration, it appears that there is a need for a comprehensive, national system of monitoring breastfeeding rates at predetermined intervals.[16,18] More recently, findings from the 2011 Growing Up in Ireland study revealed that just under 50% of babies were being breastfed when they left hospital and 57% in total had ever received breast milk.[17] Furthermore, infants whose mothers were born outside Ireland were much more likely to be breastfed that infants whose mothers were born in Ireland (83% compared to 48%). Mothers who breastfed typically stopped when the infant was three months old. The most frequent reason for discontinuing breastfeeding among those who had previously breastfed was ‘not enough milk/ hungry baby’ (37%). Among those who had never breastfed, the most frequent reason for not doing so was ‘formula feeding preferable’ (48%) or ‘inconvenience/fatigue’ (17%).[17]

FACTORS AFFECTING BREASTFEEDING INITIATION

The decision about feeding is often made by the last trimester of pregnancy. Information given during prenatal care is extremely influential and it is apparent that both advertising and healthcare providers influence a women's choice.[20] A study revealed that the leading reasons for discontinuation of breastfeeding included: concerns of insufficient milk production (45%); infants dissatisfaction with breast milk (42%); difficulty nursing (24%); sore, cracked or bleeding nipples (17%); and return to work/school (16%).[20]

For many first time mothers the prospect of breast feeding may be daunting. A 2012 Cochrane review of 52 studies from 21 countries concluded that all women should be offered support to breastfeed their babies to increase the duration and exclusivity of breastfeeding.[21] This support may be offered either by professional or lay and peer supporters, or a combination of both. Strategies that rely mainly on face-to face support are more likely to succeed. Importantly, support for which women are expected to initiate first contact, or reactive support, is unlikely to be effective. Women should be offered scheduled visits on an on-going basis so they can predict that support will be available.[21] It also imperative that women are educated regarding the option to continue to try to breastfeed, even weeks into formula feeding. It must also be acknowledged that for some mothers breastfeeding is not possible. This may be frustrating and distressing for the mothers, and they must also receive adequate support.

From a financial aspect, breastfeeding offers considerable savings compared to formula feeding.[20] Still, the formula industry has reversed feeding trends from primarily breastfeeding to primarily formula feeding through pervasive marketing strategies targeting hospitals, health providers, and the general public.[20] The impact of the infant formula industry and advertising of infant formula on breastfeeding practices is largely unknown and almost certainly complex. It is of note that Ireland produces some 15% of the world's infant formula,[22] so it follows that the influence of the industry in Ireland is not likely to be negligible.

CONCLUSIONS

The decision to breastfeed is deeply personal and individual. Breastfeeding can offer significant nutritional and non-nutritional benefits to the infant and the mother, throughout their lives. Therefore, the support and education around breastfeeding should be viewed as a major public health issue. Efforts to promote breastfeeding can succeed, but they must become a public health priority. The contribution of breastfeeding to public health should be considered and every effort should be made to ensure mothers are offered support and encouragement to initiate and maintain this invaluable, natural interaction.

References

01 Godfrey, J.R. & Lawrence, R.A. 2010, "Toward optimal health: The maternal benefits of breastfeeding", Journal of Women's Health, vol. 19, no. 9, pp. 1597-1602.

02 Gillman MW. The first months of life: a critical period for development of obesity. AmJ Clin Nutr. 2008;87(6):1587-1589

03 Flower KB, Willoughby M, Cadigan RJ, Perrin EM, Randolph G, The Family Life Project Investigative Team. Understanding breastfeeding initiation and continuation in rural communities: A combined qualitative=quantitative approach. Matern Child Health J 2008;12:402-414.

04 World Health Organization (2003) Infant and young child nutrition: Global strategy on infant and young child feeding. World Health Organization, Geneva

05 World Health Organisation [http://www.who.int/nutrition/global-target-2025/infographic_breastfeeding.pdf?ua=1] [Accessed 9th October 2015]

06 Eidelman, A.I., Schanler, R.J., Johnston, M., Landers, S., Noble, L., Szucs, K. and Viehmann, L., 2012. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 129, e827-841.

07 Horta, B., Bahl, R., Martines, J., and Victora, C., 2007. Evidence of the long-term effects of breastfeeding: Systematic reviews and meta-analysis. World Health Organization Publication, Geneva, Switzerland, pp. 1-52.

08 S. Zibadi, R.R. Watson and V.R. Preedy (eds.) Handbook of dietary and nutritional aspects of human breast milk Human Health Handbooks no. 5 - DOI 10.3920/978-90-8686-764-6_12, Wageningen Academic Publishers 2013 Musumeci and S. Musumeci p217-233 chapter 12.

09 S. Zibadi, R.R. Watson and V.R. Preedy (eds.) Handbook of dietary and nutritional aspects of human breast milk Human Health Handbooks no. 5 - DOI 10.3920/978-90-8686-764-6_12, Wageningen Academic Publishers 2013 Ch 3 Immune aspects of breast milk: an overview, Brandtzaeg p57-82.

10 Schwarz, E.B., Ray, R.M., Stuebe, A.M., Allison, M.A., Ness, R.B., Freiberg, M.S. & Cauley, J.A. 2009, "Duration of Lactation and Risk Factors for Maternal Cardiovascular Disease", Obstetrics & Gynecology, vol. 113, no. 5, pp. 974-982.

11 Rooney BL, Schauberger CW. Excess pregnancy weight gain and long-term obesity: one decade later. Obstet Gynecol 2002;100:245-52.

12 Sibolboro Mezzacappa E, Endicott J. Parity mediates the association between infant feeding method and maternal depressive symptoms in the postpartum. Arch Womens Ment Health 2007;10:259-266.

13 Hahn-Holbrook, J., Haselton, M., Schetter, C. & Glynn, L. 2013, "Does breastfeeding offer protection against maternal depressive symptomatology?", Archives of womens mental health, vol. 16, no. 5, pp. 411-422.

14 Yan, J., Liu, L., Zhu, Y., Huang, G. & Wang, P.P. 2014, "The association between breastfeeding and childhood obesity: a meta-analysis", BMC Public Health, vol. 14, no. 1, pp. 1267-1267.

15 Huh, S.Y., Rifas-Shiman, S.L., Taveras, E.M., Oken, E. & Gillman, M.W. 2011, "Timing of solid food introduction and risk of obesity in preschool-aged children", Pediatrics, vol. 127, no. 3, pp. e544-e551.

16 Moss, B.G. & Yeaton, W.H. 2014, "Early Childhood Healthy and Obese Weight Status: Potentially Protective Benefits of Breastfeeding and Delaying Solid Foods", Maternal and Child Health Journal, vol. 18, no. 5, pp. 1224-1232.

17 2011 Growing up in Ireland, National Longitudinal Study of Children, Infant Cohort http://www.growingup.ie/fileadmin/user_upload/documents/Infant_Key_Findings/Infant_Cohort_Key_Finding_No._1_Pregnancy_and_Birth.pdf

18 Gallagher, L., Begley, C. & Clarke, M. 2015, "Determinants of breastfeeding initiation in Ireland", Irish Journal of Medical Science (1971 -), .

19 http://www.euro.who.int/__data/assets/pdf_file/0016/243304/Ireland-WHO-Country-Profile.pdf?ua=1 [Accessed 7th October 2015]

20 Kaplan, D.L. & Graff, K.M. 2008, "Marketing Breastfeeding—Reversing Corporate Influence on Infant Feeding Practices", Journal of Urban Health, vol. 85, no. 4, pp. 486-504.

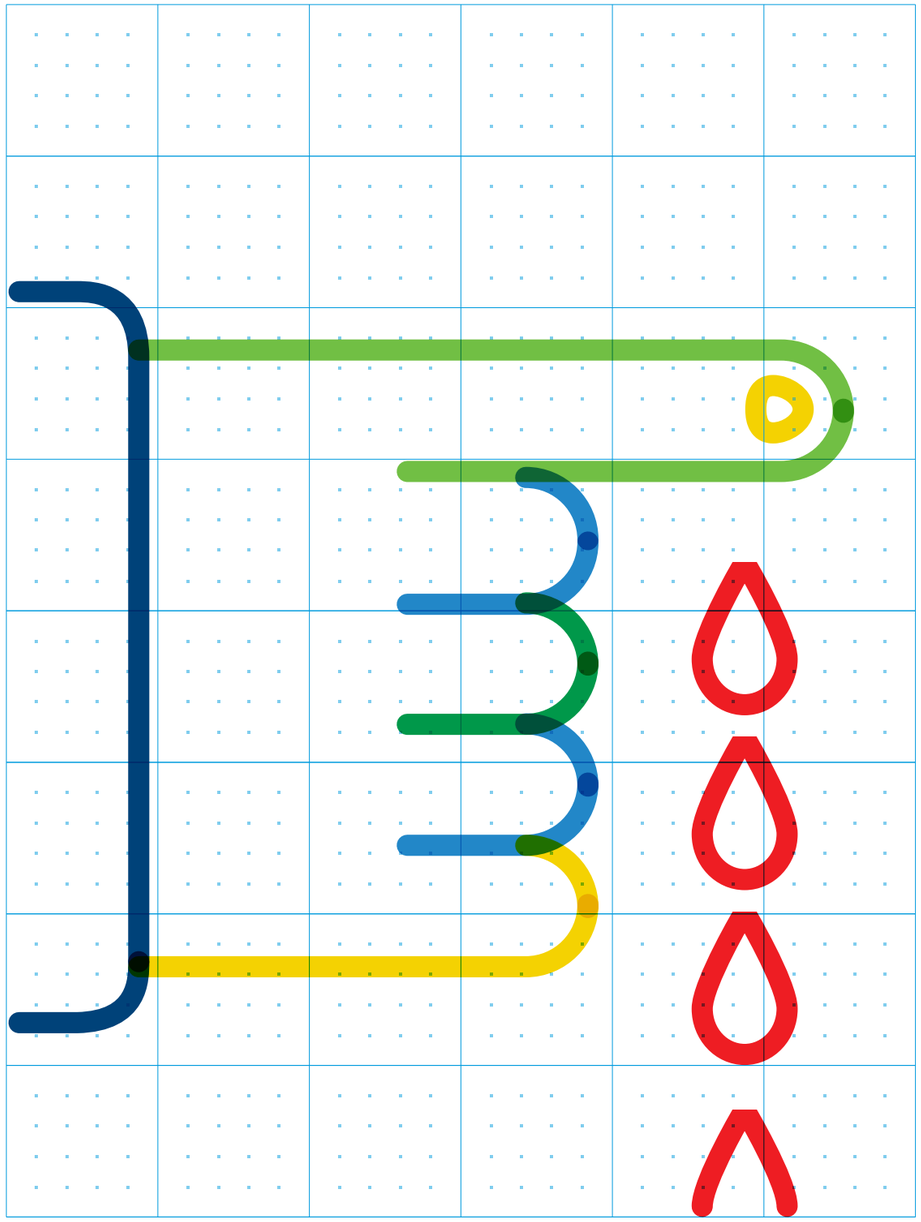
21 Renfrew, M.J., McCormick, F.M., Wade, A., Quinn, B. & Dowswell, T. 2012, "Support for healthy breastfeeding mothers with healthy term babies", Cochrane database of systematic reviews (Online), vol. 5, no. 5, pp. CD001141.

22 Ask About Ireland http://www.askaboutireland.ie/enfo/sustainable-living/farming-in-ireland-overvi/dairy-farming/[Accessed [13th March 2015]

Tranexamic Acid Use for Haemorrhage Patients: *A Reduction in Hyperfibrinolytic-Related Deaths*

Written by Sarah Devlin

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



ABSTRACT

OBJECTIVES

Tranexamic acid (TXA) is an antifibrinolytic agent with the potential to decrease mortality rates associated with post-haemorrhage acute coagulopathy of trauma (ACT). By assessing how the timing and dosage of TXA administration impacts on mortality rates pertaining to both intra- and extracranial bleeds, correct measures may be taken to integrate the treatment into emergency (including pre-hospital) protocol. A cautionary review of TXA's potential side effects was completed, also evaluating potential outcomes of TXA use in patients not experiencing ACT.

RESULTS

Optimal effects correspond to a loading dose of 10mg/kg, with subsequent infusions of 1mg/kg/hr. Higher doses do not result in increased efficacy and have been associated with convulsive seizures, linked to the structural similarities between TXA and γ-aminobutyric acid. TXA infusions less than 3 hours post-injury reduce mortality rates, significantly so when delivered less than 1 hour after the trauma. Mortality rates increase when TXA is delayed for 3 or more hours. TXA administration to patients not experiencing ACT does not lead to increased development of thromboembolic events. TXA administration is found to be cost effective based on GDP per capita per disability-adjusted life year.

CONCLUSIONS

Early treatment (<1 hour post-injury) with TXA results in the greatest reduction in deaths caused by bleeding in patients who are or may be at risk of becoming hyperfibrinolytic. It is logical to assume that early infusion (<1 hour post-injury) of TXA into severely haemorrhaging patients at risk of hyperfibrinolysis will result in reduced in mortality rates.

INTRODUCTION

Globally, trauma results in 5.8 million fatalities, accounting for 10% of world deaths. Haemorrhage is responsible for up to 40% of in-hospital trauma-induced deaths, establishing bleeding and its subsequent consequences as the major cause of avoidable death within this category.[1] Coagulopathies are present in the majority of significant haemorrhage cases, induced by clotting factor depletion as a result of haemodilution. These deleterious events result in an impaired platelet and thrombin function and reduced fibrinogen availability.[2]

Primary fibrinolysis can result in the development of Acute Coagulopathy of Trauma (ACT). ACT is diagnosed in up to 40% of patients with tissue hypoperfusion and there is a high association between trauma-induced hyperfibrinolytic activity and death (70-100%).[2] Therefore, it is plausible that the treatment of ACT with antifibrinolytic medications, such as tranexamic acid (TXA) would impact significantly on mortality rates.[2] This review will discuss the modern use of TXA in the treatment of haemorrhage within the trauma environment. Emphasis will be placed on overall relative decreases in mortality rates, timing and dosages of infusions, documented side-effects and overall cost-effectiveness of the drug on an international scale.

BIOLOGICAL ACTIVITY OF TRANEXAMIC ACID

Under normal physiological conditions, plasmin is activated by the endothelium, kallikrein-mediated plasmin activation and the release of tissue plasminogen activator (tPA). These mechanisms are modulated by tissue- and urokinase-type plasminogen activators. Conversely, inhibition is integral for haemostatic balance, a process modulated by multiple inhibitors such as thrombin-activatable fibrinolysis inhibitor, α2-antiplasmin and plasminogen activator inhibitor 1.[3] However, extensive tissue trauma may shift the equilibrium between plasmin activation and inhibition, resulting in hyperfibrinolysis that contributes significantly to haemorrhage and acute coagulopathy of trauma.[3]

Synthesized in the liver, the proenzyme plasminogen, is converted into active form plasmin by tissue plasminogen activator. Plasminogen is folded into protruding circular structures called kringles, which house the lysine-binding sites for fibrin attachment. Fibrin binds both plasminogen and tPA, localising plasmin activation to the injured region. Plasmin is a serine protease that lyses the fibrin into degradation products, sequentially exposes more lysine residues to activate more plasminogen, thus accelerating the fibrinolytic process.[4]

Tranexamic acid, a synthetic derivative and analogue of lysine, is an antifibrinolytic drug given to competitively inhibit the conversion of plasminogen to active plasmin, by obstructing the lysine-binding sites on the inactive form. TXA, like ε-aminocaproic acid (another lysine analogue) interrupts the binding of plasminogen to fibrin, an interaction necessary for activation.[1-4] Tranexamic acid has been in use since the early 1960s in treating haemophilia, and is widely used in orthopaedic and cardiac surgery. However, extensive use in the trauma population was sparked only recently by the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage (CRASH) -2 study, released in 2010.[5]

CRASH-2 TRIAL

The CRASH-2 trial investigated the effects of TXA on mortality rate, vascular occlusion and requirement for blood transfusion in trauma patients with significant haemorrhage.[5] 20,211 adult trauma patients were recruited across 274 hospitals. Those experiencing, or at risk of experiencing, significant haemorrhage were assigned randomly to either a TXA-receiving group or a placebo-receiving group. Patient assignment was completed within 8 hours of injury. Patients with a definite indication or definite contraindication for the use of TXA were excluded. The primary outcome of the study was death within 4 weeks of haemorrhage. The study concluded that TXA administration significantly reduced all-cause mortality (14.5%) compared to placebo (16%). The risk of death due to exsanguination was also lower in the TXA-group (4.9%, versus 5.7% in the control patients).[5]

I DOSE

The dose of TXA used in this trial was based on the use of this drug in surgery, where the loading doses varied from 2.5-100mg/kg.[6] However, studies indicate that the dose size had no significant impact on blood loss or blood transfusion requirements. For CRASH 2 trial patients weighing from below 50 to in excess of 100kg, an initial loading dose of 10mg/kg, with subsequent infusions of 1mg/kg/h rendered the plasma concentration sufficiently high to inhibit fibrinolysis, with no additional inferred haemostatic advantage when a higher dose is administrated.[7,8]

II TIMING

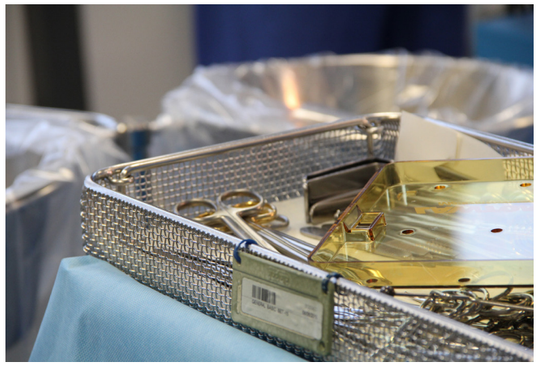
Although TXA infusions were received within 8 hours post injury, significant discrepancies in survival rates were observed depending on the timing of administration. TXA infusions delivered within 1 hour, or between 1-3 hours, following injury resulted in significantly reduced mortality rates due to exsanguination vs placebo (5.3% vs 7.7% and 4.8% vs 6.1% respectively). The mortality rates reversed when TXA was administered greater than 3 hours post injury (4.4% vs 3.1%).[5]

The severity of fibrinolysis can be assessed by measurement of D-dimers, protein fragments from fibrin degradation. The higher the concentration of D-dimers, the greater the severity of injury, as shown by Brohi *et al*. from samples that were extracted from patients at the time of hospital admission, with a median pre-hospital time of 28 minutes.[9] This early increase in fibrinolysis appears to promote exsanguination, increasing the risk of death. Therefore, early administration of an antifibrinolytic drug would be most suitable. This theory is reinforced by the CRASH-2 study that indicated delivery of TXA is most effective less than 1 hour post injury.[5]

Disseminated intravascular coagulation involves fibrin formation and coagulation, though as time progresses, the coagulation proteins are rapidly consumed and so can become exhausted, causing late bleeding. The CRASH-2 time frame of less than 8 hours was instated in order to avoid delivering an antifibrinolytic drug in this late stage of haemorrhage. It must be considered that the development of a pro-thrombotic state occurred sooner than initially anticipated in some patients.[11] Furthermore, the risk of existing acidosis or hypothermia increases with later hospital arrival. These other systemic factors may play a role in the interaction of TXA and the blood proteins. More research needs to be carried out with regards to the mechanism of TXA action when infused 3-8 hours post trauma.[11]

TRANEXAMIC ACID IN THE TREATMENT OF INTRACRANIAL HAEMORRHAGE

The efficacy of TXA for intracranial haemorrhage is also of clinical significance in the trauma environment.[15] The size of a traumatic intracranial haemorrhage is proportional to the risk of death and disability, irrespective of location.[16-18] the CRASH-2 trial suggested that if the intracranial bleeding could be reduced, the outcome of the patient may improve. After a physical trauma to the parenchyma, thromboplastin is released into the blood stream in high concentrations, disturbing the coagulation process. Furthermore, due to the damage of the cerebral endothelium, activation of clotting cascades and platelets ensues, resulting in an intravascular thrombosis and a reduction in coagulation factors.[19,20] TXA allows for the maintenance of mature fibrin and uninterrupted coagulation. It is theorized that TXA reduces secondary brain injury through two main mechanisms; firstly, by limiting fibrinolysis (and thus intracranial haematoma enlargement) and secondly, through the reduction in perilesional oedema by inhibiting the effect of tissue plasminogen activator.[19] Two high quality clinical trials[15,21] demonstrated a decrease in intracranial haematoma in the TXA cohort, deduced on the basis of total volumetric growth, new areas of haemorrhage and the presence of the mass effect.[5,15] An improved mortality rate was also seen in patients who received TXA relative to the placebo cohort. Though the individual studies' results are statistically insignificant, a meta-analysis reveal a statistically significant reduction in haemorrhage progression following the administration of TXA in patients with traumatic brain injuries.[19]



INTEGRATION OF TRANEXAMIC ACID INTO THE PRE-HOSPITAL SCENE: MILITARY AND CIVILIAN SETTINGS

Based on the research presented above, haemostatic resuscitation should begin at the earliest possible opportunity. Intervention in the pre-hospital setting presents the best chance for a positive prognosis.[28] The possibility of the administration of TXA in the pre-hospital field has been discussed at length by the WHO. Studies, many of them military based, support its pre-hospital use. The British military incorporated TXA into their formal clinical practice guidelines in 2010,[24] while 2012 saw the US military incorporate TXA use into the guidelines for tactical combat casual care.[25]

The MATTERs Military study indicated that TXA use yielded an absolute reduction in mortality of 6.5%[24,25] overshadowing the more subtle 1.5% reduction demonstrated in the CRASH-2 trial.[5] The MATTERs study also revealed a 13.7% absolute reduction in mortality in the portion of the TXA cohort who required a massive blood infusion (greater than 10 units) relative to the non-TXA cohort who required the same transfusion volume.[24] These findings suggest an increased benefit of TXA in those more seriously injured. In 2014, TXA was been introduced in the Irish pre-hospital protocol, 3 years after the NHS commenced paramedic administration of the anti-haemorrhagic agent. Further systematic review of the benefit of pre-hospital TXA infusions in the civilian setting remains to be done.[26]

TXA can be reliably stored in emergency vehicles, such as ambulances and medical helicopters. A recent study[27] demonstrated that TXA remains stable for up to 12 weeks, and can be exposed to temperatures ranging from -20 to 50 degrees Celsius without functional compromise. This functionality was determined based on the ability of TXA to completely inhibit streptokinase-induce fibrinolysis in platelet-poor plasma, as determined by D-dimer and thromboelastography evaluations.[27] The storage properties of TXA would facilitate early pre-hospital infusions for haemorrhaging patients.

SEIZURES FOLLOWING TRANEXAMIC ACID ADMINISTRATION:

Following cardiac surgery where TXA has been administered, a high number of postoperative convulsive seizures have been documented, corresponding to TXA doses that are 2-10 fold higher than those administered in the CRASH-2 trial.[5] These seizures led to an increased rate of neurological complications. A possible mechanism for TXA-induced seizures is the structural similarity of TXA and γ-aminobutyric acid as a potential cause of neurotoxicity.[5] In the adult brain, γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, plays a fundamental role in the organisation of electrical conductance patterns and the prevention of seizure-like activity.[22] The actions of antagonists against the GABA type A receptors will result in epileptic activity. Temporal lobe epilepsy is stimulated substantially by the neuronal excitability of the basolateral nucleus of the amygdala. In a 2014 study, it has been shown that TXA impairs GABA type A-mediated synaptic transmission in the murine amygdala, in a dose-dependent fashion.[23] TXA administration at doses in the region of 100 mg/kg has an indicated increased risk of seizures,[6,7] conveying the importance of a fixed initial dose in trauma. The incidence in dose-dependent seizure occurrence in the trauma situation has not yet been examined,[11] but is advised considering the listing of TXA in the WHO's list of essential medicines and thus, its global-wide use.[15]

OUTCOME IF TXA ADMINISTERED TO A PATIENT NOT EXPERIENCING ACT

Direct indication for the use of TXA would rely on a known history of fibrinolytic drug use or lab evidence of hyperfibrinolysis, such as accumulations of D-dimers or degradation products of fibrinogen. The incidence of hyperfibrinolysis in acute coagulopathy ranges from 2%-34%.[2]

However, the locational constraints in the early treatment of haemorrhage rarely facilitate full-scale hyperfibrinolytic investigations, the absolute need for which would completely exclude a pre-hospital infusion of TXA. Fortunately, the CRASH-2 study administered TXA to haemorrhaging patients at risk of ACT and indicated that there was no difference in the development of thromboembolic events in the TXA group relative to the placebo group. Furthermore, there was a decrease in the incidence of myocardial infarctions in the TXA cohort.[5] This data would suggest that there were minimal adverse effects recorded in patients of the TXA cohort who were not hyperfibrinolytic, providing treatment was administered less than 3 hours post injury.

COST-EFFECTIVENESS OF TRANEXAMIC ACID

Cost-effectiveness analysis has shown that the administration of TXA to bleeding trauma patients is financially viable in low, middle and high income settings TXA administration was found to cost $48, $66 and $64 per life-year saved in Tanzania, India and UK respectively.[29] The WHO declares medical intervention to be very cost effective if treatment costs amount to less than the GDP per capita per Disability-Adjusted Life Year averted.[30] In lower income countries, GDP per capita can range from $380 to $1,035. In middle and high income countries GDP per capita ranges from $977 to $12,615 to greater than $12,616 respectively.[31] Evidently, TXA proves very cost effective in all 3 of the studied environments.

CONCLUSIONS

The primary delay in the firm implementation of TXA into emergency medicine is related to confusion about the category of patients who should receive it.[2] However, from the available research, there is a proven reduction in mortality in TXA-receiving patients relative to non-TXA receiving patients suffering from significant haemorrhage (systolic blood pressure < 90 mmHg, Heart rate 100 bpm), where TXA is administered less than 3 hours post-injury.[5] Under these circumstances, the WHO may consider advising the use of transexamic acid in both hospital and pre-clinical settings, based on the reduction in mortality and the cost-effectiveness (cost of LY saved relative to the loss in Disability Adjusted Life Years) of said treatment.[2,5,29,30]

References

01 Curry N, Hopewell S, Doree C, Hyde C, Brohi K, Stanworth S. . The acute management of trauma hemorrhage; a systematic review of randomized controlled trials. Critical Care 2011; 15(2): (accessed 12 October 2014).

02 Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE.. Tranexamic Acid in Trauma: How should we use it? J Trauma Acute Care Surg 2013; 74(6): 1575-1586.

03 Levy JH.. Antifibrinolytic therapy: new data and new concepts. The Lancet 2010; 376(9734): 3-4. (accessed 31 October 2014)

04 Roberts I, Preito-Merino D. Applying results from clinical trials: tranexamic acid in trauma patients. Journal of Intensive Care2014; 2(10): http://www.jintensivecare.com/content/2/1/56 (accessed 20 October 2014).

05 CRASH -2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y etc al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet 2010; 376(9734): 23-32.

06 Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2007; 4: CD001886

07 Fiechtner BK, Nuttall GA, Johnson ME, et al. Plasma tranexamic acid concentrations during cardiopulmonary bypass. Anesth Analg 2001; 92: 1131-36.

08 Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL. The dose-response relationship of tranexamic acid. Anesthesiology 1995; 82: 383-92.

09 Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfbrinolysis. J Trauma 2008;64:1211-17

10 Sawamura A, Hayakawa M, Gando S, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. Thromb Res 2009; 1214: 608-13.

11 CRASH-2 collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. The Lancet 2011; 377(9771): 1096-1101

12 Pasche B, Ouimet H, Francis S, Loscalzo J. Structural changes in platelet glycoprotein IIb/IIIa by plasmin: determinants and functional consequences. Blood 1994; 83: 404-14.

13 Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. Br J Haematol 2005; 129: 307-21.

14 Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Tait G, Beattie WS. The risk-benefi t profi le of aprotinin versus tranexamic acid in cardiac surgery. Anesth Analg 2010; 110: 21-29.

15 Dewan Y, Komolafe EO, Mejia-Mantilla J, Perel P, Roberts E, Shakur H et al. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. Trials 2012; 13. http://www.trialsjournal.com/content/13/1/87 (accessed 31 October 2014).

16 MRC CRASH Trial Collaborators, Perel P, Arnago M, Clayton T, Edwards P, Komolafe E et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ 2008; 336; http://www.bmj.com/content/336/7641/425.long (accessed)20 October 2014

17 Maas AI, Steyerberg EW, Butcher I, et al. Prognostic value of computerized tomography scan characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007; 24(2): 303-14.

18 Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. BMC Emerg Med 2009, 9(15)

19 Zehtabchi S, Abdel Baki SG, Falzon L, Nishijima DK.. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. The American Journal of Emergency Medicine2014; 32(9): http://www.ajemjournal.com/article/S0735-6757(14)00674-3/pdf (accessed 1 November 2014).

20 Stein SC, Smith DH. Coagulopathy in Traumatic Brain Injury. Neurocritical Care 2004; 1(4): 479-488.

21 Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. BMC Emerg Med 2013; 13; 20-27

22 Freund TF, Buzsáki G: Interneurons of the hippocampus. Hippocampus 1996; 6 (4) :347-470

23 Kratzer S, Irl H, Mattusch C, Burge M, Kurz J, Kocks E et al. Tranexamic acid impairs γ-aminobutyric acid receptor type A-mediated synaptic transmission in the murine amygdala: a potential mechanism for drug-induced seizures? Anesthesiology 2014; 120(3); 639-649

24 Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg 2012; 147(2); 113-9

25 Pusateri AE, Weiskopf RB, Bebarta V, Butler F, Cestero RF, Chaudry IH et al. Tranexamic Acid and Trauma: Current Status and Knowledge Gaps With Recommended Research Priorities. Shock; 2013; 39(2); 121-126

26 Schöchl H, Schlimp CJ, Maegele M. Tranexamic acid fibrinogen concentrate and prothrombin complex concentrate: data to support prehospital use? Shock 2014; 41; 44-46

27 De Guzman R, Polykratis IA, Sondeen JL, Darlington DN, Cap AP, Dubick MA. Stability of tranexamic acid after 12-week storage at temperatures from -20 °C to 50 °C. Prehospital Emergency Care; 2013; 17 (3); 394-400

28 Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic Acid for rauma Patients: A critical review of the literature. Journal of Trauma Injury, Infection and Critical Care. 2011; 71(1)

29 Guerriero C, Cairns J, Perel P, Shakur H, Roberts I, et al. Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial. PLoS ONE 2011 6(5)

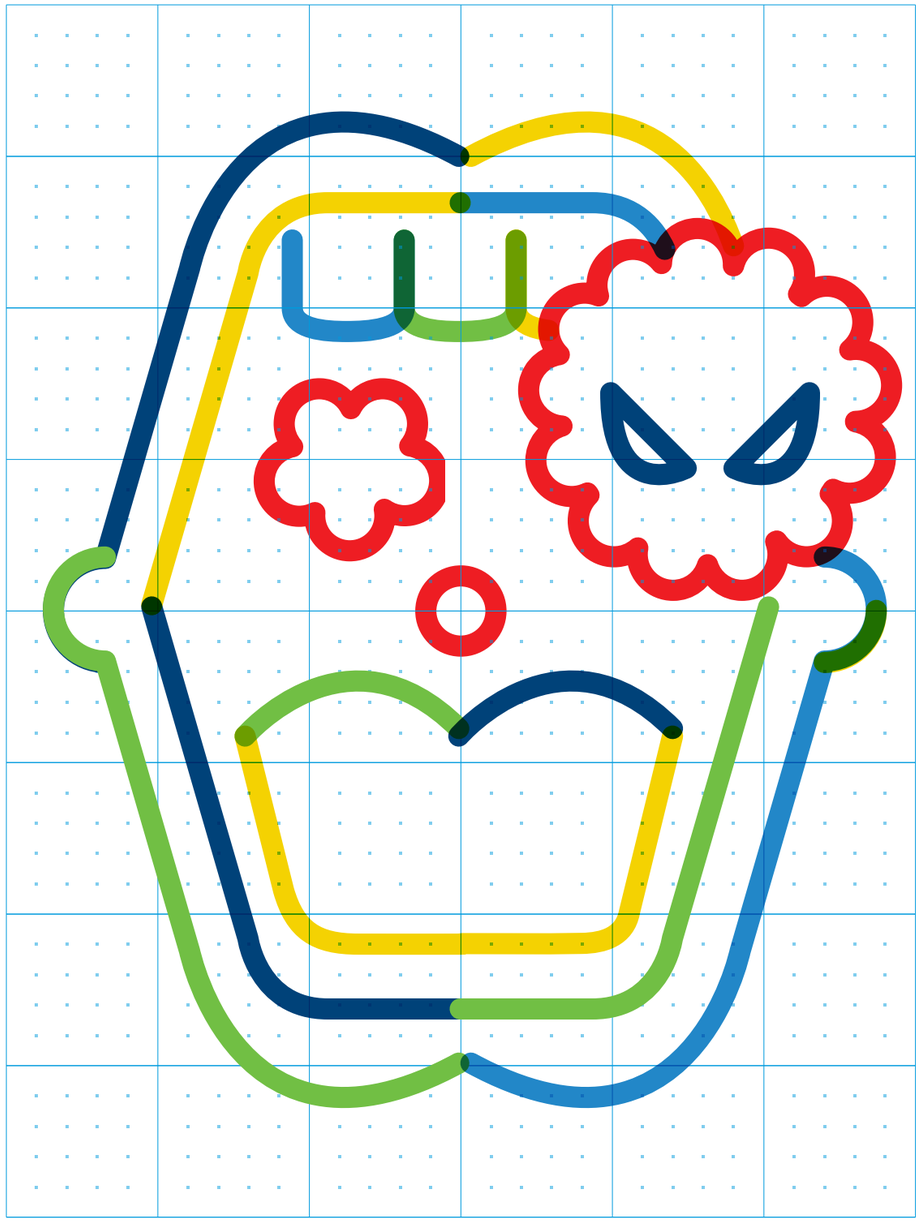
30 Commission on Macroeconomics and Health (2001) Macroeconomics and health: investing in health for economic development. Geneva: World Health Organization.

31 The World Bank. New Country Classifications. http://data.worldbank.org/news/new-country-classifications (accessed 30 October 2014)

Human Papilloma Virus *and the Rising Incidence of Oropharyngeal Squamous Cell Carcinoma*

Written by Kevin O'Malley

Edited by UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



ABSTRACT

Human Papillomaviruses (HPVs) are considered ubiquitous in the sexually active adult population. In recent years, much attention has been paid to the role of HPVs in the development of cervical neoplasia. Less attention is given to HPV-associated head and neck cancers, despite the fact that rates have increased by 225% in recent decades.[1]

This paper examines recent epidemiological data while exploring the mechanisms underlying HPV-mediated ongenesis, the associated risk factors for HPV-positive malignancy and the implications of tumour HPV-status in prognostication and treatment. Vaccination programs are discussed with regard to efficacy and safety, and with reference to public health initiatives both in Ireland and abroad. Finally, recommendations are provided for ways in which the burden of HPV-associated disease can be reduced.

HUMAN PAPILLOMAVIRUSES (HPVS)

Human Papillomaviruses are a sexually transmitted infection, now held to be the most common sexually transmitted disease in the United States.[2] HPVs are considered ubiquitous in the sexually active adult population. Transmission of HPVs occurs via sexual contact, including oral, vaginal and anal sex. Non-sexual, vertical transmission from mother to child can also occur during pregnancy and childbirth.[3] There are over 100 identified strains, which differ substantially in their pathogenecity. Low risk strains include HPV-6 and HPV-11 which are linked with anogenital warts, oral squamous papillomas and recurrent respiratory papillomas. High risk HPV strains include HPV-16, HPV-18, HPV-31, HPV-33, HPV- 45, HPV-52 and HPV-58. Of these, HPV-16 and HPV-18 are by far the most prevalent.[4] The vast majority of anal cancers (90%) and cervical cancers (99.7%) are attributed to infection with these HPV strains.[5] It is estimated that three of every four new diagnoses of oropharyngeal squamous cell carcinoma (OPSCC) are HPV-positive.[6] HPV-16 is the main causative agent of OPSCC and is mainly seen in patients with limited tobacco or alchol use.

HPV-MEDIATED ONCOGENESIS

HPV-mediated oncogenesis arises from the disruption of DNA repair mechanisms and regulators of the cell cycle which facilitates uncontrolled proliferation and ultimately malignant transformation.[4] Specifically, HPV can integrate into the host DNA genome resulting in abnormal, uncontrolled expression of the viral oncoproteins E6 and E7.[7] The oncogenic potential of E6 is related to its ability to inactivate p53, which is a key cellular tumour suppressor protein responsible for cell cycle arrest and apoptosis in the presence of cell injury and DNA damage in particular. Viral inactivation of p53 results in a significant decrease in p53 tumour-suppressing activity. In contrast to non-HPV OPSCC, where carcinogenic exposure causes mutation of the p53 gene, the HPV E6 protein binds p53 and inactivates its transcriptional activity.[7] Similarly, E7 inhibits retinoblastoma protein (pRb) another tumour suppressor protein which prevents abnormal cells from progressing to the synthesis (S) phase of cell division.[4] The inhibition of these tumour suppressor genes in affected epithelial membranes renders cell genomes unstable and susceptible to the development of malignancy.[4,5]

HPV AND HEAD & NECK CANCER

Head and neck cancers typically arise from the mucosal layers of the lip, oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract and nasopharynx.[7] Squamous Cell Carcinoma (SCC) is the predominant histological type.[7] The oropharynx is by far the most common site of HPV-related SCC, with the lingual and palatine tonsils most often affected.[8] The lymphoid tissues at these sites feature an incomplete basal cell layer and a disrupted, porous basement membrane which facilitates their immunological role. It has been suggested that this cellular layout may contribute to the early metastatic potential of OPSCC tumours.[9] HPV is reliant on the proliferative capacity of these cells in order to cause infection and undergo further viral synthesis (4).[4] Division of infected cells then allows the virus to spread.[4]

The incidence of head and neck cancer has increased so sharply in recent decades it has been described as epidemic.[9] Squamous Cell Carcinoma of the head and neck (HNSCC) is the fifth deadliest cancer worldwide[5] with OPSCC expected to surpass cervical cancer as the most common HPV-related cancer in the United States in the next five years.[1] In the period spanning 1988 to 2004, it is estimated that HPV-associated OPSCC increased by 225%.[1] In Ireland, the National Cancer Registry shows that the incidence of OPSCC in Ireland has doubled in the past two decades, from 50 cases in 1994, to 100 cases in 2012.[10] The general consensus attributes this dramatic rise squarely on the shoulders of HPV.

IMPLICATIONS OF HPV-STATUS OF TUMOURS

HPV-positive SCC demonstrates a malignant process, presentation, treatment response and prognosis distinct from that of HPV-negative SCC.[9] The most common initial symptom of HPV-positive OPSCC is a neck mass. In contrast, HPV-negative OPSCC most often presents with sore throat.[11] The TNM system used to stage tumours and in prognostication is limited in its application to HPV-positive HNC. This system is based on the size of the primary tumour, the extent of nodal spread and the presence of metastasis. Curiously, HPV-positive OPSCC usually presents with smaller primary tumours but more advanced nodal involvement.[8] Compared to HPV-negative tumours, HPV-positive tumours exhibit greater loco-regional control and rarely metastasise. When metastasis does occur however, HPV-positive disease exhibits a tendency to disseminate to multiple organs and unusual sites such as the skin and pancreatic tail.[12]

Recent years have seen an increasing incidence of HNSCC in individuals with no history of significant smoking or alcohol use. Traditionally HNSCC has been associated with heavy smoking or tobacco use and alcohol consumption, typically observed in older males in their sixth or seventh decade of life.[5,13] Additional risk factors include chemical exposure (asbestos, chromium, arsenic) and environmental exposure to ionising radiation. In comparison, the new demographic are predominantly Caucasian males, non-smokers, with low alcohol intake, higher educational attainment and higher socioeconomic status.[13]

RISK FACTORS FOR HPV-ASSOCIATED CANCER

In stark contrast to the aforementioned rise in HPV-positive OPSCC, there has been a 50% decline seen in rates of HPV-negative HNSCC in the same period.[5] The rise in incidence of HPV-positive OCSCC may be primarily attributed to two behavioural shifts in society. First, the significant decrease in smoking compared to previous generations may make HPV-related cancer more statistically visible. Second, shifts in sexual behaviour, particularly an increase in oral sexual partners and engaging in oral sex at a younger age, may make HPV-related cancer more common.[7]

Oral sexual behaviour and a history of multiple vaginal sexual partners in males have both been identified as strong risk factors for HPV-associated disease.[9] It has been suggested that higher rates of HPV-associated OCSCC in men may be due to the greater prevalence of the virus in cervical tissue (compared to penile tissue) which may be transferred when a male performs oral sex on a female.[7] When compared to those without cervical neoplasia, women with cervical cancer were five times more likely to have a husband with over 20 sexual partners in his lifetime.[5] In addition, studies have demonstrated significantly greater incidence of oral, pharyngeal and laryngeal cancers in the husbands of women diagnosed with cervical cancer.[5]

TESTING FOR HPV

HPV can be tested for via a number of methods. The most common is polymerase chain reaction (PCR) and tissue-based in situ hybridisation (ISH).[4] Currently screening is available for cervical and anal cancer however there is no standard protocol for oropharyngeal cancer screening.[5]

TREATMENT OPTIONS

The HPV status of a tumour is important to prognosis and will influence the course of treatment. Despite the sharp increase in the prevalence of HPV-associated OPSCC, these malignancies show more favourable outcomes with regard to treatment response, recurrence rates and overall survival when compared with HPV-negative OPSCC.[9] HPV-positive OPSCC demonstrates increased sensitivity to chemo- and radiotherapy versus HPV-negative OPSCC thus concomitant chemoradiotherapy has emerged as the current mainstay of treatment.[3,7,14] Chemo-sensitivity is proposed to stem from the presence of wild type P53 in tumour cells, such that the cells retain intact cellular apoptotic pathways.[15] In increased radio-sensitivity is attributed to impaired DNA repair mechanisms in tumour cells.[16]

Thoughts regarding best practice in terms of treatment are undergoing a shift. Given the younger, healthier profile of these patients, the harmful but inevitable complications associated with chemotherapy and radiotherapy are becoming less acceptable. Both modalities carry significant burden in terms of associated morbidity. Toxicity-induced sequelae include nephrotoxicity, neutropenia, ototoxicity, osteoradionecrosis and dysphagia amongst many others.[17,18] One study of patients undergoing concurrent chemoradiotherapy found that 43% experienced severe late toxicity.[18]

In light of such findings, recent research has begun to focus on the extent to which chemoradiotherapy can be de-intensified without compromising on treatment efficacy.[8] Others have advocated the use of surgery in the management of patients with HPV-positive HNSCC, highlighting the benefits of minimally-invasive transoral robotic surgery and laser microsurgery.[17,19] Where previously highly invasive and often requiring extensive dissection, surgical options for OPSCC have advanced greatly in recent years and may offer comparable oncologic outcomes with potentially better functional outcome.[17]

SURVIVAL RATES

It is difficult to ascertain the extent to which treatment modality influences patient outcome as HPV-positive status confers advantage regardless of the treatment course pursued.[20] The innumerable confounding factors present in the patient population must be acknowledged. For instance, the survival advantage observed in HPV-related malignancy is likely due, in some part, to younger patient age, lower alcohol- and smoking-related morbidity, and the ability to withstand more aggressive treatment.[14] Nevertheless, when these factors are controlled for, the prognostic advantage persists.[8] Two-year survival rate for HPV-positive OPSCC is 95% compared to 62% in HPV-negative OPSCC.[3] A 2012 meta-analysis of 42 studies found the five-year survival rates for patients with HPV-positive HNSCC to be 70-80% compared with 25-40% for patients with HPV-negative HNSCC.[14] HPV-positive OPSCC demonstrates 63% less likelihood of cancer recurrence and overall mortality 53% lower than HPV-negative cohorts[14], findings which parallel with Dayyani *et al.* who reported similar figures.[21]

HPV-VACCINATION

There are currently three groups of prophylactic HPV-vaccines available. The bivalent *Cervarix* targets HPV-16 and HPV-18 and the quadrivalent *Gardasil* targets HPV-6, HPV-11, HPV-16 and HPV-18. HPV-6 and HPV-11 are most commonly implicated in benign anogenital warts.9 There also exists a 9-valent vaccine targeting HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58.[22]

The full impact of HPV vaccination programs will not be apparent for decades. Currently, researchers look to the incidence of pre-invasive cervical intraepithelial neoplasia 2 and 3 and adenocarcinoma in situ (collectively referred to as CIN2+) as an indicator of vaccination efficacy.[22] Within 5 years of implementing a free, school based vaccination program, Australia has experienced a huge decrease in external genital warts which is anticipated to translate into similar declines in the rate of cervical cancer in future decades.[23]

The efficacy of vaccination in males has also been demonstrated in the literature. A recent study of over 4000 men aged 16-24 found that vaccination led to a 90.4% reduction in external genital lesions (linked to HPV-6, HPV-11, HPV-16 or HPV-18) and demonstrated 89.4% efficacy against condylomata acuminata, a type of genital wart.[24] The authors suggest these effects will likely translate to the prevention of anogenital cancers, intraepithelial neoplasia and oropharyngeal cancers in the future.[24] Notwithstanding this, it will be decades before the true impact of HPV vaccination on malignant disease will be fully established.[25]

The Irish HPV Schools Immunisation Programme commenced in May 2010.[26] The routine Irish vaccination programme is currently offered to adolescent females in second level education, and involves three doses of the Gardasil vaccine. Uptake of the vaccination in Ireland compares well with international statistics. Based on figures as of June 30th 2015, 84.9% of girls in first year of second level education are recorded as having completed the full course.[27] Uptake of a catch-up vaccine, offered to older adolescents females has been lower, with approximately 44.6% of girls in sixth year completing the course.[27]

HPV-VACCINE-ASSOCIATED ADVERSE DRUG EVENTS (ADES)

HPV-vaccinations pose an interesting challenge in the age of immunisation-sceptics. A key criticism is that the long term benefits of the HPV-vaccine "rest on assumptions rather than solid research data".[28] Critics highlight the necessity for a very narrow margin of tolerance for serious ADRs, especially in the case of vaccines with undetermined benefit.[28] They maintain that there is no evidence to support the claim that either Gardasil or Cervarix can actually prevent any type of cervical cancer, and that no vaccine currently in use can eradicate existing HPV infections or arrest their progression to CIN 2/3 lesions.[28] In addition, HPV vaccines have documented adverse effects in a small minority of recipients, although the majority are considered non-serious. The Irish Medicines Board (IMB) actively monitors the reports of adverse events associated with the HPV vaccine Gardasil. In line with the US Food and Drugs Administration (FDA) and the Therapeutic Good Administration in Australia (TGA), the IMB maintains the safety of Gardasil.[26]

As with virtually all vaccines, local injection site reactions can occur including pain, redness and swelling. These are short-lived and spontaneously resolve in the vast majority of recipients.[29] Non-serious adverse events included syncope, dizziness, nausea, fever and urticaria.[29] In the United State as of March 2014, 67 million doses of HPV-vaccines had been administered, with no significant increase in adverse events reported.[2] The US Vaccine Safety Datalink reports no increased risk of Guillain-Barre syndrome, seizures, stroke, venous thromboembolism, anaphylaxis or other allergic reactions, in those who have received the HPV-vaccination.[30] There is also no evidence of a link between HPV vaccines and demyelinating disorders.[31]

PARENTAL ATTITUDES

Other less pressing concerns include the belief of some parents that prophylactic vaccination equates to the condoning of sexual behaviour at an earlier age and may promote the practice of unsafe sex.[32] Studies of sexual behaviour in young adolescents following vaccination have found such concerns to be unfounded, with those vaccinated no more likely to engage in sexual activity than their unvaccinated peers.[33]

SHOULD MALES BE VACCINATED?

When considering HPV and vaccination, much emphasis has been placed on cervical cancer. Virtually all vaccination programmes are aimed, at least in the initial stages, at pre-adolescent females. The suggestion of herd immunity conferred to males via the vaccination of females embodies a number of flaws as it is based on assumptions regarding the sexual activity of males. The National Cancer Institute estimates that over half of the cancers diagnosed in the United States in the next five years will be "oropharyngeal rather than cervical" which demonstrates a clear predominance in males.[34]

A universal vaccination policy would carry a number of benefits.[35] Primarily, universal vaccination would reduce the burden of HPV-associated diseases and malignancies in the general population, and facilitate more rapid control of the most common strains in circulation. Such a policy would also reduce the risk posed to males by unvaccinated females and extend protection to men who have sex with men (MSM) who do not benefit from herd immunity.[35] A recent study conducted with MSM in Ireland found that 69% of men tested had detectable HPV DNA.[36]

RECOMMENDATIONS

A number of useful recommendations can be drawn from the above literature which could be employed to reduce the burden of HPV-associated cancer, including:

- Extension of HPV vaccination programs to include males and confer protection against HNSCC.[4]
- A targeted campaign for MSM, who do not benefit from herd immunity.
- Development of more sensitive screening tools for this group of malignancies, given propensity for unusual metastatic sites.
- Education workshops for primary care clinicians in relation to atypical symptoms associated with HPV-positive HNC.
- Development of a comprehensive staging algorithm for HPV-positive HNSCC.[12]

References

01 Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of Clinical Oncology. 2011 November; 29(32).

02 Katz AR. The Hidden Epidemic: Sexually Transmitted Diseases in 2014. Hawai'i Journal of Medicine & Public Health. 2014 August; 73(8).

03 Young D, Xiao CC, Murphy B, Moore M, Fakhry C, Day TA. Increase in head and neck cancer in younger patients due to human papillomavirus (HPV). Oral Oncology. 2015 June; 51.

04 Allison DB, Maleki Z. HPV-related Head and Neck squamous cell carcinoma: An update and review article. Journal of the American Society of Cytopathology. 2015 December; IN PRESS.

05 Hoffman-Ruddy B, Miller S, Silverman E, Lewis V, Ho H, Spaienza C. The Contagious Head and Neck Cancer: The role of Human Papillomavirus HPV. Journal of Women's Health Care. 2015; 4(2).

06 Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri Vea. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cance- systematic review and meta-analysis of trends by time and region. Head Neck. 2013 May; 35(5).

07 Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus related cancer epidemic. The Lancet: Oncology. 2010; 11(781-89).

08 Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumour status upon head and neck squamous cell carcinomas. Oral Oncology. 2014 October; 50.

09 Moore K, Mehta V. The Growing Epidemic of HPV-positive Oropharyngeal Carcinoma: A Clinical Review for Primary Care Providers. Journal of the American Board of Family Medicine. 2015; 28(4).

10 Sheahan P. Changing paradigms for oropharynx cancer: swinging of pendulum back towards surgery. Irish Medical Journal. 2015 July.

11 McIlwain WR, Sood AJ, Nguyen SA, Day TA. Initial symptoms in patients with HPV-positive and HPV-negative oropharyngeal cancer. Journal of the American Medical Association- Otolaryngology: Head and neck surgery. 2014; 140.

12 Huang SH, Perez-Ordonez B, Weinreb I, Hope A, Massey C, Waldron JN, et al. Natural course of distant metastases frollowing radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. Oral Oncology. 2013.

13 Sturgis E, PM. C. Trends in head and neck cancer incidence in relation of smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007 October; 110(7).

14 O'Rorke MA, Ellison MV, Murray LJ, Moran M, James J, Anderson LA. Human Papillomavirus related head and neck cancer survival: A systematic review and meta-analysis. Oral Oncology. 2012; 48(12).

15 Fahkry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. Journal of Clinical Oncology. 2006; 24.

16 Arenz A, Ziemann F, Mayer C, Wittig A, Dreffke K, Preising Sea. Increased radiosensitivity of HPV-positive head and neck cancer cell lines due to cell cycle dysregulation and induction of apoptosis. Strahlentherapie und Onkologie. 2014 September; 190(9).

17 Yeh DH, Tam S, Fung K, MacNeil SD, Yoo J, Winquist Eea. Transoral robotic surgery vs. radiotherapy for management of oropharyngeal squamous cell carcinoma- A systematic review of the Literature. European Journal of Surgical Oncology. 2015; 41.

18 Machtay M, Moughan J, Trotti A, Harden AS, Weber RS, Cooper JS. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: An RTOG Analysis. Journal of Clinical Oncology. 2008 June; 26(21).

19 Mydlarz WK, Chan JYK, Richmon JD. The role of surgery for HPV-associated head and neck cancer. Oral Oncology. 2015; 51.

20 Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. Journal of Clinical Oncology. 2008; 26(4).

21 Dayyani F, Etzel CJ, Liu M, Ho CH, Lippman SM, Tsao AS. Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). Head and Neck Oncology. 2010 June; 29(2).

22 Hariri S, Markowitz LE, Bennett NM, Niccolai L, Schafer S, Bloch KC, et al. Monitoring effect of Human Papillomavirus vaccines in US population, Emerging Infections Program, 2008-2012. Emerging Infectious Diseases. 2015 September; 21(9).

23 Read TR, Hocking JS, Chen MY, Donovan B, Bradshaw CS, Fairley CK. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vacccination program. Sexually Transmitted Infections. 2011; 87.

24 Giuliano AR, Palefsky JM, Goldstone S, Moreira ED, Penny ME, Aranda C, et al. Efficacy of Quadrivalent HPV Vaccine against HPV Infection. New England Journal of Medicine. 2011 February; 364(5).

25 Graham DM, Isaranuwatchai W, Habbous S, de Oliveira C, Liu G, Siu LL, et al. A cost-effectiveness analysis of Human Papillomavirus Vaccination of boys for the prevention of oropharyngeal cancer. Cancer. 2015 June; 121(1785- 1792).

26 IMB IMB. Overview of National monitoring experience with Gardasil. Dublin:; July 2011.

27 HPSC HPSC. HPV vaccine uptake in Ireland 2013/2014. Dublin, Ireland: Health Service Executive HSE, Health Protection Surveillance Centre; 2015.

28 Tomljenovic L&SCA. Human Papillomavirus (HPV) vaccine policy and evidence-based medicine: Are they at odds? Annals of Medicine. 2013; 45(2).

29 Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar Sea. Comparative immunogenicity and safety of human papillomavirus (HPV)16/18 vaccine and HPV 6/11/16/18 vaccine: follow-up from months 12-24 in a phase III randomised study of healthy women aged 18-45 years. Human Vaccines. ; 7(12).

30 CDC CfDCaP. CDC Grand rounds: Reducing the burden of HPV associated cancer and disease. MMWR Morb Mortal Wkly Rep. 2014; 63(4).

31 Scheller NM, Svanstrom H, Pasternak B, Arnheim-Dahlstrom L, Sundstrom K, Fink Kea. Quadrivalent HPV vaccination the risk of multiple sclerosis and other demyelinating diseases of the central nervous system. Journal of the American Medical Association. 2015; 313(1).

32 Dempsey AF, Zimet GD,DRL, Koutsky L. Factors that are associated with parental acceptance of Human Papillomavirus vaccines: A randomised intervention study of written information about HPV. Pediatrics. 2006; 117(1486).

33 Bednarzyk RA, Davis R, Ault K, Orenstein W, Omer SB. Sexual activity-related outcomes after human papillomavirus vaccination of 11- to 12-year olds. Pediatrics. 2012; 130(5).

34 NCI NCI. National Cancer Institute Factsheet: HPV and Cancer. ; 2014.

35 Audisio RA, Icardi G, Isidori AM,LCA, Lombardi A, Mariani Lea. Public health value of universal HPV vaccination. Critical Reviews in Oncology/ Hematology. 2016; 97.

36 Sadlier C, Rowley D, Morley D, Surah S, O'Dea S, Delamere S, et al. Prevalence of human papillomavirus in men who have sex with men in the era of an effective vaccine: A call to act. HIV Medicine. 2014 September; 15(8).

37 IARC IAfRoC. Primary end-points for prophylactic HPV vaccine trials/ IARC HPV Working Group. Vol. 7. Working Group reports. Lyon, France:; 2013. Report No.: 978-92-832-2451-8.

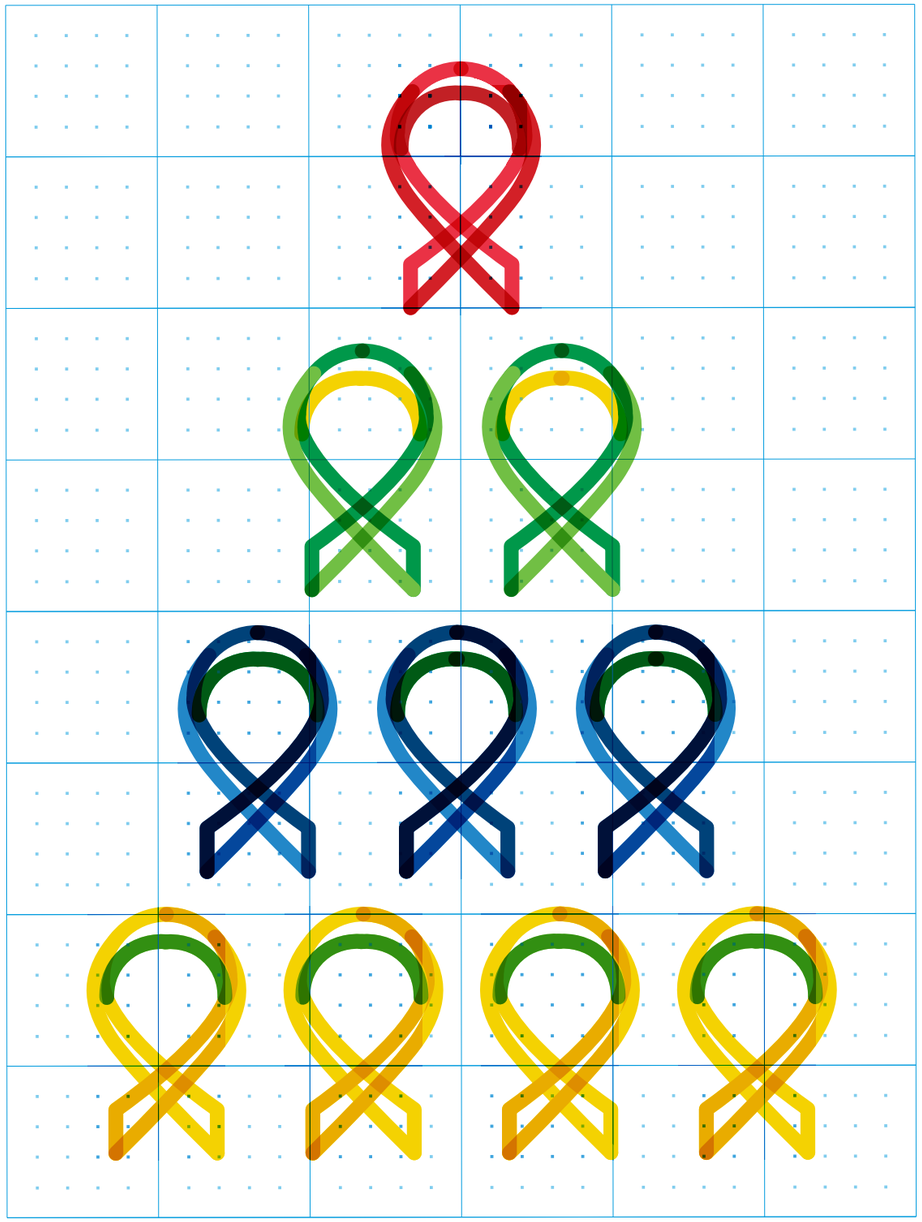
38 Mirghani H, Amen F, Tao Y, Deutsch E, Levy A. Increased radiosensitivity of HPV-positive head and neck cancers: Molecular basis and therapeutic perspectives. Cancer Treatment Reviews. 2015; 41.

39 Sher DL, Schwartz DL, NL, Khan S, Hughes R, Fidler MJea. Comparative effectiveness of induction chemotherapy for orpharyngeal squamous cell carcinoma: A population-based analysis. Oral Oncology.

Increasing the Accuracy of CVD Risk Prediction *in HIV Patient Populations*

Written by Luke O'Brien

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



ABSTRACT

HIV infection is associated with an increased risk of cardiovascular disease (CVD). This increased risk is thought to occur due to a higher prevalence of traditional CVD risk-factors, the effects of the HIV virus itself and toxicities associated with taking antiretroviral therapy (ART). There is a need to accurately assess CVD risk in patients living with HIV in order to identify whether these patients need to undergo lifestyle modifications and/or take cholesterol-lowering drugs such as statins.

A number of CVD risk-prediction models have been developed for clinical use in the general population, such as the Framingham Risk Score. However, none of the general population models have been validated in HIV-infected subjects. For instance, the Framingham Risk Score has been shown to underestimate and overestimate risk in HIV-infected subjects, depending on individual risk factors and geographic origin.

An HIV-specific CVD risk-prediction model known as the DAD Risk Score was developed following a longitudinal study in a cohort of HIV-infected subjects taking ART, however this model has not been validated in other cohorts of patients living with HIV. Despite the lack of validation, the European AIDS Clinical Society (EACS) Guidelines 8.0, published in October 2015, recommend clinicians use the Framingham Risk Score to assess CVD risk in patients living with HIV. In order to improve CVD risk-prediction there is a need to identify and incorporate more specific prognostic biomarkers involved in the pathogenesis of CVD in HIV-infected patients.

Molecular biomarkers of inflammation (Interleukin-6 and C-Reactive Proteins), thrombosis (D-dimer), and the use of imaging as biomarkers have the potential to be incorporated into pre-existing models to improve their accuracy at predicting risk in the setting of HIV. However, controlled clinical-trials with hard clinical endpoints are required to determine the optimal approach to CVD risk-prediction in these patients.

INTRODUCTION

Atherosclerosis is the process whereby lipids, leukocytes, calcium and other substances deposit in the intima of an artery, forming a plaque.[1] Atherosclerosis usually occurs in medium to large arteries.[1] Plaques can grow large enough to significantly reduce blood flow through an artery or they may rupture leading to the formation of blood clots (thrombosis). These clots can travel to smaller arteries causing complete blockage.[1] Cardiovascular disease (CVD) is a general term referring to a group of diseases of the heart and blood vessels.[2] There are four main types of CVD: coronary heart disease; stroke; peripheral arterial disease; and aortic disease.

Since the introduction of antiretroviral therapy (ART) there have been huge improvements in life-expectancy and quality of life for HIV-infected patients.[3] However, non-HIV related co-morbidities are of increasing concern as this population ages.[4] Premature atherosclerotic CVD is one of the leading non-AIDS-related causes of morbidity and mortality in patients living with HIV.[5] HIV-infected patients are at increased risk of developing cardiovascular disease compared to HIV-negative controls matched for age, gender, race and smoking status.[6] This increased risk is thought to be caused by a combination of higher prevalence of traditional CVD risk-factors including dyslipidemia, smoking, obesity, the effects of the HIV virus itself and toxicities associated with taking antiretroviral therapy (ART).[7]

CURRENT BIOMARKERS USED IN CVD RISK PREDICTION MODELS

Due to the increased risk of CVD in HIV-infected patients, screening and prevention is vital in managing CVD risk. The EACS Guidelines 8.0, published in October 2015, recommend that clinicians use the Framingham Risk Score and an ECG to assess CVD risk in HIV-infected patients at diagnosis, prior to ART-initiation and at regular follow-ups every 2 years.[8] Risk assessment models like the Framingham Risk Score are algorithms that calculate the risk of a patient having a CVD event over a certain period of time (5 or 10 years). The calculation is based on a number of relevant risk factors or biomarkers including age, gender and total cholesterol. The resulting risk score is used to help clinicians determine whether the patient should receive preventative treatment such as statins in addition to lifestyle modifications.[9]

CARDIOVASCULAR DISEASE RISK ASSESSMENT MODELS

The Framingham Risk Score was first developed in 1998 for use in the general population and is based on data obtained from an ongoing longitudinal study known as the Framingham Heart Study.[9] The most recent version of the Framingham risk score was published in 2008 and predicts the 10-year risk of a CVD event based on age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, hypertension-treatment, presence or absence of diabetes mellitus, and whether the patient is a current smoker.[9] However, it is important to note that the cohort of subjects recruited to the Framingham study are not HIV-infected and the Framingham model has not yet been validated in a cohort of HIV-infected subjects. The Framingham model does not take into account additional HIV-specific risk factors and has been shown to underestimate and overestimate risk in HIV-infected subjects, depending on individual risk factors and geographic origin.[9]

An HIV-specific CVD risk score was developed following the Data Collection on Adverse Effects of Anti-HIV Drugs (DAD) Study.[9] The DAD study is a prospective observational study involving the collaboration of 11 cohorts of HIV patients from Europe, America and Australia.[9] The DAD Risk Score is currently the only model for predicting CVD risk developed specifically for HIV-infected patients. The DAD Risk Score predicts the 5-year risk of a CVD event based on relevant risk-factors or biomarkers, some of which are specific to HIV patients.[9] In contrast to the Framingham risk score, the DAD Risk Score does not account for the use of anti-hypertensive medication, but does account for 5 other CVD risk factors or biomarkers that are relevant for HIV patients. This includes whether the patient is currently being treated with indinavir, lopinavir or abacavir, the number of years taking indinavir or lopinavir, smoking history, the presence of diabetes mellitus, and a family history of CVD.[9] Still, the DAD model has not been validated in a second cohort of HIV-infected subjects and is not recommended for use by the most-recently published EACS guidelines. Although it has been suggested that the DAD model may be more accurate than the Framingham model, there has not been a trial directly comparing the clinical outcomes of HIV-infected subjects assessed and treated using the Framingham Risk Score compared with HIV-infected subjects assessed and treated using the DAD Risk Score.

In 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) developed a new CVD risk assessment model known as the ACC/AHA Pooled Cohort Equations Risk Calculator.[10] In the United States, this model is now recommended for use in the general population ahead of the Framingham Risk Score.[11] The risk-assessment model was designed using data published from major National Heart, Lung, and Blood Institute-funded cohort studies.[10] Importantly this model includes stroke as a clinical endpoint and incorporates race into the risk algorithm. This allows better risk prediction, especially in African-American patients.[10] This model has not been validated in a cohort of HIV-infected subjects. However, this risk score could potentially be adapted and used in the future to improve CVD risk assessment in patients living with HIV.

BIOMARKERS OF THE FUTURE

There are additional biomarkers strongly associated with the pathogenesis of atherosclerosis in HIV that are not currently being used in assessing risk for CVD in this population. It is believed that these biomarkers could be incorporated into pre-existing risk-assessment models and screening protocols to improve the accuracy of CVD risk-prediction in patients living with HIV.[5] Some examples include molecular biomarkers of inflammation, atherosclerosis and thrombosis, and the use of imaging techniques as biomarkers of CVD progression.[5]

In recent years, it has become widely recognised that atherosclerosis does not only involve the passive build-up of cholesterol in arteries.[12] In fact, inflammation plays a pivotal role in all stages of atherosclerosis.[13] In HIV patients, the inflammatory response is increased and contributes to a heightened risk of CVD. Inflammation is reduced following viral suppression as a result of ART. However, the level of inflammation does not return to normal levels.[14] Therefore, molecules released into circulation during the disease process of atherothrombosis, such as IL-6, CRP and D-dimer have the potential to improve CVD risk prediction in HIV-infected patients. These biomarkers can be easily measured with a blood test. A number of studies, have investigated the correlation between these biomarker levels and the incidence of CVD events in HIV-infected subjects.

Interleukin-6 (IL-6) is a cytokine released by leukocytes and endothelial cells which plays an important role in the inflammatory cascade involved in atherosclerosis.[5] C-reactive protein (CRP) is produced by the liver and released into circulation by macrophages and T-cells following IL-6 secretion, in order to activate the complement system.[5] High-sensitivity CRP (hs-CRP) can be measured at extremely low concentrations using laser nephelometry.[5] This level of sensitivity enables hs-CRP levels to be used as a biomarker of low-grade chronic inflammation.[5] Higher levels of IL-6 and hsCRP in the general population correlate with an increased risk of CVD events and death from any cause.[5] As a result of the chronic inflammation associated with HIV infection, monitoring levels of inflammatory markers such as IL-6 and hsCRP could improve CVD risk-prediction in HIV-infected patients.

Following atherosclerosis, plaques may become fragile and rupture leading to blood-clotting (thrombosis), which can cause artery-occlusion and myocardial infarction or stroke.[1] D-dimer is a protein released into circulation following degradation of fibrin-clots by fibrinolysis, which can be used as a biomarker of thrombosis.[5] However, D-dimer is a non-specific marker which reflects increased thrombotic-activity and may be elevated in response to inflammatory stimuli.[5]

CLINICAL TRIALS USING BIOMARKERS

Duprez et al. investigated the predictive value of hsCRP, IL-6, and D-dimer for CVD morbidity and mortality in HIV-infected patients enrolled in The SMART Study beyond other measured CVD risk-factors.[15] Out of the 5098 patients enrolled in the trial, 252 patients had a CVD event over a median follow-up of 29 months.[15] The researchers found that the addition of the 3 biomarkers to a pre-existing model significantly improved risk-prediction.[15] Area under the curve (AUC), which measures the performance of biomarkers, significantly improved with inclusion of the 3 biomarkers to a pre-existing model from 0.741 to 0.771 ($p<0.001$).[15]

In a study by Nordell et al., the researchers investigated the prognostic value of inflammatory and thrombotic biomarkers IL-6, hsCRP and D-dimer for fatal outcomes among HIV-infected patients that experienced a CVD event.[16] Data was used from 3 international HIV trials including the SMART trial, the ESPRIT trial and the SILCAAT trial. Biomarker levels were measured at baseline for the 9,764 patients, all of whom were HIV-positive with no history of CVD.[16] Of these patients, the researchers focused on the 288 that experienced either a fatal (n=74) or nonfatal (n=214) CVD event over a median of 5 years.[16] The researchers found that IL-6 and D-dimer levels at baseline were significantly higher for those patients who experienced a fatal CVD event compared with the patients that experienced a non-fatal CVD event.[16] The level of hsCRP was also higher in these patients, but this was not statistically significant.[16] It was concluded that the chronic inflammation and thrombosis associated with HIV leads to a poor outcome when a CVD event occurs.[16]

De Luca et al. investigated whether certain biomarkers can independently predict CVD risk in HIV-infected patients.[17] The researchers conducted a retrospective nested case-control study in HIV patients already enrolled in 2 studies; the Icona Foundation Cohort and the CUSH study.[17] The researchers included patients aged 35-69 that were being treated with ART.[17] Patients which had undergone a major CVD event were included in the case group (n=35) and patients that were free from CVD events for at least 5 years from starting ART were included in the control group (n=74).[17] The control patients were matched to the cases for diabetes and smoking status.[17] Levels of hsCRP, D-dimer, P-selectin, IL-6, tissue plasminogen activator, and plasminogen activator inhibitor-1 were measured and statistical analysis was carried out.[17] The researchers found that high levels of hsCRP were associated with CVD risk, independent of traditional risk factors, HIV replication and the type of ART received at the time of sampling.[17] It was also found that higher IL-6 and P-selectin levels were independently associated with increased CVD risk, although this association was weaker than for hsCRP.[17]

IMAGING BIOMARKERS

Various techniques of arterial imaging have potential for use as predictive biomarkers to improve screening for CVD risk assessment in HIV-infected patients and uncover the correlation between HIV-infection and atherosclerotic CVD.[18] Some of the promising imaging techniques for this purpose include carotid ultrasound, cardiac computed tomography and brachial artery ultrasound.[18]

Carotid Ultrasound is a technique which can be used to measure carotid intima-media thickness (IMT) and assess for plaque presence in the carotid arteries of the neck.[18] Increased carotid IMT is associated with an increased risk of myocardial infarction and stroke.[18] Over 20 studies have measured carotid IMT in HIV-infected individuals. Combining data from these studies shows that average carotid IMT is 0.04 mm thicker in the HIV population compared to HIV-negative controls.[18]

Cardiac computed tomography is a technique used to measure coronary artery calcium (CAC), or for angiography (CTA) to assess the presence and nature of coronary plaques.[18] Both CAC and CTA are used to aid in the prediction of CVD risk in the general population.[18] Currently, CTA is promising for clinical use as it can identify the presence of both calcified and non-calcified plaque.[18] Studies involving the Multicentre AIDS Cohort described an increased prevalence of non-calcified plaque in HIV-infected individuals compared to HIV-negative controls.[18]

Brachial artery ultrasound is a technique used for brachial arterial reactivity testing (BART) in order to assess flow-mediated dilation, a marker of endothelial function that predicts future CVD risk.[18] Studies involving brachial artery ultrasound have demonstrated that HIV-infected patients show a much higher prevalence of endothelial dysfunction when compared to control groups without HIV-infection.[18]

CONCLUSION AND FUTURE PERSPECTIVE

Accurate CVD risk prediction in HIV-infected patients is vital due to the increased risk of CVD in this population. CVD risk-prediction allows physicians to prescribe lifestyle modifications and cholesterol-lowering medication, such as statins, to patients with high CVD risk. In fact, is it conceivable to advocate that all patients living with HIV should be administered statins as prophylaxis to prevent the occurrence of atherosclerotic CVD. This strategy is currently being investigated in a large multicentre study funded by the National Institutes of Health called REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV).[19] REPRIEVE is investigating whether Pitavastatin, a newer statin that does not have substantial interactions with ART drugs, can prevent CVD events over time in a cohort of HIV-infected subjects without known CVD.[19]

The CVD risk-prediction model currently recommended for use in HIV-infected patients by the EACS, the Framingham Risk Score, was developed for use in the general population and has not been validated in a cohort of HIV-infected subjects. Molecular biomarkers of inflammation and thrombosis, and imaging biomarkers have all shown potential for use in improving CVD risk prediction. However, there is a need for properly-designed, large clinical trials with hard clinical endpoints to fully investigate whether the incorporation of these biomarkers into pre-existing risk-prediction models can improve CVD risk-prediction.

References

01 Venketaraman V. Atherosclerosis: pathogenesis and increased occurrence in individuals with HIV and Mycobacterium tuberculosis infection. HIV/AIDS - Res Palliat Care. 2010;211.

02 Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481-8.

03 Aberg JA. Cardiovascular complications in HIV management: past, present, and future. J Acquir Immune Defic Syndr. 2009;50(1):54-64.

04 Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J. 2014;35(21):1373-81.

05 Baker J V, Duprez D. Biomarkers and HIV-associated cardiovascular disease. Curr Opin HIV AIDS. 2010;5(6):511-6.

06 Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92(7):2506-12.

07 Triant VA. HIV infection and coronary heart disease: an intersection of epidemics. J Infect Dis [Internet]. 2012 Jun 1 [cited 2016 Feb 12];205 Suppl (suppl_3):S355-61. Available from: http://jid.oxfordjournals.org/content/205/suppl_3/S355.full

08 European AIDS Clinical Society Guidelines 8.0 [Internet]. 2015. Available from: http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf

09 Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil. 2010;17(5):491-501.

10 Preiss D, Kristensen SL. The new pooled cohort equations risk calculator. Can J Cardiol [Internet]. 2015 May [cited 2016 Jan 4];31(5):613-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25843167

11 Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation [Internet]. 2014 Jun 24 [cited 2014 Jul 10];129(25 Suppl 2):S49-73. Available from: http://circ.ahajournals.org/content/129/25_suppl_2/S49

12 Highleyman L. Inflammation, immune activation, and HIV. BETA. 2010;22(2):12-26.

13 Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation. 2004;109(21 Suppl 1):II2-I10.

14 Dubé MP, Sattler FR. Inflammation and complications of HIV disease. J Infect Dis [Internet]. 2010 Jun 15 [cited 2016 Feb 10];201(12):1783-5. Available from: http://jid.oxfordjournals.org/content/201/12/1783.full

15 Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS One. 2012;7(9):e44454.

16 Nordell AD, McKenna M, Borges ÁH, Duprez D, Neuhaus J, Neaton JD. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. J Am Heart Assoc. 2014;3(3):e000844.

17 De Luca A, de Gaetano Donati K, Colafigli M, Cozzi-Lepri A, De Curtis A, Gori A, et al. The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case-control study. BMC Infect Dis. 2013;13(1):414.

18 Stein JH, Currier JS, Hsue PY. Arterial disease in patients with human immunodeficiency virus infection: What has imaging taught us? JACC Cardiovasc Imaging. 2014;7(5):515-25.

19 Gilbert JM, Fitch K V, Grinspoon SK. HIV-Related Cardiovascular Disease, Statins, and the REPRIEVE Trial. Top Antivir Med [Internet]. Jan [cited 2016 Feb 5];23(4):146-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26713505

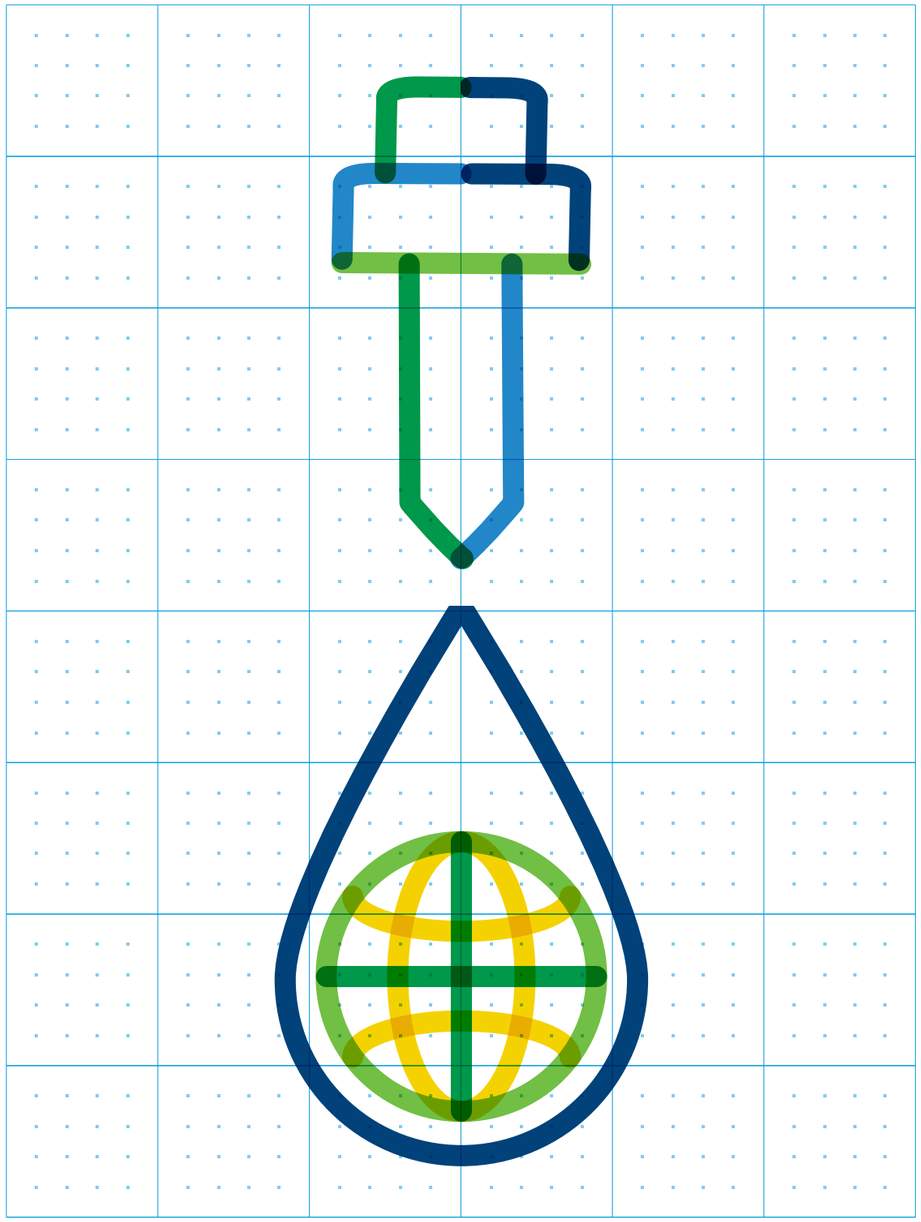
Assessing the Feasibility of Implementing Mass Vaccination Campaigns *Using Oral Cholera Vaccination*

Written by Conrad Flaczyk

Department of Bioresource Engineering
McGill University, Quebec, Canada

Co-author Dr. Jan Franklin Adamowski

Department of Bioresource Engineering
McGill University, Quebec, Canada



Written by Conrad Flaczyk
Co-author Dr. Jan Franklin Adamowski

ABSTRACT

The 2010 Haitian cholera epidemic exposed major weaknesses in the traditional approach to cholera remediation. As a result, the World Health Organization (WHO) revised its cholera-response guidelines in 2011 to recognize Oral Cholera Vaccination (OCV) as a viable cholera control mechanism.

The WHO currently recommends that OCVs be administered in conjunction with existing interventions for cholera remediation. Although OCVs have satisfied clinical trials, few studies have investigated the feasibility of implementing mass OCV campaigns in endemic regions; there remains considerable debate about cost-effectiveness, logistical challenges, and acceptability of OCVs by local populations.

The author of this article aims to assess the feasibility of implementing mass OCV campaigns in cholera-endemic regions. He outlines three recommendations for the successful implementation of such campaigns:

(1) building local capacity and educating populations about choler prevention techniques during OCV campaigns;
(2) developing affordable vaccines, subsidized by international communities; and
(3) using qualitative research methods to understand local socio-cultural variables before OCV campaigns.

INTRODUCTION

Cholera continues to pose a significant public health burden for many regions of the world that have restricted access to basic sanitation infrastructure. Cholera is an acute and highly infectious diarrheal infection that is caused by the bacterium Vibrio cholerae.[1,2] The main symptoms of cholera infections are characterized by extensive watery diarrhea and vomiting.[2] If left untreated, cholera infection can result in severe dehydration within a couple of hours, leading to shock and/or death in some cases.

According to the 2012 World Health Organization (WHO) Report on Cholera,[3] 1.4 billion people worldwide are at risk of cholera infection. Moreover, the WHO reports that there are approximately 2.8 million cholera infections each year and approximately 91,000 deaths in cholera-endemic countries worldwide.[3,4] The WHO also reports that since 2000, the absolute number of cholera incidence has been increasing worldwide,[2,3] in addition to the proportion of cholera infection worldwide.[2,3] Note that the 2010 Haitian cholera epidemic accounts for a significant proportion of cholera infections and death during that period. Between October 2010 and May 2013, Haiti reported over 600,000 cases of cholera infection and more than 8,000 deaths.[5]

In the light of the 2010 Haitian cholera epidemic, the World Health Assembly in 2011 declared that cholera is a global priority and called on the international community to re-evaluate its approach to cholera remediation.[2] Traditionally, cholera remediation efforts focused on the widespread provision of clean drinking water and basic sanitation infrastructures.6 While these efforts are necessary to treating existing cholera infections, they are not sufficient in remediating acute cholera epidemics.[6] The 2010 Haitian cholera epidemic is one case that highlighted major limitations to the traditional approach. As a result, the WHO revised its cholera-remediation guidelines in 2011.[1]

Under the more recent guidelines, the WHO recognizes Oral Cholera Vaccination (OCV) as a viable cholera remediation strategy. At present, two OCVs are qualified and licensed by the WHO: Dukoral and Shanchol.[6,7] Clinical trials conducted in 2011 in Kolkata, India, found that Shanchol is 65% effective in preventing cholera infection five years after vaccination.[4] Both vaccines are administered as a two-dose regimen and both have been proven safe in the laboratory.[6] Today, the WHO recommends that OCVs be administered in cholera-endemic regions in conjunction with traditional interventions.

While OCVs have satisfied the WHO's clinical trials, there remains considerable debate regarding the feasibility of implementing mass OCV campaigns in cholera-endemic regions of the world.[1,4,8] The main questions in this debate center around cost-effectiveness, logistical challenges, and acceptability of OCVs by local populations.[9,10] Few studies have considered the socio-cultural determinants that can influence the results of OCV campaigns. Consequently, this paper aims to fill that gap by reviewing the current knowledge on mass vaccination campaigns in developing regions.

LITERATURE REVIEW

Since OCVs have only been proposed in the last decade, real-world, practical experience with OCV campaigns is limited.[6] Much of the real-world experience with OCV campaigns comes from small-scale cholera interventions in Asia.[11-14] The first major study on a large-scale OCV campaign was published in 2013 by Ciglenecki and colleagues. It described the large-scale OCV campaign implemented in Guinea between April 2012 and June 2012. It was initiated to control an acute cholera epidemic in Guinea. A total of 312,650 doses of vaccine were administered and it was the first time that Shanchol vaccine was administered to control an acute cholera epidemic.[6] Overall, Ciglenecki and colleagues found that the campaign was generally well received by local populations. High vaccination coverage was achieved, despite the short preparation time. They found that feasibility, timeliness of implementation, and delivery costs, were similar to those of other mass vaccination campaigns.[6]

More recently, Kar et al.[4] conducted a study accessing the feasibility of using Shanchol vaccine in a mass vaccination campaign, while relying almost exclusively on local public-health infrastructures. They found that mass vaccination campaigns using Shanchol are viable, however, require detailed micro-planning. The authors suggest that before implementing a mass vaccination campaign using Shanchol, it is necessary to implement social mobilization activities to engage local stakeholders. For instance, the authors recommend that a detailed micro-plan be developed in consultation with local health volunteers and community leaders.[4] This was achieved by meeting with public health officials and making site visits before the campaign. The authors suggest that cost is a major barrier to the successful implementation of OCV campaigns. They therefore argue that the costs of a campaign must significantly be reduced through planning.

Socio-cultural determinants must also be considered before implementing mass OCV campaigns. Emerging literature on the topic suggests that the success of such campaigns largely depends on the unique socio-cultural determinants of the populations. Almost unanimously, higher education was associated with an increased willingness to participate in remediation treatments.[2] Merten et al.[2] studied the effects of education on the local population's willingness to pay for OCVs. They found that level of education influenced vaccine acceptance at all price levels. Not surprisingly, they found that higher educated populations were willing to pay a price premium for OCVs. Nevertheless, at the highest price levels, "material insecurity" was more predictive than education.

According to Merten et al.,[15] the price of the vaccine is the most important determinant of program participation in cholera-endemic regions. Consequently, they investigated local perceptions of acute diarrhea illness and anticipated vaccine acceptance in two sites within the Democratic Republic of Congo. 360 randomly selected adults were interviewed through a semi-structured questionnaire. Anticipated vaccine acceptance at 'no cost' was approximately 97%. At lower costs (free - $5 USD), anticipated vaccine acceptance is relatively high at more than 80% acceptance. These findings suggest that mass OCV campaigns are viable when the vaccine is relatively affordable.[15]

In another study by Merten et al.[2], community acceptance of OVC campaigns was assessed. The authors argued that while price is the most important determinant of program participation, several other contextual determinants can influence the success of the campaign. These contextual determinants must be deeply understood before initiating the campaign. For instance, Kar et al.[4] found that program participation in Kolkata, India, was lowest on Thursdays. They attribute this to the Hindu culture, which prohibits eating meat on Thursdays. Through semi-structured interviews, the implementation team found that some local participants feared that vaccines contain animal by-products.

Several studies have investigated the role of vaccination campaigns in educating local populations and building capacity. In recent a study, Aibana et al.[1] examined the effectiveness of including an educational component in OCV campaigns. The authors conducted surveys before and after an OCV campaign in rural Haiti to assess the impacts of the campaign on the wider community. The authors documented a substantial increase in the rate of sanitary practices used in the community, such increased hand-washing, the cooking of foods, and decreased drinking of untreated water. Similarly, Beau De Rochars et al.[16] found major improvements in the frequency of water treatment practices in Haiti following a mass OCV campaign with an education component. The frequently of water treatment increased from 31% to 74% after the OCV campaign.

CASE STUDY: GUINEA

Guinea regularly experiences cholera endemics during its rainy season in July.[6] In February 2012, an early cholera outbreak, coupled with the ongoing cholera endemic in neighboring Sierra Leone, hinted that a possible cholera epidemic was approaching.[6] Consequently, the Ministry of Health of Guinea, in partnership with Doctors Without Borders, decided to implement a mass OCV campaign. The aim of this campaign was to control the spread of cholera infection by pre-treating high risk populations.

This case-study highlights the potential effectiveness of mass OCV campaigns. The Ministry of Health of Guinea implemented two mass OVC campaigns. The first campaign was situated in the Boffa District, located on the north-west coast of Guinea. The second campaign was situated in the Forecariah District, located on the south-west coast of Guinea. In total, 320,000 OCV doses were administered. These administrations occurred in two sessions, which were spaced over two to three weeks. In both the Boffa and Forecariah Districts, weekly numbers of reported cholera cases were significantly lower than in the country of Guinea overall.[2]

The relative success of this OCV campaign can be used as a case-study for future cholera remediation efforts. Ciglenecki et al.[6] attribute the success of this campaign to the low-cost of vaccine administration and to the stakeholder mobilization efforts carried out before the start of the campaign. During the campaign, the cost per dose of vaccine was $2.89 USD, which included $1.85 for the vaccine itself and approximately $1.00 USD for delivery and implementation. As a result of the relatively low treatment cost, program participation was high at nearly 90%.

In terms of capacity building and stakeholder engagement, this case-study serves as an excellent model for a bottom-up approach to mass vaccinations. Prior to the start of the OCV campaign in Guinea, both of the targeted districts were visited by health promoters, who provided the local populations with information about the vaccination. Interestingly, the health promoters were selected in earlier stakeholder mobilization efforts and they were influential leaders in their community.[6] Together with Doctors Without Borders representatives, the community leaders went door-to-door in an effort to raise awareness for the OCV campaign and answer individual questions.

RECOMMENDATIONS

There remains considerable debate in the literature on whether the implementation of mass OCV campaigns is feasible in cholera-endemic regions. While the literature may be divided on the advantages and disadvantages of mass OCV campaigns, there is an overwhelming agreement that cholera epidemics must be studied in context. Although OCVs may pass clinical trials, this does not necessarily imply that the vaccinations will be effective in practice. As studied by Mazzeo and Chierici,[8] each social environment is characterized by a complex system of values, beliefs and knowledge. They warn against top-down remediation practices that are removed from context. The first recommendation in this paper is the need to draw on qualitative research methods when developing international remediation strategies. Qualitative research methods enable researchers to develop a fuller understanding of the institutions and processes for promoting social change and improving the health of local populations.[8,16] This is particularly important during cholera epidemics because they are often characterized by a rapid onset and swift progression. For this reason, the need to mobilize people and resources quickly and efficiently is critical to an effective remediation strategy.

Smith examined the challenges to developing partnerships between civil society and international organizations for development.[17] He argues that the greatest challenges to forming these partnerships are differences in how each group envisions the process and goals for development. Still, these challenges are not insurmountable.[17,18] The Guinea case-study is one example of how international organizations and NGOs can work to engage local populations. Doctors Without Borders partnered with local community leaders to raise awareness for cholera

vaccination, promoting basic sanitation practices. At the heart of this initiative was the thorough use of qualitative research techniques.[6] In their study, Ciglenecki and colleagues relied on snowball sampling methodologies to find community leaders before implementing a campaign. Snowball sampling is a qualitative research technique that relies on referrals to locate relevant stakeholders. Understanding the needs and concerns of stakeholders allows health promoters to align their objectives with those of the target populations.

Secondly, there is an urgent need for OCV funding. As described by Ciglenecki et al., the single greatest predictor of program participation is the cost of the treatment. A difference of one or two dollars can have a major impact on local participation.[15] OCVs present a unique challenge for donor organizations. Since cholera is characterized by a rapid onset and swift progression, it is essential to have a stockpile of vaccines for the timely implementation of mass campaigns.[6] International donor organizations must have sufficient resources to generate these vaccines. In the literature, the most viable approach to reducing the cost of remediation is developing a single-dose vaccine. At present, the WHO is working on developing a single-dose oral cholera vaccine. In practice, this could reduce the treatment costs by more than half, in addition to operating and administration costs. Though, further research is needed to explore this option.

Finally, this paper recommends that OCV campaigns be implemented to serve a capacity building function in cholera-endemic regions. The literature overwhelmingly agrees that mass OCV campaigns have the potential to link knowledge with practice. Vaccination campaigns are excellent tools for educating, raising awareness, and building capacity among local populations because they serve to aggregate the population in times of crisis. In developing countries, this is critical for remediation. It enables health care providers to distribute essentials resources like water and food, and it also allows them to train and educate the population on basic sanitation. An effective OCV campaign must combine the traditional approach to cholera remediation, which includes the distribution of clean water resources, hand sanitizers, antiseptics and other sanitation infrastructures, with the administration of preventative vaccines and capacity building programs.

CONCLUSION

The 2010 Haitian cholera epidemic exposed major weaknesses in the traditional approach to cholera remediation. As a consequence, the international community set out to find a viable remediation treatment for endemic cholera infection. Today, the WHO recommends that oral cholera vaccinations be administered to control cholera infection in conjunction with traditional interventions.

OCVs are newly developed vaccines and there remains considerable debate about their feasibility in mass campaigns. recent implementations of mass OCV campaigns exhibited tremendous success in controlling the spread of cholera infection. More work needs to be done to access the feasibility of implementing mass OCV campaigns in cholera-endemic regions of the world. Future efforts will necessitate the application of qualitative research methods to develop fuller understandings of contextual constraints and researchers will require support to develop more cost-effective, single-dose vaccines.

References

01 Aibana O, Franke MF, Teng JE, Hilaire J, Raymond M, Ivers LC. Cholera campaign contributes to improved knowledge regarding cholera and improved practice relevant to waterborne disease in rural Haiti. PLoS Negl Trop Dis. 2013; 7: e2576.

02 Merten, S, Schaetti C, Manianga C, Lapika B, Chaignat CL, Hutubessy R, Weiss MG. Local Perceptions of cholera and anticipated vaccine acceptance in katanga province, Democratic Republic of Congo. BMC Public Health. 2013; 13: 52-60.

03 World Health Organization. Cholera, 2011. Weekly Epidemiology 2012; 289-304.

04 Kar SK, Sah B, Patnaik B, Kim YH, Kerketta AS, Shin S, Rath SB, Ali M, Mogasale V, Khuntia HK, et al. Mass vaccination with a new, less expensive oral cholera vaccine using public health infrastructure in India: the Odisha model. PLoS Negl Trop Dis. 2014; 8: e2629.

05 Ministère de la Santé Publique et de la Population: Haiti 2013 MSPP daily reports on the progress of cholera in Haiti. 2013. Accessed 01 April 2014. http://www.mspp.gouv.ht/site/index.php.

06 Ciglenecki I, Sakoba K, Luquero F, Heile M, Grais R, Verhoustraeten F, Legros D. Feasibility of Mass Vaccination Campaign with Oral Cholera Vaccines in Response to an Outbreak in Guinea. PLoS Medicine 2013; 10: e1001512.

07 Sundaram N, Schaetti C, Chaignat CL, Hutubessy R, Nyambedha EO, Mbonga LA, Weiss MG. Socio-cultural determinants of anticipated acceptance of an oral cholera vaccine in Western Kenya. Epidemiol Infect. 2013; 141: 639-650.

08 Mazzeo J, Chierici, R. Social foundations for a communications-based public health cholera campaign in Borgne, Haiti. Human Organization. 2013; 72: 312-322.

09 Date K, Hyde T, Mintz E, Vicari A, Danovaro-Holliday MC. Considerations for oral cholera vaccine use during outbreak after earthquake in Haiti, 2010-2011. Emerging Infectious Disease. 2011; 17: 2105.

10 Cumberland S. An old enemy returns. Bull World Health Organization. 2009; 87: 85-86.

11 Anh DD, Lopez AL, Thiem VD, Grahek SL, Duong TN. Use of oral cholera vaccines in an outbreak in Vietnam: A case control study. PLoS Negl Tropical Disease. 2011; 5: e1006.

12 Calain P, Chaine JP, Johnson E, Hawley ML, O'Leary M. Can oral cholera vaccination play a role in controlling a cholera outbreak? Vaccine. 2004; 22: 2444-51.

13 De Brettes A, de Carsalade GY, Petinelli F, Benoit Cattin T, Coulaud X. Le cholera a Mayotte. Bulletin Epidemiologique Hebdomadaire. 2001; 8: 33-35.

14 Beatty ME, Jack T, Sivapalasingam S, Yao SS, Paul I. An Outbreak of Vibrio cholerae O1 infections on Ebeye Island, Republic of the Marshall Islands, associated with use of an adequately chlorinated water source. Clin Inf Dis. 2004; 38: 1-9.

15 Merten S, Schaetti C, Manianga C, Lapika B, Hutubessy R, Chaignat CL, Weiss M. Sociocultural determinants of anticipated vaccine acceptance for acute watery diarrhea in early childhood in Katanga Province, Democratic Republic of Congo. The American Journal of Tropical Medicine and Hygiene. 2014; 83: 419-425.

16 Beau De Rochars VE, Tipret J, Patrick M, Jacobson L, Barbour KE. Knowledge, attitudes, and practices related to treatment and prevention of cholera, Haiti, 2010. Emerging Infectious Disease. 2011; 17(11): 2158-2161.

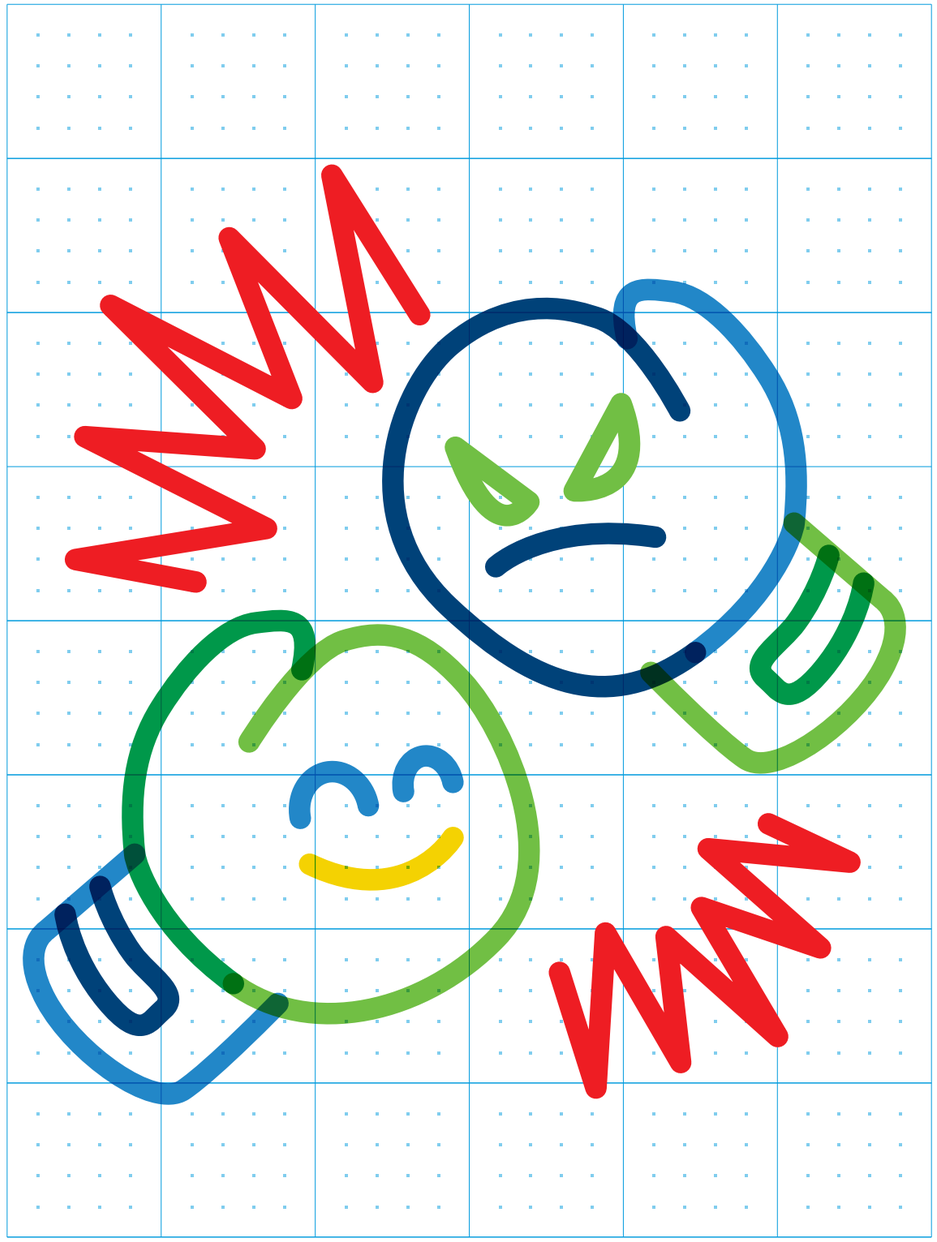
17 Smith, Jennie M: When the Hands are Many: Community Organization and Social Change in Rural Haiti. Ithaca, N.Y.: Cornell University Press. 2001.

18. Schuller, Mark: Killing with kindness: Haiti, international aid, and NGOs. New Brunswick, N.J.: Rutgers University Press. 2012.

The ‘Cancer Stem Cell’ *as a Novel Chemotherapeutic Target*

Written by Calvin Flynn

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



ABSTRACT

Cancer stem cells (CSCs) have been implicated in the processes of metastasis, tumour recurrence, and drug resistance so it is not surprising that they have become a major focus of cancer research in recent years. However, it remains to be seen whether CSCs can be targeted successfully, and if so, without adversely affecting normal stem cells within the body. This review highlights the evidence for the existence of CSCs and their potential use as a chemotherapeutic target in the future.

In discussing the therapeutic potential of targeting CSCs, it is necessary to examine the CSC hypothesis and the biology of CSCs, focusing on their ability to evade conventional chemotherapeutic agents. The evidence reinforces the theory that drugs may be required in the treatment of cancer which target CSCs, killing them before drug-resistant tumours may metastasise or tumour recurrence occurs.

CSC-targeting agents should ideally be used in combination with conventional chemotherapeutics which target the rapidly proliferating, primary neoplastic cells. However, more research needs to be done on the complexity of CSC cellular processes before this type of drug can be used clinically.

INTRODUCTION

The treatment of cancer has come a long way in the last number of decades. Scientists have made massive leaps in both understanding tumour biology and developing drugs which target cancer cells. Chemotherapy has hugely benefited cancer patients by shrinking their tumours, reducing incidence of metastasis and relapse, and improving their overall survival. It is true, however, that conventional chemotherapy works better for some forms of cancer than others, and it is not without its limitations or side effects. Numerous recent studies have suggested that cancer stem cells (CSCs) are responsible for many of the limitations of conventional chemotherapy, such as therapeutic refractoriness and disease relapse. As chemotherapy frequently targets actively proliferating cells, residual dormant cells are often left behind. These quiescent cells, or CSCs, are largely responsible for any metastasis, tumour recurrence, or drug resistance that may occur.[1] CSCs can also overcome chemotherapy by accumulating mutations that lead to drug resistance. Therefore, drugs which target CSCs, in addition to primary neoplastic cells, are required so that these boundaries can be overcome.

WHAT ARE CANCER STEM CELLS?

The stochastic evolutionary model suggests that tumour growth is a random process in which all cells within the tumour can contribute. However, the CSC hypothesis postulates that there is a subpopulation of cells within a tumour that are similar to normal stem cells and have the ability to divide asymmetrically.[1] In recent years, it has become clear that many tissues, both malignant and non-malignant, are arranged in a Stem-Progenitor-Differentiated cell hierarchy. In this arrangement, the dormant CSCs sit at the apex and differentiate into progenitor cells, which then produce differentiated neoplastic cells. The CSCs can then return to their quiescent state.[2] This hierarchy allows CSCs to have a heightened ability over differentiated neoplastic cells to generate new tumours, a process known as tumour seeding. The first evidence for the existence of CSCs came to light in the 1960s. Kleinsmith and Pierce demonstrated that a single embryonal carcinoma cell was capable of seeding new tumours when transplanted into SCID mice.[3] However, the term “cancer stem cells” was not introduced until 2001. Since then, there has been increasing evidence to support the CSC hypothesis, with CSCs being discovered in many other forms of cancer.[1] Although controversial, the self-renewal of CSCs may promote tumour growth, and understanding CSC biology may allow the identification of attractive therapeutic targets.

The origin of CSCs is not fully understood. Research has shown that CSCs involved in carcinoma arise, at least partially, due to a process known as epithelial-mesenchymal transition (EMT).[4] EMT is an important process in embryogenesis and organogenesis but occurs pathologically in the setting of carcinoma. Various signalling pathways (e.g., Wnt signalling) induce the EMT pathway in epithelial cells and cause expression of a series of transcription factors which repress epithelial genes and activate mesenchymal genes.[5] During this process, epithelial cells lose their characteristic phenotype and gain features of mesenchymal cells including increased motility, invasiveness, and resistance to apoptotic factors, permitting dissemination of carcinoma. Certain types of EMT have also been shown to allow some cells to exhibit traits of CSCs, such as self-renewal. Mani et al. showed that human mammary epithelial cells which had undergone EMT expressed surface proteins similar to those found on breast CSCs.[4] These cells also displayed a heightened ability to seed new tumours, verifying the generation of CSCs. It has also been theorised that CSCs may arise due to mutations in normal stem cells or progenitor cells. Driessens et al. observed that progression from benign papilloma to malignant squamous cell carcinoma in mice is associated with an expansion of the CSC population and a decrease in the production of non-stem cells.[6] This study suggests that the most likely source of CSCs are normal stem cells that accumulate mutations.

CSCs are believed to be more resistant to conventional therapies in comparison to other cell populations located within the tumour.[1,7] This resistance has obvious important clinical implications regarding tumour relapse. Understanding the mechanisms underlying resistance is imperative if promising therapeutic targets are to be identified. It has been demonstrated experimentally that human mammary epithelial cells induced into an EMT have increased resistance to radiotherapy and chemotherapy.[8] Following EMT induction, these cells showed a 10-20 fold increase in resistance to common chemotherapeutic agents such as paclitaxel, doxorubicin, and dactinomycin. The mechanisms by which EMT enhances this resistance are unknown. The slow turnover of CSCs compared to other neoplastic cells, and their increased quiescence, are other obvious mechanisms of resistance to chemotherapeutics targeting rapidly-proliferating cells.[2] Additionally, CSCs express high levels of anti-apoptotic proteins such as Bcl-2, as well as ATP binding cassette (ABC) efflux pumps, which are both associated with drug resistance.9 The cytoplasmic enzyme aldehyde dehydrogenase is thought to be involved in CSC resistance in colorectal tumours to cyclophosphamide.[7] This enzyme oxidises and inactivates the toxic product of the drug, aldophosphamide. Dylla et. al. discovered that treatment of colorectal cancer with cyclophosphamide results in survival and enrichment of CSCs, resulting in the rapid regeneration of tumours expressing increased levels of oncogenes.[7] This selective outgrowth of drug-resistant cells highlights the role of CSCs in the relapse of multi drug-resistant tumours.

HOW CAN WE DEVELOP DRUGS WHICH TARGET CSCS?

Although research on the formation and resistance of CSCs has led to a greater understanding of how drugs targeting these cells could potentially be developed, experimentation on CSC-targeting drugs is very problematic, largely due to the difficulty in isolating CSCs and growing them in culture.[10] This makes it very difficult to test agents for specific toxicity against them. One method of overcoming this obstacle is to induce epithelial cells into an EMT. As already discussed, this enriches cells with CSC-like properties, including increased chemotherapeutic resistance.4 Screening for agents with selective toxicity against these cells can then be performed. One experiment by Gupta et al. screened approximately 16,000 compounds for selective toxicity against EMT-induced CSCs. Only 32 of the 16,000 substances displayed any selective toxicity against these cells, of which only four were found to be suitable for further study. Salinomycin was established to be the drug with the greatest potential. Further investigations revealed that salinomycin inhibited 100 times more breast CSCs than paclitaxel, the major conventional chemotherapeutic used to treat breast cancer.[8] However, salinomycin is very toxic to the body and could potentially cause serious side effects in vivo.[11]

Another study by Visnyei et al. looked at drugs which target CSCs in glioblastoma.[12] This study took a different approach to trigger CSC enrichment by culturing glioblastoma samples in neurosphere media containing suitable growth factors. This medium triggered an enrichment of CSCs, while a control medium did not. Approximately 30,000 compounds were then screened to see if they adversely affected the proliferation and survival of glioblastoma CSCs, of which four selectively toxic compounds were used to pre-treat glioblastoma CSCs before implantation into SCID mice. The pre-treated CSCs produced a substantially decreased tumour mass compared to untreated CSCs. This reduction in tumour mass occurred due to specific loss of glioblastoma CSCs following treatment with the compounds. Although the cells were cultured in an in vitro environment, the tumours that formed were genetically and phenotypically identical to the original glioblastomas. However, it is not known if in vivo administration of these drugs would be safe or effective. Therefore, developing drugs which interfere with specific CSC cellular processes could prove to be more effective at causing their selective destruction in vivo.

Perhaps the technique with the most potential is blocking cellular processes involved with induction and maintenance of the stem cell state. For example, it has been discovered that epithelial cells secrete inhibitors which block pro-EMT factors such as Wnt proteins and TGF-beta, preventing entrance into EMT under normal physiological conditions.[5] Therefore, derivatives of these molecules could potentially reduce the proportion of CSCs in a tumour. However, it is very difficult to target Wnt signalling in CSCs without targeting normal stem cells involved in homeostasis. For example, in animal studies, the inhibition of Wnt signalling in colorectal cancer resulted in severe defects in intestinal development.[13] The Hedgehog signalling pathway has also been implicated in a number of CSC cellular processes, particularly cell self-renewal.[14] This has been characterised in a number of cancers including chronic myeloid leukaemia, pancreatic adenocarcinoma, and multiple myeloma.[15-17] Cyclopamine is an active compound capable of inhibiting the Hedgehog pathway, and is therefore a potential CSC-targeting drug.[18] A derivative of this drug has entered clinical trials and has exhibited anti-tumour activity against basal cell carcinoma.[19] A derivative is also being used in clinical trials in combination with gemcitabine for the treatment of pancreatic adenocarcinoma.[20] However, it remains to be seen whether this type of drug will affect CSCs without adversely affecting the normal stem cell population within the body.

A recent interesting study by Song et al. has identified mitochondria as potential drug targets in CSCs.[21] Cancer cells are more susceptible to mitochondrial injury due to their extensive metabolic rearrangements.[22] Mitochondria are thus a potential target for inducing apoptosis of multi-drug resistant CSCs. Hirsch et al. discovered that the anti-diabetic drug metformin leads to the selective destruction of breast CSCs. It is thought that inhibition of the mitochondrial protein Complex I (NADH Dehydrogenase) leads to inactivation of a stress response and resultant inactivation of the pro-inflammatory transcription factor NF-⊠B. Since CSCs have a heightened inflammatory regulatory circuit, breast CSCs are selectively killed.[23] This could explain why diabetic patients taking metformin have a reduced incidence of a multitude of cancers.[24] It was also discovered that a combination of metformin and doxorubicin accelerates CSC apoptosis in mouse xenografts compared to doxorubicin monotherapy.[25] Another study by Alvero et al. used an isoflavone derivative to target mitochondrial function in ovarian CSCs.[26] This led to a decrease in concentrations of ATP, Complex I, and Complex IV in CSC mitochondria, as well as an increase in the concentration of reactive oxygen species. Following this, activation of two distinct cellular pathways culminated in the induction of CSC apoptosis. Although targeting CSCs in this manner is very exciting, there is potential for serious side effects due to the sharing of metabolic pathways and cell surface markers between CSCs and normal stem cells within the body.[21] Therefore, a more in-depth understanding of mitochondrial function and CSC metabolism is required.

An alternative method of targeting CSCs is to induce their differentiation into primary neoplastic cells, making them susceptible to conventional chemotherapeutic agents. This must be done without inducing the differentiation of normal stem cells. Sachlos et al. investigated whether neoplastic haematopoietic stem cells (HSCs) in acute myeloid leukaemia (AML) could be differentiated without inducing the differentiation of normal HSCs within the bone marrow.[27] After screening a wide range of compounds, treatment with the anti-psychotic drug thioridazine was found to selectively induce this differentiation. This drug acts via a dopamine receptor and appears to work by reducing the levels of Oct4 in CSCs, a transcription factor that is involved in maintaining stem cells in an undifferentiated state and promoting self-renewal.[28] The drug also upregulates genes which are specifically involved in the differentiation of neoplastic HSCs.[27] Therefore, thioridazine induces differentiation of CSCs in AML but has little effect on normal HSCs. Since thioridazine acts via a dopamine receptor, it is likely that neoplastic HSCs express this receptor, while normal HSCs do not. Therefore, this may be a likely candidate which could be targeted by selective agents in the future.

Immunotherapy has become an exciting avenue in the treatment of many different forms of cancer in recent years. These new “magic bullet” type drugs have become the focus of huge interest in the scientific community and the public alike. Drugs like ipilimumab used for the treatment of melanoma have revolutionised the way in which we treat some cancers.[29] Therefore, it is not surprising that efforts are being made to use immunotherapy to target CSCs. This form of treatment could work by using one of the unique cell surface markers expressed by CSCs as a target for the patient’s own immune system. There are challenges to this type of therapy, however, particularly the autocrine secretion of anti-inflammatory proteins by CSCs, namely TGF-beta.[5] Nonetheless, the development of monoclonal antibodies that target the unique cell surface markers should be explored in the future. For example, CD133 is highly expressed in many different CSCs, including those of glioblastoma, lung cancer, and breast cancer.[30] Therefore, treatments targeting these CD133 markers may be an alternative therapeutic option. Additional research is required in order to identify specific cell surface markers and exploit them therapeutically.

CONCLUSION – CAN CSCS BE USED AS A CHEMOTHERAPEUTIC TARGET?

Although conventional chemotherapy has greatly improved the prognosis of cancer, it has many limitations which must be overcome with new therapeutic options. This fact is highlighted by newer cancer treatments such as immunotherapies, which have significantly improved the prognosis for patients with a wide variety of cancers. However, targeting CSCs may be a more efficacious alternative. In order to develop such drugs, further research regarding the metabolic pathways unique to CSCs and the influence of their tumour microenvironment is required. Despite the need for further research, many potential strategies for targeting CSCs have been identified in the last number of years. These include inducing CSC differentiation into normal neoplastic cells, interfering with unique metabolic pathways, and targeting unique cell surface markers. Of course, there is still some work to be done before drugs like this become available in the clinic, but recent advances have shown that this is an exciting therapeutic option that we will no doubt be hearing more about in the future.

References

01 Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001; 414(6859):105-11.

02 Ffrench B, Gasch C, O’Leary JJ, Gallagher MF. Developing ovarian cancer stem cell models: laying the pipeline from discovery to clinical intervention. Mol Cancer. 2014; 14(3):275-91.

03 Kleinsmith LJ and Pierce GB. Multipotentiality of Single Embryonal Carcinoma Cells. Cancer Res. 1964; 24:1544-51.

04 Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M, Campbell LL, Polyak K, Brisken C, Yang J, Weinberg RA. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell. 2008; 133(4):704-15.

05 Scheel C, Eaton EN, Li SH, Chaffer CL, Reinhardt F, Kah KJ, Bell G, Guo W, Rubin J, Richardson AL, Weinberg RA. Paracrine and autocrine signals induce and maintain mesenchymal and stem cell states in the breast. Cell. 2011; 145(6):926-40.

06 Driessens G, Beck B, Caauwe A, Simons BD, Blanpain C. Defining the mode of tumour growth by clonal analysis. Nature. 2012; 488(7412):527-30.

07 Dylla SJ, Beviglia L, Park IK, Chartier C, Raval J, Ngan L, Pickell K, Aguilar J, Lazetic S, Smith-Berdan S, Clarke MF, Hoey T, Lewicki J, Gurney AL. Colorectal cancer stem cells are enriched in xenogeneic tumors following chemotherapy. PLoS ONE. 2008; 3(8).

08 Gupta PB, Onder TT, Jiang G, Tao K, Kuperwasser C, Weinberg RA, Lander ES. Identification of Selective Inhibitors of Cancer Stem Cells by High-Throughput Screening. Cell. 2009; 138(4):645-59.

09 Zhou S, Schuetz JD, Bunting KD, Colapietro A, Sampath J, Morris JJ, Lagutina I, Grosveld GC, Osawa M, Nakauchi H, Sorrentino BP. The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. Nature Med. 2001; 7(9):1028-34.

10 Liu H, Lv L, Yang K. Chemotherapy targeting cancer stem cells. Am J Cancer Res. 2015; 5(3):880-93.

11 Rowan K. High-Throughput Screening Finds Potential Killer of Cancer Stem Cells. J Natl Cancer Inst. 2009; 101(21):1438-9.

12 Visenyei K, Onodera H, Damoideaux R, Saigusa K, Petrosyan S, De Vries D, Ferrari D, Saxe J, Panosyan EH, Masterman-Smith M, Mattahedeh J, Bradley KA, Huang J, Sabatti C, Nakano I, Kornblum HI. A Molecular Screening Approach to Identify and Characterize Inhibitors of Glioblastoma Stem Cells. Mol Cancer Ther. 2011; 10(10):1818-28.

13 De Soussa DM, Vermuelen L, Richel D, Medema JP. Targeting Wnt signaling in colon cancer stem cells. Clin Cancer Res. 2011; 17(4):647-53.

14 Merchant A and Matsui W. Targeting Hedgehog - a Cancer Stem Cell Pathway. Clin Cancer Res. 2010; 16(12):3130-40.

15 Dierks C, Beigi R, Guo GR, Zirlik K, Stegert MR, Manley P, Trussell C, Schmitt-Graeff A, Landwerlin K, Veelken H, Warmuth M. Expansion of Bcr-Abl-positive leukemic stem cells is dependent on Hedgehog pathway activation. Cancer Cell. 2008; 14(3):238-49.

16 Feldmann G, Dhara S, Fendrich V, Bedja D, Beaty R, Mullendore M, Karikari C, Alvarez H, Iacobuzio-Donahue C, Jimeno A, Gabrielson KL, Matsui W, Maitra A. Blockade of hedgehog signaling inhibits pancreatic cancer invasion and metastases: a new paradigm for combination therapy in solid cancers. Cancer Res. 2007; 67(5):2187-96.

17 Peacock CD, Wang Q, Gesell GS, Corcoran-Schwartz IM, Jones E, Kim J, Devereux WL, Rhodes JT, Huff CA, Beachy PA, Watkins DN, Matsui W. Hedgehog signaling maintains a tumor stem cell compartment in multiple myeloma. Proc Natl Acad Sci U S A. 2007; 104(10):4048-53.

18 Gould A, Missailidis S. Targeting the hedgehog pathway: the development of cyclopamine and the development of anti-cancer drugs targeting the hedgehog pathway. Mini Rev Med Chem. 2011; 11(3):200-13.

19 Jimeno A, Weiss GJ, Miller WH, Gettinger S, Eigl BJC, Chang ALS, Dunbar J, Devens S, Faia K, Skliris G, Kutok J, Lewis KD, Tibes R, Sharfman WH, Ross RW, Rudin CM. Phase I Study of the Hedgehog Pathway Inhibitor IPI-926 in Adult Patients with Solid Tumors. Clin Cancer Res. 2013; 19(10):2766-74.

20 Kim EJ, Sahai V, Abal EV, Griffith KA, Greenson JK, Takebe N, Khan GN, Blau JL, Craig R, Balis UG, Zalupski MM, Simeone DM. Pilot clinical trial of hedgehog pathway inhibitor GDC-0449 (vismodegib) in combination with gemcitabine in patients with metastatic pancreatic adenocarcinoma. Clin Cancer Res. 2014; 20(23):5937-45.

21 Song IS, Jeong JY, Jeong SH, Kim HH, Ko KS, Rhee BD, Kim N, Han J. Mitochondria as therapeutic targets for cancer stem cells. World J Stem Cells. 2015; 7(2):418-27.

22 Kroemer G, Pouyssegur J. Tumor cell metabolism: cancer’s Achilles’ heel. Cancer Cell. 2008; 13(6):472-82.

23 Hirsch HA, Iliopoulos D, Struhl K. Metformin inhibits the inflammatory response associated with cellular transformation and cancer stem cell growth. Proc Natl Acad Sci U S A. 2012; 110(3):972-7.

24 Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ. 2005; 330(7503):1304-5.

25 Hirsch HA, Iliopoulos D, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer Res. 2009; 69(19):7507-11.

26 Alvero AB, Montagna MK, Holmberg JC, Craveiro V, Brown D, Mor G. Targeting the Mitochondria Activates Two Independent Cell Death Pathways in Ovarian Cancer Stem Cells. Mol Cancer Ther. 2011; 10(8):1385-93.

27 Sachlos E, Risueno RM, Laronde S, Shapovalova Z, Lee JH, Russell J, Malig M, McNicol JD, Fiebig-Comyn A, Graham M, Levadoux-Martin M, Lee JB, Giacomelli AO, Hassell JA, Fischer-Russell D, Trus MR, Foley R, Leber B, Xenocostas A, Brown ED, Collins TJ, Bhatia M. Identification of Drugs Including a Dopamine Receptor Antagonist that Selectively Target Cancer Stem Cells. Cell. 2012; 149(6):1284-97.

28 Boyer LA, Lee TI, Cole MF, Johnstone SE, Levine SS, Zucker JP, Guenther MG, Kumar RM, Murray HL, Jenner RG, Gifford DK, Melton DA, Jaenisch R, Young RA. Core transcriptional regulatory circuitry in human embryonic stem cells. Cell. 2005; 922(6):947-56.

29 Larkin J, Hatswell AJ, Nathan P, Lebmeier M, Lee D. The Predicted Impact of Ipilimumab Usage on Survival in Previously Treated Advanced or Metastatic Melanoma in the UK. PLoS One. 2015; 10(12).

30 Chen K, Huang YH, Chen JL. Understanding and targeting cancer stem cells: therapeutic implications and challenges. Acta Pharmacol Sin. 2013; 34(1):732-40.

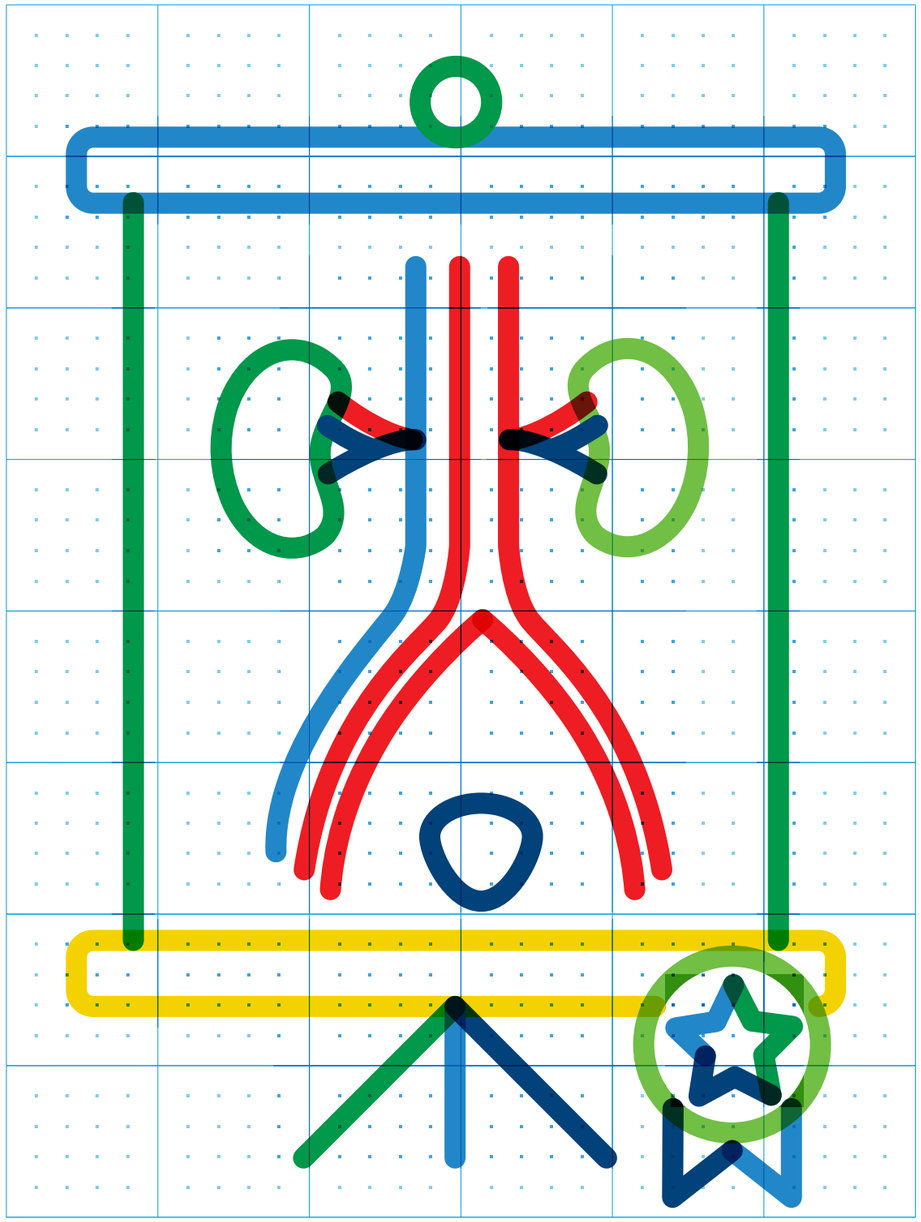
The James B. Coakley Medal: *Dissecting an Extraordinary Experience*

Written by Ning Xuan Ho

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.

and Dr Michelle L. Smith

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



Written by Ning Xuan Ho
Dr Michelle L. Smith

The James B. Coakley Medal: Dissecting an Extraordinary Experience

The James B. Coakley Medal in Dissection is an annual dissection competition in University College Dublin (UCD) which takes place during the summer months. James B. Coakley was a professor of Anatomy in UCD from 1962 – 1988. To honour his distinguished career and his dedication to excellence in the teaching of human anatomy, the Coakley Medal is awarded to a current student based on exemplary dissection of an assigned specimen.

I applied to take part in the 2015 competition, with the application process beginning in May. After the application forms were submitted and reviewed, candidates were selected based on academic performance. Myself and three other candidates, Esther Shan Lin Hor, John Harford and Michael Gilligan were chosen to compete for the medal. Once notified, we were offered four projects to choose from and asked to list them in order of preference. The projects were then allocated according to GPA ranking. By good fortune we each ranked different projects highly and were therefore allocated our first choice, as follows:

- Dissection of the central visual pathway – Michael Gilligan
- Superficial and deep dissection of the knee – Esther Shan Lin Hor
- Dissection of pelvic topography – John Harford
- Dissection of the structures of retroperitoneum – Ning Xuan Ho

The competition involves judgment of three components: the quality of our dissections, the educational value of our posters and the quality of our oral presentations. Prior to commencing the competition, we each submitted a proposal outlining how we would approach the dissection. After a discussion with each participant, Doctors Feeney and Smith offered feedback and guidance for our dissection technique. We were also invited to attend an induction and photography technique session held in the human anatomy dissection laboratory which proved useful.

The dissection component of the competition took place from early July to late August. During this period, participants were notified of the days during which they would be afforded access to the human anatomy laboratory to perform dissection. Upon completion, the resulting specimens were assessed by a panel of academic staff from the Department of Anatomy at UCD.

Although we were allowed access to the dissection room from the first week of July, I commenced my project towards the end of July due to other commitments. However, my advice for future participants would be to start their projects early to get the best out of the competition. Upon completion of the dissection, it was time to design and complete our posters. My poster focused mainly on the photographic representation of my project and some discussion of the related anatomy. I also chose to feature some of the anomalies encountered during the dissection. However, there were no strict guidelines for poster content, and participants are encouraged to be creative in this aspect of the competition. We were permitted one week to complete the poster, which was reviewed by the academic staff in a digital format. The oral presentation took place at the beginning of the academic year. We gave a presentation containing images of our prosections to other students, anatomy demonstrators and professors. I found this experience quite daunting, however I enjoyed the novelty and excitement associated with communicating about my medical endeavors to an audience of my peers and mentors.

I had a number of reasons for opting to dissect the retroperitoneum. First, I had recently completed a module on renal biology, and the concept of the retroperitoneum was still fresh in my mind. I thought this project was a good opportunity for revision, as well as a chance to gain a better understanding and appreciation of the area. Second, I believed that due to the depth of the retroperitoneal structures, I would encounter a wealth of anatomy as my dissection progressed from superficial to deep structures. I anticipated having the opportunity to examine the structures of the anterior abdominal wall and each of the intra-abdominal organs as I progressed with my dissection. As it developed, my project became even more interesting as I discovered several anatomical anomalies and pathologies.

In my approach to this dissection, I began by identifying and marking the surface anatomy prior to making an incision. Once I had verified that the markings were correct, I incised the anterior abdominal wall, revealing the contents of the abdominal cavity. After examining the complex structure of the peritoneum and the mesentery, the peritoneal viscera were carefully removed. Following this step, the structures of the retroperitoneum were exposed. Using the camera provided, I took photographs at every stage of my dissection. This enabled me to document my progress and ensure that I had a record of all of the structures I encountered This photographic record proved useful for my poster and oral presentation.

Moving on to the retroperitoneum, I exposed the kidneys and the path of the ureters. At this point, I noticed a duplicate ureter emerging from the right kidney. This is one of the more commonly described congenital anomalies, and is referred to in medical literature as a “duplex renal system”. Embryologically, this phenomenon occurs when two ureteral buds arise from the mesonephric duct during development. The pattern of duplication can vary. In this case, two completely separate ureters drained the right kidney. This system is seen in 0.7% of the normal adult population and in 2-4% of patients investigated for urinary tract symptoms.[1]

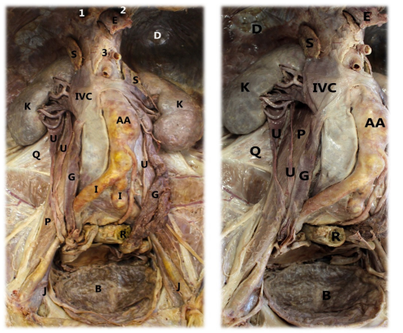


Figure 1

Anteriorview of primary retroperotoneal organs and the urinary pathway.

AA: Abdominal Aorta
IVC: Inferior Vena Cava
E: Oesophagus
S: Suprarenal (Adrenal) Gland
K: Kidney
U: Ureter
P: Psoas Major Muscle
Q: Quadratus Lumborum Muscle
B: Urinary Bladder
R: Rectum
I: Common Illiac Artery
J: External Illiac Artery
G: Gonadal Vein
D: Diaphragm
1: Caval Opening (T8)
2: Oesophageal Hiatus (T10)
3: Aortic Hiatus (T12)

Duplex renal systems usually do not require any treatment per se, however complications may necessitate intervention. Duplicated ureter is reportedly more common in females compared to males. However, this may reflect more frequent investigation of the female urinary tract owing to their higher susceptibility to urinary tract infections, rather than a true increased frequency of this anatomical anomaly.[2] Duplicate ureters are usually discovered incidentally post-mortem, as was the case with our donor. Fascinated by this finding, I further examined the kidney by making a coronal section from the medial to the lateral surface. I discovered two completely separate renal pelvises, where the upp er pole system was slightly smaller than the lower pole.

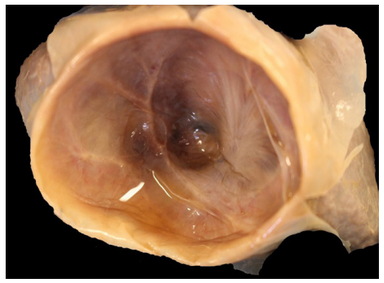


Figure 2

Substantial depression on the inferior pole of kidney, due to largecyst previously present.

Next, I examined the left kidney. As I removed the pre-renal fascia I palpated an area with a much softer texture than the surrounding tissue. Upon exposing the renal capsule, I noted a cystic structure on the inferior pole. After draining off the fluid within this structure, there was a substantial depression on the antero-inferior and posterior segments of the kidney. We concluded that this was likely to be a simple cyst. Simple renal cysts are relatively common and measure approximately 10- 50 mm in diameter, with some measuring up to 100 mm. In this case, the cyst measured approximately 50 mm in diameter. Simple renal cysts are a common post-mortem finding. They are usually asymptomatic and have no clinical significance.[3] The function of the glomeruli which are compressed by the cyst may be impaired or obliterated, however due to the large reserve of filtering tissue in the kidney, this would not necessarily affect renal function.

Some intra-abdominal anomalies and pathologies were discovered during the dissection. First, the donor had an enlarged and discoloured liver with a grossly abnormal appearance. This was an interesting finding and a great learning point for all those involved in the competition, as we tried to correlate the observed anatomy with the pathology covered in lectures. As the dissection progressed, we noted various other pathological findings, including splenomegaly, severely calcified arteries and a large thrombus within the left ovarian vein. Collectively, these findings suggest the donor may have had portal hypertension. Unfortunately, we did not have access to medical records to confirm or refute this diagnosis.

Another interesting anomaly in the peritoneal region was a 'splenunculus'. This appeared as a small, solid mass measuring approximately 20 mm in diameter. It was located just below the inferior pole of the spleen and covered by peritoneum. The splenunculus appeared to have its own local blood supply upon removal of the peritoneum. At first I wasn't certain what it was, and sought the opinions of various anatomy lecturers. Following histological analysis, it was identified as splenic tissue. This demonstrates that learning human anatomy is not merely about appreciating the structures as 'text book' specimens, but that fascinating variations are also possible. Over the course of my project, I have learned to appreciate both normal and variant anatomy, as well as pathological appearances.

A significant amount of preparation was required in advance of beginning the dissection. I relied heavily on Grant's Dissector,[4] which I found to be an extremely helpful and reliable resource. For students involved in this competition in future, I recommend visiting the library and examining a number of different atlases, texts and dissection guides, as certain books will vary in their suitability for particular dissections. I recommend that prospective Medal students make use of the allocated practical sessions to hone dissection skills. As I was working through my project, it took time to grasp certain techniques and to master the use of different dissecting tools to prevent damaging the tissues. However, after some practice, my dissection proficiency improved as I became more experienced and confident with the tools.

Although I did not win the medal in 2015, I must say that this was a one-of-a-kind experience and I have gained so much more than I expected. My interest in a surgical career was certainly strengthened by participating in this competition and I would definitely consider surgery as an option in the future. The skills obtained and knowledge acquired were a huge part of what made this project worthwhile. Through this competition, I was able to develop my dissection skills, investigate several anatomical anomalies, as well as interact with various health science academics. I also had the opportunity to deliver an oral presentation to my peers and mentors, which although daunting at first, was a very rewarding experience. These are just some of capabilities I have developed during the competition. If asked would I do it all over again, my answer would be a resounding "Yes! Most definitely!"

Acknowledgements

I'd like to express my sincere gratitude to the donors and their families for the sacrifice that they make in order for this project (and all anatomical dissection at our medical school) to be possible. I would also like to thank the anatomy technicians, demonstrators and faculty of the School of Medicine for the valuable advice given throughout the project. Last but not least, to my fellow participants; John, Esther and Michael, thank you for making the dissection sessions so enjoyable and motivating. Finally, congratulations to Michael Gilligan on winning the 2015 James B. Coakley Medal in Dissection!

For those who are interested, students who have completed one year of Anatomy are eligible to apply to take part in the James B. Coakley Medal in Dissection. This includes students in undergraduate and graduate entry medicine, BHLS, radiography and physiotherapy programs. Further information will be posted on Blackboard in the coming months.

References

01 Hacking, C and Jones, J et al. Duplex Collecting System. Radiopaedia.org (http://radiopaedia.org/articles/duplex-collecting-system-http://radiopaedia.org/articles/duplex-collecting-system)

02 Gatti, J.M., Koo, H.P., Williams, J.F., Murphy, J.P., Ureteral Duplication, Ureteral Ectopia, and Ureterocele (September 2013) (http://emedicine.medscape.com/article/1017202)

03 Kumar, V., Abbas, A.K., Aster, J.C. Robbins and Cotran Pathologic Basic of Disease (9th ed.)

04 Tank, P.W. Grant's Dissector 15th edition. 2013. Chapter 4: The Abdomen.

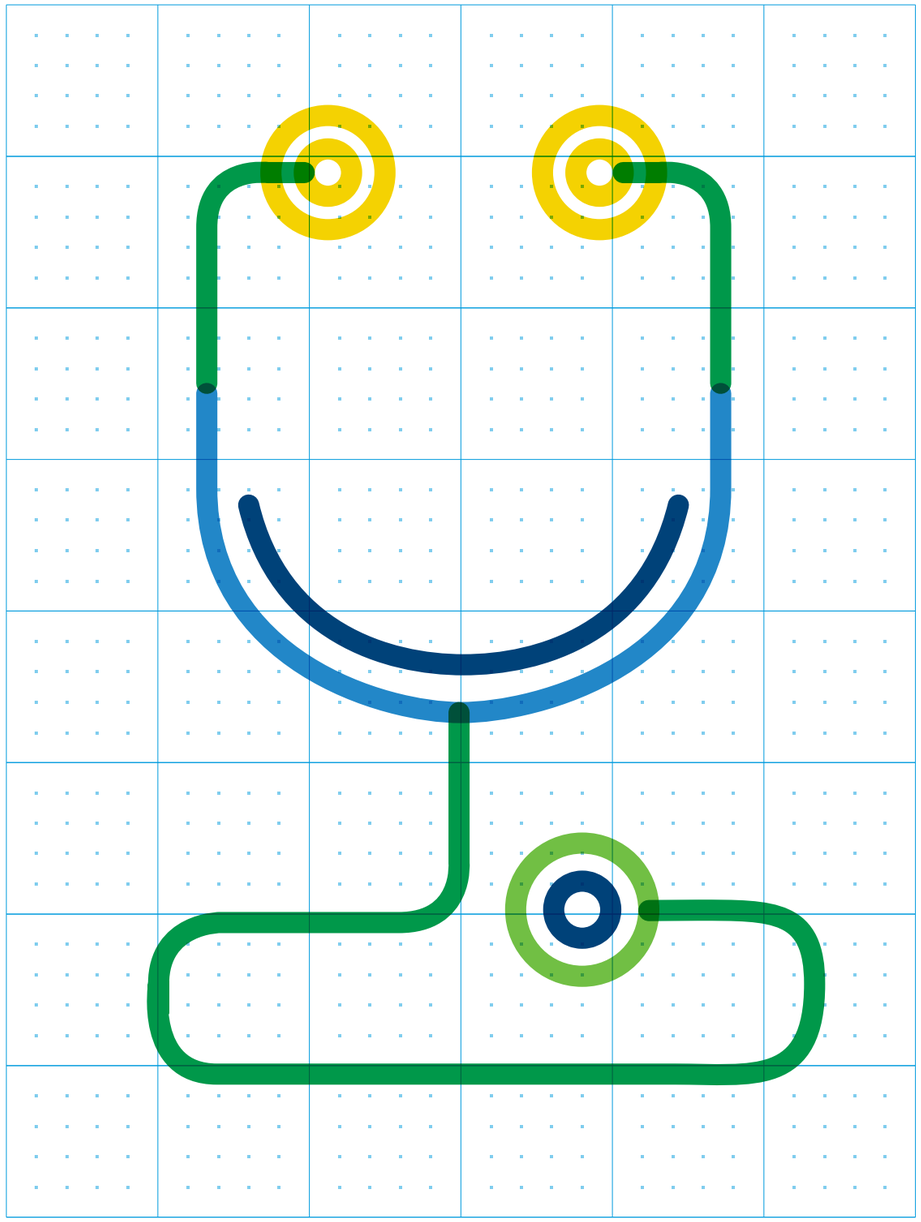
Listen to My Heart: *Really Hearing What the Patient is Saying*

Written by Meggan Connell

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.

and Karen Mulligan

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



Written by Meggan Connell
Karen Mulligan

We all think we know how to listen, but there is a difference between hearing people talk and listening to what they're saying. Let's imagine a Monday morning half way through the semester. You have big plans for the week; review all the lectures, start and finish several assignments – in other words, get on top of things. Between your first and second lecture you run to grab a coffee with your friend Orla, chatting on the way to save time. You ask how her weekend was but your mind is multi-tasking: half listening, half thinking about how much you need to do later and how you can possibly fit it all in. "Oh it was fine," she says, "I didn't get up to much." You don't think anything of it. You go to class together and your week carries on, busy, busy, busy.

Orla isn't really fine though. Her weekend wasn't fine. What would have happened if you had taken the time to quiet your thoughts for a moment when you asked her how she was? What if you had observed her body language and listened to her tone of voice during your chat? These non-verbal cues may have helped you realise that Orla didn't actually mean her weekend was fine. You could have asked, "Is everything okay, is there anything you want to talk about?" That is active listening. Active listening, at its very core, is making the choice to listen to somebody else. To not just hear them saying words but to really think about what those words mean.

Let's pick up the Monday morning conversation with Orla. Imagine instead that you decided to actively listen. In this scenario Orla noticed that you were listening closely, and that you were offering her the chance to talk, so she opened up. She mentioned that she had spent most of the weekend worrying and she hadn't slept well. You have now been presented with second opportunity to practice your active listening. You could say "Oh I know how you're feeling, I'm really stressed about exams and assignments lately too." Or you could put aside your own worries and say, "What has you worrying so much?"

Active listening means making the choice to tailor the conversation to the other person, giving them the chance to feel listened to. This means surrendering the reigns of the conversation and following their lead. In this hypothetical situation, you may infer that Orla, like yourself, is stressed out about college. If you start talking about yourself and your own stresses then Orla has to sit back and let you feel heard too. However, it turns out Orla is actually worried because she went for an STI check last Friday and she's anxiously awaiting the results. If you direct the conversation toward your personal stress, Orla loses the opportunity to open up about what is bothering her. By quieting your own thoughts you give Orla the chance to communicate what she needs to say.

In medicine, poor listening skills can lead to misdiagnosis and poor outcomes. Our listening skills require not only hearing and processing the information patients offer, but evaluating, analysing and problem solving. Taking a thorough history is an integral aspect of determining an accurate diagnosis. This aspect of medical care relies almost entirely on effective communication and active listening. Patients need to feel comfortable with their doctors in order to disclose what are often very personal details. Their comfort level during a consultation is our responsibility and active listening is our greatest asset.

During preclinical years we are often told to convey 'empathy'. In fact you may have heard this word so often that it has lost all meaning. Here are some practical ways by which we can show our patients that we care:

BODY LANGUAGE

Be open to a conversation, sit back in your chair, lean against a wall – basically look like you are comfortable or even better actually be comfortable so that you are prepared to have a sensitive conversation.

PHONE

Put it away if you want to have a real conversation.

SILENCE

Don't be afraid of it. Everybody feels the need to fill silences, so wouldn't it be better if the person you're listening to fills it instead of you?

QUESTIONS

Ask questions that follow on from what the person has said to you. This will encourage them to follow their train of thought or elaborate on an idea a little further. This means asking open questions, but it doesn't mean you have to use vague stock type questions like the ever dreaded "How does that make you feel?" The best way to ask a good question is to actually care about the answer.

Active listening can't be mastered by applying a few buzzwords and perfecting conversation skills. While these are important, they can only take you so far. You have to actually care about what the person is telling you and really try to understand what it means for them. This act of trying to understand and showing that you are trying to understand is the very essence of empathy. The clinical psychologist Julian Treasure claims that people rarely listen effectively to one another. He describes four steps to listening better: RECEIVE, APPRECIATE, SUMMARISE and ASK. This tool kit can help us to listen actively and convey that we care about what others are saying.

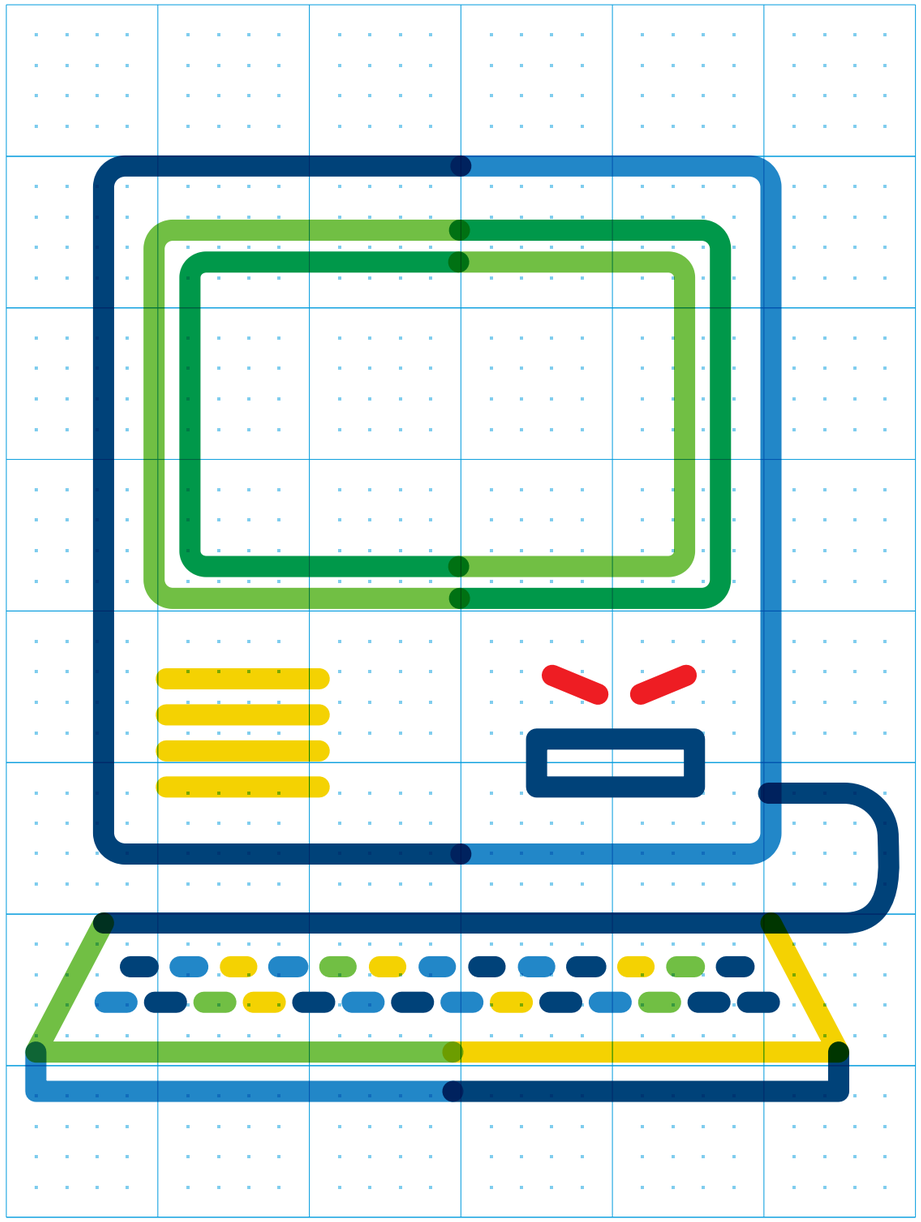
Reflect for a moment on your day so far. Most of us are experts at receiving information and retorting with socially appropriate responses. We do this without actually appreciating what has been said. The phrase "How are you?" has become something we say in passing rather than a genuine question requiring a response that will be appreciated and acted upon. Have you taken the time to actively listen to anybody today? Active listening is a skill that takes time and practice to perfect, it's not something that comes naturally to anybody. Let's start practicing now, in both our personal and professional lives, so that when we meet the patients that need us to actively listen we will be ready.

Give it a go. See what happens.

Hey Siri, What's Wrong with Me? *Watson Health and the Future of Artificial Intelligence in Healthcare*

Written by Laura Mannion

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



"Human beings have dreams. Even dogs have dreams, but not you, you are just a machine. An imitation of life. Can a robot write a symphony? Can a robot turn a canvas into a beautiful masterpiece?"

– Detective Del Spooner, I, Robot

In the sci-fi action film 'I, Robot' there is a scene in which police detective Del Spooner is interrogating Sonny - a robotic murder suspect. During questioning, the cyborg reveals he has been programmed to feel emotions, and even experience dreams. Spooner reacts strongly to this news, snapping back with contempt and derision. Certain that Sonny is nothing more than an imitation, he maintains that a machine cannot possibly contribute to society in any creative, meaningful way.

Multinational technology and consulting corporation IBM has a wildly different opinion! Two years ago they unveiled 'Watson', a computer system worth 1 billion US dollars.[1] Although a far cry from the hyper-intelligent cyborg featured in 'I, Robot', some similarities are notable. Watson is part of a new generation of computers which operate by simulating human thought processes; a computing method known as 'cognitive computing'.[2]

"While Watson can't have dreams or get sad, it does have the ability to solve problems that the average computer system cannot."

Ask a search engine like Google to give information on a topic, and it will present a list of results ranked by popularity. However, Google will be unable to summarize this information, or to suggest how it might be applied in the real world. These situations require more introspective analysis, which Watson hopes to deliver.

Working to determine the underlying links between data, Watson offers suggestions based upon patterns and relationships, not popularity. This ingenuity allowed it to defeat the current human world champions in the contextual game show 'Jeopardy'.[3] Watson took home the 1 million US dollar prize and undoubtedly wounded a few egos in the process.

Since then, Watson has invented a recipe for barbeque sauce and developed methods to help win fantasy football leagues. The things your dad does on a daily basis! However, these are only side projects in comparison to IBM's latest Watson initiative. According to a recent press release, the application Watson Health "will help improve the ability of doctors, researchers and insurers to innovate by surfacing insights from the massive amount of personal health data being created daily."[4]

In short, IBM intends to use Watson to diagnose and treat disease. Watson Health is already in use at several cancer treatment institutes in the US and Canada where it assists in choosing individualised patient therapies.[5] It is hoped that such an approach can use the vast trove of online data, finding crucial connections between specific cancers and their treatment.

Suggesting appropriate diagnoses and treatment represents a great step forward for Watson Health. In evidence of this, Watson business chief Manoj Saxena has announced that amongst nurses using the application, 90% follow its guidance.[6] Still, IBM has been slow to place Watson on the frontlines of medical care, limiting system access to institutions with only the highest levels of funding and prestige.

This lack of application to the general public can lead us to wonder whether artificial intelligence is making headway in medical treatment at all. Like many medical students, Watson Health is currently studying for its USMLE exam and is waiting in the wings to prove its use in the real world. However, IBM's partners in making Watson Health aren't doctors and nurses, but multinational corporations that demand evidence of commercial success before a project like this can proceed.

As a result, IBM's marketing strategy for Watson Health is aimed squarely at global industry. Big business has been intensively courted, with giants such as Apple, Johnson and Johnson, and Medtronic all signing on to incorporate the new software into their products. The public may see elements of Watson Health included in current Apple health tracker app HealthKit™ for example, laying the foundations for the real life implementation of AI in healthcare.[7] What IBM may ultimately want however, is an even more lucrative collaboration. In 2012, expenditures for private health care insurance totalled $884 billion dollars in the US alone.[8] The successful integration of this sector and Watson Health could spell incredible profit for the computing firm.

What could such artificial intelligence bring to private healthcare clients and who will ultimately benefit? The evidence to date points to worrying trends. In a 2012 executive paper Jamie Bisker, the Research Relationship Manager for IBM, describes how insurance premiums are set and maintained.[9] He reports that social media has emerged as a prime source for the data which determines these premiums. For now at least a large proportion of the public are unaware of this development. Insurers are not omniscient, however. With four zettabytes (10^{21} bytes) of information as of 2013, the sheer volume of material contained within the internet presents any search engine with a formidable investigative problem. Enter Watson Health.

Bisker proposes that IBM's new system, with its superior pattern recognition capabilities, will slip astutely through the online minefield of "irrelevant tweets and blog entries" to capture the valuable information amongst them. Along with other AI advocates, he maintains that the more appropriate the information Watson collects, the more effectively risk can be calculated and the more cost effective insurance policies can become.

Speculation aside, computing systems like these will confer large companies with even greater access to personal information. The idea of a multinational corporation trawling insidiously through Facebook, evaluating our daily life in terms of the liability it poses, is unsettling. However, there is also concern that simple overuse of AI could lead to problems. For example, doctor-patient relationships may suffer if physicians defer unduly to the machine's authority. Medical teaching and learning might also be impacted, with apathy and disinterest setting in as computers effortlessly assimilate the trickier aspects of medical knowledge. In this sense, Watson resembles that high flying classmate; prodigious but infuriating!

"Turning illness into a commodity is something to be fastidiously avoided. As big business gains access to increasingly powerful technology, the opportunity to misuse such technology increases in tandem."

To borrow a phrase, "knowledge is power - and with great power comes great responsibility". Will responsibility matter if it stands in the way of profit?

It lies with the public, legislators, and medical practitioners to ensure that patient welfare unequivocally comes first. Artificial intelligence has already begun to change patient outcomes for the better. Watson Health has bolstered the treatment provided by oncologists and nurses, and started to interpret the masses of health data created each day.

If Watson can successfully integrate into everyday life, it may yet overturn the assumptions of the gruff 'I, Robot' protagonist, who sees no merit to what machines can contribute to society. With the potential to improve diagnosis and support, there is every indication that AI will soon be a significant benefit to a great number of people.

References

01 IBM Online Press Release Team. IBM. [Online].; 2011 [cited 2015]. Available from: http://www-03.ibm.com/press/us/en/presskit/27297.wss.

02 Ardire S, Roe C. Cognitive Computing: An Emerging Hub in IT Ecosystems. IT Systems Report. Studio City, California: Dataversity Education LLc; 2014.

03 Adam Gabatt and agencies. The Guardian. [Online].; 2011. Available from: http://www.theguardian.com/technology/2011/feb/17/ibm-computer-watson-wins-jeopardy.

04 IBM Online Press Release Team. IBM. [Online].; 2012. Available from: http://www-03.ibm.com/press/us/en/pressrelease/37235.wss.

05 IBM Online Press Release Team. IBM. [Online].; 2015. Available from: http://www-03.ibm.com/press/us/en/pressrelease/47623.wss.

06 BBC Tech News. BBC. [Online].; 2014. Available from: http://www.bbc.com/news/technology-26366888.

07 Campbell M. Apple Insider. [Online].; 2105. Available from: http://appleinsider.com/articles/15/04/13/apple-partnership-with-ibms-watson-health-cloud-nets-healthkit-and-researchkit-secure-cloud-data-analytics-.

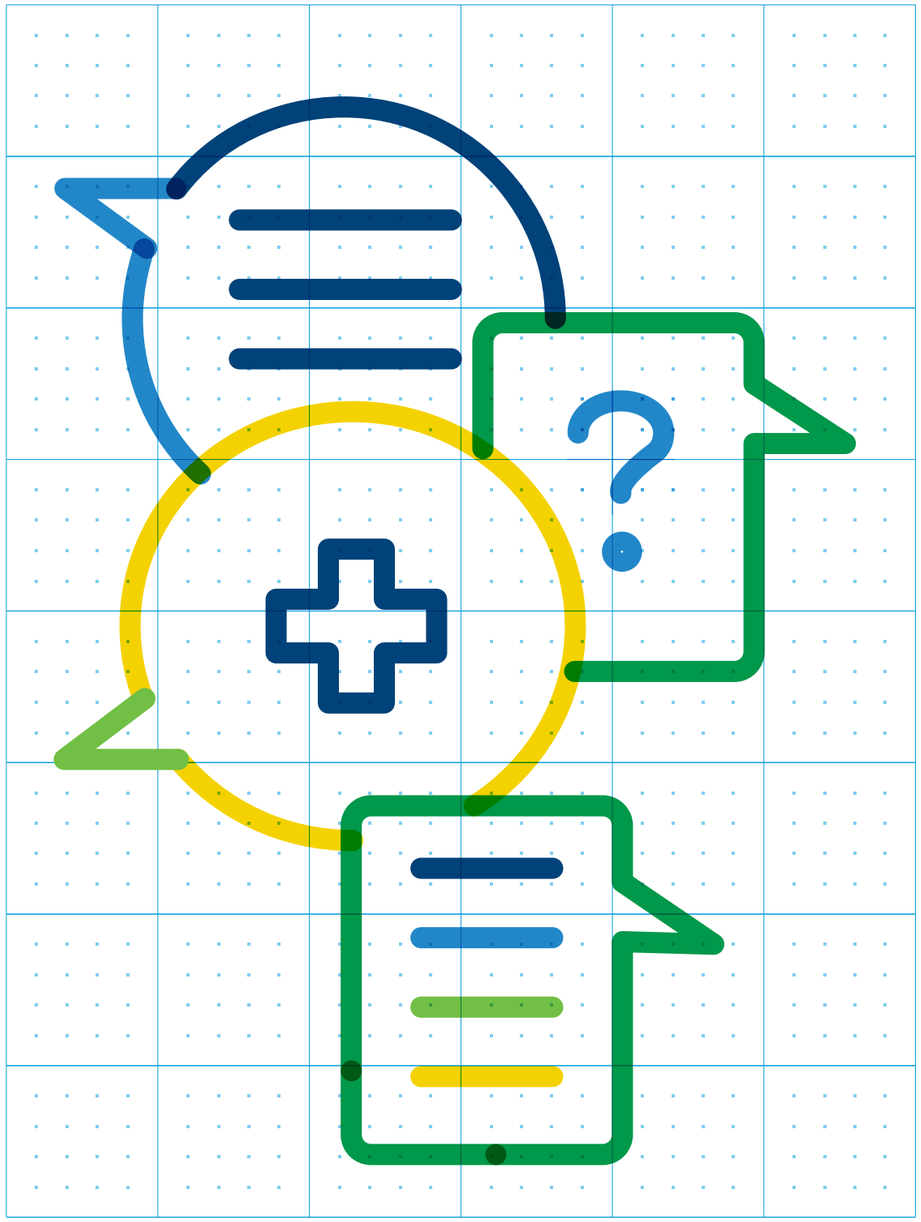
08 MD DM. PNHP. [Online].; 2013. Available from: http://pnhp.org/blog/2013/07/31/friedman-analysis-of-hr-676-medicare-for-all-would-save-billions/.

09 Jamie Bisker, IBM Research Relationship Manager. IBM. [Online].; 2012. Available from: http://www-935.ibm.com/services/multimedia/Insuranceintheageofanalytics.pdf.

Genetic and Rare Diseases in Ireland *an Interview with Anne Lawlor*

Written by Lade Adeusi

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.



The Genetic and Rare Disorders Organisation (GRDO) acts as a national alliance for voluntary groups representing the views and concerns of people affected by, or at risk of developing, genetic or other rare disorders.

Anne Lawlor is the Information & Development Officer at the GRDO, as well as the founder of '22q11 Ireland'. The GRDO often works closely with Irish medical schools including UCD, and have given presentations as part of the Rare Diseases module in the School of Medicine. This interview outlines some of the great work that GRDO and 22q11 Ireland are doing for patients with rare and genetic diseases.

→ What is your role at GRDO?

I am the information and development office, so essentially I share information. As much as I can to as many people as I can. I am particularly interested in parents and families and what happens to them when they have a child diagnosed with a rare condition.

→ How did you start working with GRDO?

I have an adult daughter who is now 32 years old. She was diagnosed with 22q deletion syndrome when she was 15. I quickly realized that 22q11 was a relatively rare condition. To find help for it would mean to go out and talk to other people who had some experience in the area of genetic and rare disorders, so I joined the GRDO itself and actually sat on the board for a while. There was no staff at all at that time.

The board was made up of interested parties in the field of rare diseases who were all working in their own separate areas but who wanted to bring the awareness of rare conditions more to the forefront and to develop policies. In 2011, GRDO got a small amount of funding for the community and voluntary government department, enough to employ a part time information officer. Two years ago the post became vacant and I resigned from the board to take up the position. So that's what I do. I'm also the chairperson of the 22q11 support group in Ireland.

→ Is the area of genetics and rare diseases always something you wanted to work in?

No! I knew nothing about it and I have subsequently become totally immersed in and fascinated with the whole area. I don't think we realize how important our genetics and family history are in terms of our own lifestyles, its an extraordinary area. I have become wholly fascinated with it both through my personal experience with my daughter, and with the work that I do for GRDO.

→ What types of legislation are you working on that would help people with rare diseases in Ireland?

Well one thing that we're proud of is the Rare Disease Task Force. It is a combination of people and representatives of various different organizations; Cystic Fibrosis, cancer, Alpha 1, Huntington's, Debra Ireland, lots of different organizations who came together to develop policies in the area. The other thing that we're very proud of is that the Ireland Rare disease plan was published in 2014. Our focus now would be on the implementation of that plan.

→ What do you think is the largest challenge facing patient advocacy groups as they try and help patients navigate the healthcare system?

The largest challenge I think is the lack of awareness of genetics.

"I think the level of genetic awareness in Ireland is very low amongst the general population and amongst a lot of healthcare providers."

We don't have what we would consider a robust genetic service. In fact, we have a genetic service that currently has one of the worst staffing quotients in Europe. So there are lots of things, I don't think I could give the biggest challenges, there lots of challenges. There is lack of awareness, lack of resources, lack of understanding that genetics are actually a pivotal part of healthcare.

→ What would you say the biggest issue is that people with genetic and other rare disorders face in Ireland?

Again, I would say the lack of awareness. My own personal experience is that once you are diagnosed with a genetic or rare condition you are mostly on your own. There are so many of them, there are over 8,000, so no clinician is going to know all of them, its not possible. Generally, it falls to the patient or the patient's family to go out and get the information for themselves. Very often we find that patients and parents are actually educating the healthcare providers about their specific condition.

→ How has being a parent of a child with a genetic disorder changed your perspective?

Well I wouldn't have had a perspective really because I would have been like most people.

"Genetic and rare disorders are an alien term unless we bring them into the general language, and unless we use them in the daily discourse."

I think unless you're particularly in those fields, you're not going to be too concerned about genetic and rare disorders. It's like everything else, its not until something that comes onto your own doorstep and into your line of vision that you take an active interest in it.

→ Please tell me a little bit about your work with 22q11 Ireland.

22q11 Ireland came about when I got my daughter Aine's diagnosis of DiGeorge syndrome. I was told it was because of this deletion on her 22nd chromosome. The doctors did some basic checks on her and that was it. There was no follow up, there was no support. There was very little in the way of information and this was pre 'Dr. Google'. It took me quite some years to get information that related to living on a day-to-day basis with a genetic condition. It was easier to get medical and clinical information.

It's a very isolating place to be when you get a diagnosis like that. For many years after her diagnosis, maybe 7 years, there was nowhere for me to go and I remember going to my first international conference on 22q11. I was totally taken aback at the complex nature of this condition. It is so variable, it reaches into every aspect of a person's life; physical, mental, social. There are a couple of things that stand out from that first conference, and one was that I met only one other Irish person out of 400 attendees. He was a psychiatrist with a particular interest in schizophrenia. If you are born with a 22q deletion you have a 30% higher chance of developing schizophrenia than a person in the general population, on top of the many other medical issues that go with the condition.

I came back home to Ireland and then I went to a conference closer to home in the UK and they had quite a substantial following over there for their support group and they were quite well established. I met an Irish couple there from Cork and I asked them if they would think about setting up a support group in Ireland. We set one up in 2007 with three families and that same psychiatrist, Professor Kieran Murphy. In 2015 we have 140 families in the support group with children of all ages.

Every year I hold a national conference, and we have had the international conference here in 2013. In 2017 we will be hosting the second European 22q conference. We are quite excited about that. We have also gotten involved in research and our latest collaboration is with Trinity College in the School of Education. Children with 22q have quite significant learning disabilities.

I think perhaps the greatest challenge for me as the person running the support group is that 22q is an 'invisible condition'. You won't necessary know straight away that a person has 22q, so its quite challenging, both for me as the chairperson and as a parent personally with my daughter. I do a lot of work, I speak to medical students both in UCD and Trinity College and I've co-authored some publications on 22q. I am also not only interested in the deletion, but there is also a 22q duplication. I now have a broader interest in chromosomal conditions.

→ You have some teaching and awareness initiatives, how is awareness in both healthcare and the general public about genetic and rare diseases important for the future of healthcare?

People can carry mutations that have no effect until later in life, for example Huntington's disease, which is devastating for the families involved. If we are better informed about genetics we can make better choices, we can deliver better healthcare. If we have more awareness about conditions like 22q we can help children by preventing misdiagnosis and wrong or ineffective treatment. We can help children in an educational setting, one of the things we are doing in Trinity College is looking at how genetic conditions impact on a child in the classroom. We can better tailor services for adults with 22q. There is a huge gap in the transition from pediatric to adult care for those with rare conditions. There is a lot we could do to deliver better healthcare especially by developing our genetic and genomic service and network in Ireland.

→ Do you have any advice for health care students in their future interacting with patients with GRD's.

I think it is really exciting that healthcare students are getting involved in this area as there is a major lack of awareness. I think that healthcare students can become marvelous advocates; they are the future doctors, nurses, therapists, consultants, surgeons etc.

"I think that if they have a better understanding of the complex nature of genetic conditions now, they will be much better at interacting with these patients throughout their career."

Also if we had students involved with patient groups earlier on, doing research in rare conditions, it would be wonderful. For instance, there is a lot known about children with 22q but not necessarily adults. If students get involved with patient groups, then they would not receive just a medical/ clinical education, but they would get an insight into what is like to live with a genetic or rare condition.

Paediatric Rotation

UCD Partnership with Harvard Medical School and the Massachusetts General Hospital

Written by Nathaniel McHugh

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.

WHAT IS THE PAEDIATRIC ROTATION COMPETITION?

Each year UCD School of Medicine award a number of scholarships to Stage 5 medical students to carry out electives abroad. This particular award gave me the opportunity to study the paediatric portion of my degree in Harvard Medical School. Study involved a 6-week rotation in Massachusetts General Hospital (MGH) while attending lectures with Harvard medical students. I then returned to Ireland and sat the UCD paediatric exams with my class.

WHEN DOES THE ROTATION TAKE PLACE?

To fit in with the Harvard schedule, I had to leave 3 weeks before I was due to start my paediatric rotation at UCD. I went in March, which meant missing the last 2 weeks of internal medicine in Mullingar and the week of exams. Unfortunately, this did mean sitting my missed exams in August. However, do not let this deter you too much. A 6-week 'break' in the middle of the year was very welcome, as the other students had exams and started straight back into placement. Alternatively, two additional students were sent on the rotation in August.

HOW DO I APPLY FOR THE COMPETITION?

Applications opened in late February or early March. The process may vary from year-to-year but we were initially invited to apply via e-mail. We then had our academic record reviewed, underwent interviews, and submitted an essay. It is not necessary to have taken the USMLE Step 1.

WHAT DID THE ROTATION COST?

There was a bursary to cover both flights and accommodation. The Harvard fee is also waived, leaving only spending money to be supplied by you.

I would highly recommend applying for some form of an international elective. It was a great experience being immersed in a different healthcare system, not to mention the fact it was great fun and you meet lots of interesting people.

WEEK 1

Monday consisted of an induction alongside five Harvard medical students who were also starting their 6-week paediatric placement. This was their last rotation before sub-internship so they were already playing an integral role in the medical team; from admitting/discharging patients to carrying pagers and going on-call. We were soon to discover the same was expected of us which was a bit out of our comfort zone to say the least! I was also given an iPad for the 6 weeks which had a Twitter account already set-up for me. The plan was that every evening a question would be tweeted and we had 24 hours to re-tweet an answer. My first rotation was respiratory medicine or pulmonology as it's called there. The week mainly consisted of outpatient clinics which varied from immunology to sleep disorders. Patients flew from all over America to attend these clinics so I got to see several rare disorders that I probably won't see again soon. The professor of paediatrics, Dr Kinane, is a UCD graduate so he was helpful at easing me into the new system. Teaching sessions took place each day.

"These included a 'simulation' tutorial where we worked as a team managing emergencies on an eerily realistic doll. The doll had pulses, breath sounds and could even vomit! "

On Friday, the students on placement in other hospitals came to MGH for lectures. These were pretty interactive which was a bit daunting. As it turned out we were all roughly on the same level. A large portion of the Harvard students final grade rested on the evaluation of their involvement in rotation so they were all very driven and vocal when it came to questions. UCD has a strong emphasis on clinical examinations and OSCEs which stood to us in the practical tutorials.

WEEK 2

I spent Monday on pulmonology again, having missed the first Monday for induction. As it was my second week the bar was raised and I was sent to do a consultation on a new-born with a rare interstitial lung disease. It was meant to be an evaluation day but, being near the start, I don't think expectations were too high. For the rest of the week I got to choose a speciality of interest. I chose to attend the Massachusetts Eye and Ear centre on the ENT service. My schedule was busy so while I attended most clinics, I didn't get to scrub into the surgical theatre. However, I got to perform a small part of a bronchoscopy which was a milestone! One of the surgeons mentioned he will soon be pioneering a new surgery involving a hypoglossal nerve transplant. On Friday, it was our turn to move for lectures so we got to finally make the trip out to Harvard Medical School.

WEEK 3

This week I was assigned to the paediatric intensive care unit. This was a very different experience to my two outpatient weeks. We were each put in charge of a patient. We were responsible for following up on consults and test results and ultimately formulating a management plan to present to the team. To manage this required leaving the house at 5:30 AM to have the time to check on the patient before rounds. Initially, we felt that the nurses would be better off paging the resident or a 'real doctor' with requests, or that the parent's questions would be better directed elsewhere. Still, by the end of the week, as we got to know our patients better, we definitely felt more confident. Here I witnessed my first 'code' which ended in an emergency intubation and was a distressing event for the whole team. At the end of the week, it was time to make the journey out to campus again for lectures.

WEEK 4

For the second block of three weeks I was assigned to the general paediatric ward. Here I saw patients with a wide variety of conditions. Some patients I had seen in the intensive care unit had been transferred to the general ward and it was a nice continuity-of-care to see them improving. I followed several patients over the week including a teenager with Tourette's syndrome and boy with an invasive cholesteatoma. When the team learned I was interested in surgery they organised for me to attend the removal of the cholesteatoma.

"Rounds occurred similarly to the intensive care unit but with slight differences. I was a bit rusty at the start accidentally printing a 104-page article out on prescription paper!"

I was also tasked with researching any questions posed on rounds and then presenting my findings to the team the next day.

WEEK 5

I survived my first-night on-call which was actually extremely enjoyable. Without the distraction of tutorials and rounds breaking up the day I was able to keep track of patients in the emergency department that were ready to be admitted and I got to be the first team member to assess several patients. I gained more confidence in presenting on rounds and was more comfortable making a plan on the spot without having it pre-prepared. Towards the end of the week, there was a change-over and I was the only longstanding member on the team so I was asked a lot of questions about the in-patients... no pressure. On Friday, we travelled out to the Brigham and Women's Hospital instead of attending lectures. Here we did a day of emergency simulation tutorials that were very beneficial. During our stay, we were temporarily assigned to an academic 'house' that met up weekly. We had a final extended meeting at the end of this week which took place in the 'Harvard Gardens' with several lecturers in attendance. I found this to be an interesting tradition.

WEEK 6

I spent Saturday on call for the day shift but, being that it was my last week, I got to leave early. We also got half of Monday to attend the Boston marathon, which I did. We had a review session on Wednesday to help the Harvard students prepare for their exam. It was useful for us and I found there was a lot of repetition, suggesting I must have learned something over the course of the rotation! Thursday was our last day and it was business as usual up until mid-day when we had to reluctantly hand back our iPads and not-so-reluctantly our pagers. We then attended a graduation for the other students who were at the end of their clinical training. Afterwards Dr Kinane invited Robbie and I out for dinner. It was an enjoyable evening, hearing all about UCD back in the day when John B. Coakley was an anatomy lecturer and not just the name of a medal. The next day I got a tour of the campus dormitories and then Robbie and I bought the obligatory Harvard sweaters to mark our time there. The rotation was an invaluable experience and I've taken a lot more from it than I ever expected. I would definitely do it again.

I couldn't write this without thanking everyone in the UCD international office for providing me with this unique opportunity. I would encourage anyone to put themselves out there if a similar opportunity arises for them in the future. You won't regret it!

Bereavement & Studying Medicine *In Memory of My Mother*

Written by Darren O'Gorman

UCD School of Medicine,
University College Dublin, Belfield, Dublin 4.

My mother Ann died on the 29th of August 2005 in the Intensive Care Unit of St. Vincent's University Hospital. She was 38 years old and left behind a husband and four children. Her illness was short, she had no idea that she was dying; these are both comforts.

At the time, the situation made me feel helpless, but in the days, months, and eventually years that have since passed, this helplessness has slowly chipped away. It has steadily eroded as my life has transformed and advanced in a way that it maybe always would have. As this time passes, I have felt an increasing urge to mark the significance that my Mother had and continues of have on my life.

Mam died on the Monday before the end of summer holidays and Dad wisely suggested that returning to school as normal was in our best interests. Returning to school would enforce some level of normality to our lives that were upset by such a significant loss.

I don't remember the transition back to school feeling particularly laborious. That is, until we came to Patrick Kavanagh's poem "In Memory of my Mother" in class. I could sense a palpable discomfort within the room as we turned to the page and read the title. The teacher called on a classmate to read the words aloud. As he did, I felt hot, salty tears begin rolling down my cheeks. I got up and left the room to compose myself. The class as a whole felt more comfortable to fail to acknowledge what was happening.

In the poem Kavanagh paints a picture of the warm affection he had for his mother. Although I share this sentiment, this is the only comparison I can draw between my Mother and his. My Mam was not the type for "second Mass on a summer Sunday." However, the poem and my encounter with it still stick out in my memory. It marks a time when I had to publicly acknowledge the grief of having lost Mam.

While this was an upsetting occurrence, I'm not particularly resentful of the teacher for choosing to cover the material as normal. The experience prepared me for the many other instances like this in my personal and academic life, particularly since starting graduate medicine this past year.

Acknowledging the loss of my Mother is something I forced myself to consider when pursuing a medical career. It would be disingenuous of me to suggest that her loss didn't affect my choice to study medicine. However, I also greatly enjoy science and how it forms the tools of medical understanding. Still, I fully expected that there would be – and will be – many more experiences like the reading of Kavanagh's poem. When I started at UCD, I went to bereavement counselling for the first time, to try and mitigate some of the exposure to my loss that I believed lay ahead. It surprises me that after ten years, acknowledging the loss of Mam still inspires similar feelings to hearing Patrick Kavanagh's poem read aloud in class that day.

I was perhaps unprepared for just how often this acknowledgement would occur. During first year, it seemed that every time cancer was mentioned, the particular and quite rare cancer that Mam died from got a mention. I quickly learned that this makes logical sense from a medical perspective. The cancer she had is predictably caused by a particular agent, a prime learning example for budding doctors. It was also oddly comforting to learn that this type of cancer is reliably fatal. This helped me appreciate that regardless of when her cancer was detected, there was actually nothing at all that could have been done to prevent her death.

With the prospect of hospital work ahead, I have also given thought to the potential for me to end up practising on the ward where she died. I hope that, similar to hearing that poem in my Junior Cert year, the experience will in some way be constructive.

These reminders I have had in the pursuit of my medical education along with the significant milestone of ten years since Mam died have moved me to write this tribute. The tribute that I can offer my Mother is not a romantic description of her daily goings-on as Kavanagh did for his. Instead, my tribute is to appreciate that the presence of my Mother in my life has shaped it so much more than her loss ever will. The friendship that I had the privilege of sharing with her has given me all that I will achieve. The qualities that she valued and encouraged in all of her children are what have given me the ability to cope with her loss. The actions of the husband she left behind, my Dad, gave example to us on getting through. The resilience we as a family have shown together means that I almost take these actions for granted. Her qualities in all of us that inspired this resilience would have been nothing without Dad's example.

Many years have passed, as will many more. As a doctor, I will likely witness many losses just like mine. There will be more times I'll be reminded that I've lost her. But this is all part of her tribute that I live every day.

DISSECTION

Rory Plant

1

I need you in your threes and fours!
Around this table gather!
This Lab is private,
LOCK THE DOORS!
Come meet our dear cadaver.

Your clinical skills aren't up to scratch,
(You've only started Med),
But I assure you that I've double checked,
This man is truly dead.

2

Nervous laughter is what I hear,
From my jokes and darkened wit,
But in your eyes I see that morbid fear.
Ignore. Let's get on with it.

Remember we are scientists,
Pursuit of knowledge is our mission,
So before we begin our captains log,
ASSUME ANATOMICAL POSITION!

On second thoughts I've changed my mind,
(This move is quite the stunt)
I'll grab his head, you grab his legs,
And lets flip him on his front!

3

Most wonderful, most wonderful!
Are we ready to begin?
Take the scapels in your hands,
And lets incise the skin!

Observe as I reflect these layers,
I hope you're keeping track!
Gently peel it all away and...
Voilá! The structures of the back.

Are you ok boy?
Lost in thought? Thinking about life?
That reflection's for a different course,
Now hand me down the knife.

4

With Traps our man could questions shrug,
With Lats, a high wall climb,
Note the wonders of the rotator cuff,
Be quick! We don't have time!

Lets turn our man back again,
Be gentle, not too rough,
Oh do stop sobbing my dear boy.
Be calm like me, stay tough!

We don't have time to catch our breath,
To stop and pant our tongues,
Lets open the chest cavity,
To meet our friends the lungs.

5

The lungs look small, but take a breath,
(And please ignore the smell),
For its only when they're filled with air
That these spongy sacks do swell.

'Yes, see they're discoloured black,
And that tells us of this bloke,
Coupled with his yellowed nails,
I believe this man did smoke.

6

I digress! We must not stop!
Look sharp, don't miss a beat!
Our next stop along our quest,
The heart- Oh what a treat!

The heart is the source of love,
At least you have been told,
But such a claim, it is näive,
It is a muscle not of gold.

Note these chambers and their walls,
They pumped blood and they pumped life,
It beat faster when he was under stress,
Or spellbound by his wife!

C

7

Oh don't look so upset my boy,
Dejected and forlorn,
You are disrupting the whole class,
Now stay or go and mourn!

Lets dive into the abdomen,
Explore the inner treasure,
If only we had sufficient time,
To examine at our leisure!

8

The liver is a solid blob,
Much larger than you'd think,
But we have this talented mass to thank,
For enjoying the odd drink.

But this man here, I would predict,
Was no stranger to the bars,
Look at the surface of his liver,
Its covered all in scars!

T

9

Lets trace along the digestive tract,
It's long you must admit,
It assimilates all that food you eat,
And turns it into shit!

No need to look so disgusted boy,
You should be more forgiving,
I'm sure our man would agree with me-
Shit happens to the living!

Yes it is a dirty thought,
So what keeps the body clean?
I'll give you all a cheeky clue,
It's shaped quite like a bean!

10

The kidneys are a selfish pair,
They're misers for the salt,
But all these cysts could've killed our man.
And brought him to a halt.

Alas we must finish now,
Our privilege must end,
We could not cover everything,
Next year we shall amend.

I

11

Why so ashen, my dear boy?
You're really quite a state,
But you know you cannot drop this class.
Can you not accept your fate?

'I've no problem with 'my fate',
And my interest has now doubled.
But there's still alot I do not know,
And that is why I'm troubled.'

O

12

'There is a cure for that, my boy
You only have to ask,
So don't delay and quiz away,
I'm equal to the task!

I'm sorry sir, forgive me sir,
But I must admit to my great shame,
I know this person inside out,
But I don't even know his name.

The students of the UCD School of Medicine deeply appreciate the generous donations made through the body donation program. These donations allow teaching and research in medical science and the training of the next generation of doctors, radiographers, nurses and physiotherapists.

The School is eternally indebted to the many individuals who chose to donate their bodies to clinical education and their families who support this generous gift. Each year, the UCD School of Medicine holds memorial services to honour and thank family and friends for their sacrifices.

N

Lending criteria, terms and conditions apply to all credit cards. Credit cards are subject to Government Stamp Duty of €30. Credit cannot be offered to anyone under 18 years of age. Bank of Ireland is regulated by the Central Bank of Ireland.