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Contact Details: All enquiries on submissions, subscriptions, permissions and advertising to the Editorial Office, The Ulster Medical Journal, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. United Kingdom.
T/ F: +44 (0) 28 9097 5780 **E:** umj@qub.ac.uk **W:** http://www.ums.ac.uk/journal.html

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Guest Editorial

The Physician's Duty to Warn Their Patients About the Risks Associated with Medical Intervention: A Review and Discussion.

CG Leonard and JG Toner

Key words: Medicolegal; Consent; Ethics

ABSTRACT

Since the landmark case of Montgomery v Lanarkshire in 2015[1], much has been written in medical press regarding the implications for medical practice. The moral duty - varied though it has been over this time, has been discussed since the earliest days of the medical profession. The law has sought to define this duty in response to changes in society, and the nature of the relationship between doctor and patient. The moral and legal duty are intrinsically linked, but the latter must surely follow the former for "the law has little to do with morally required forms of communication in the clinic and in the research environment."[2] The common law nature of this process has resulted in an inconsistent and often tortuous path as societal standards have shifted. Accordingly, the ultimate definition of the legal doctrine, "informed consent," has changed since its relatively recent entry into the medicolegal vocabulary. These parallel shifts in the legal and moral duty to disclose risk have resulted in a confusing melee of evidence and recommendations for clinicians. We address the development of the law of "informed consent," as the legal mirror of the moral duty upon a clinician to disclose risk to their patient.

FROM DECEPTION TO CONSENT!

In Ancient Greece during the 4th Century BC, in the Hippocratic writings, patient involvement in decisions surrounding their treatment was considered undesirable. Physicians should inspire confidence; the discussion of risk was felt to erode confidence and even cause psychological harm.[3] On this basis the role of deception remained key to the doctor patient relationship during medieval times. Doctors at this time sought to offer comfort and hope whilst being manipulative and deceitful to affect a treatment or cure.[4]

Even as recently as the 18th and 19th centuries the majority of medical literature advocated avoiding disclosure of any information that may upset and thus harm the patient.[5,6] It was only in the early 1900's that this view began to change. In 1912, *Luka v. Lowrie,* [7] examined a case where a child underwent emergency amputation of a crushed limb. The parents were unavailable and the surgeon, prior to carrying out the procedure, consulted four other physicians. Each concurred with his medical opinion and the proposed course of action. The court ruled that had the parents been available, they would have agreed with the need for the amputation on the grounds of the multiple opinions sought. The "professional test," (later given the eponymous name "Bolam,") was born, and reflected the ongoing paternalistic nature of health care. Just two years later Justice Cardozo stated in *Schoendorff v. Society of New York Hospital,*[8] "every human being of adult years in sound mind has a right to determine what shall be done with his own body." In one sentence, so much of what we now consider normal practice was expressed. Justice Cardozo set the scene for the significant changes seen in the pursuit of patient autonomy during the 20th century.

The duty to disclose risk was subsequently deemed a part of the duty to disclose the nature and consequences of the planned treatment.[9] The moral duty between the doctor and the patient, was now encapsulated legally by two questions. Firstly, was there consent? Secondly was it adequate, or "informed consent?" In the same year as Schoendorff was decided, the courts in the United Kingdom heard *Bolam v Friern HMC* and brought about the eponymous test of consent, dependent upon the body of medical opinion. Despite this, more than twenty years passed before "informed consent," became part of the vocabulary of the English courts.[10] On both sides of the Atlantic, consent to surgery was now no longer, merely a consent to technical assault, but a consent based on a knowledge of the nature, risks and benefits of the treatment. Consent had been imposed upon a medical profession by the judiciary. Ironically, just as the paternalistic approach adopted by the medical community reduced the autonomy of the patient, these rulings were viewed as a reduction in the autonomy of the medical profession. It is perhaps not surprising that the response from the medical profession was critical. At this time there was limited judicial guidance or precedent to establish the legal definition of "informed consent," or indeed what actions by a doctor would satisfy the requirements of the courts. What little common law that did address this point was articulated in such broad terms that it did nothing to dissuade the view that the demands of informed consent were considered clinically impossible.[11] Legally, morally and clinically, there was then as now great uncertainty surrounding the practicalities of risk disclosure.

DEVELOPMENT OF THE LEGAL DOCTRINE: "INFORMED CONSENT."

Sidaway v. Governors of Bethlem Royal Hospital[12] afforded the House of Lords the opportunity to address and examine consent and the doctor's duty to disclose. The plaintiff underwent a spinal cord decompression for neck pain, and suffered paralysis the risk of which was established as at less than 1%, but about which she had not been informed. The House of Lords, judged that negligence was the most appropriate means by which to regulate a physicians duty to disclose information to their patients. The standard of care was predicated on professional practice but Lord Scarman, dissenting, introduced the possibility of the needs of the hypothetical 'reasonable patient.'

Subsequently in *Blyth v. Bloomsbury*[13] the Court of Appeal found in favour of the respondent based solely on professional practice approach but noted that some risks were so central to the decision-making process, that no reasonable doctor could withhold the information. *Bolitho v. City and Hackney Health Authority*[14] expanded upon *Blyth* that all expert evidence must stand up to logical analysis. These two conditions now established the parameters of the professional test, but neither increased patient autonomy.

Chester v. Afshar,[15] examined a case where the plaintiff having undergone spinal surgery, suffered cauda equina syndrome. She had not been informed of such a risk; which occurred in approximately one to two percent of cases. It was deemed that the plaintiff would have considered and pursued alternatives had she been made aware of this risk. A duty to disclose a "small, but well established, risk of serious injury or as a result of surgery," entered the medicolegal field in support of patient autonomy. The General Medical Council (GMC) referenced *Chester* in its guidance on consent published in 2008[16] and recommended that patients should be told of any possible significant adverse outcomes of a proposed treatment. In doing so the GMC advanced the cause of patient autonomy and patient centred decision making (whilst rescinding medical paternalism), ahead of the courts. The GMC guidance explained the need to listen, discuss, share knowledge and to maximise the opportunity for patients to decided for themselves. The GMC also supported the position that consent was a process rather than an event.[17] This wide ranging and detailed guidance on consent, has subsequently been reinforced within the broader GMC document, Good Medical Practice.

It was in this environment, that majority of current junior doctors have entered the profession, and thus will have been taught the shared model of decision making, that the role of the courts re-emerged. In the well-publicized case of *Montgomery v. Lanarkshire Health Board*, the plaintiff, whose son was delivered vaginally, was not aware of the increased risk of the significant complications the child suffered as a result of a vaginal rather than caesarean delivery. Her obstetrician had not disclosed the increased risk of shoulder dystocia and cerebral palsy owing to the plaintiff's stature, and diabetes.[18] The Supreme Court found in her favour, rejecting the majority opinion of *Sidaway* and instead bringing the dissenting view articulated by Lord Scarman to the fore. In doing so they established that patients should be told that which they would wish to know. The GMC, who intervened to make submissions as an independent party, were quick to clarify that this simply brought the law into line with the guidance already in place. However, just as followed the *Salgo* decision and in light of the changing environment of medical practice in the 1970s and 1980s, the response of the medical profession was varied its members voiced concern about the implications for clinical practice.[19]

THE CURRENT POSTION

The prudent patient or "reasonable person in the patient's position," test recognises that non-medical factors can affect the patient's decision. It enhances the patient's autonomy and revokes medical paternalism. The clear moral duty existing between doctor and patient is now supported by a clear legal and professional duty to disclose risk.

The ruling in *Montgomery* sought to clarify further issues relating to clinical practice. Firstly, that materiality cannot be measured as a percentage alone. The nature and effect of the risk, the benefits of treatment and any available alternative treatments are all relevant to an assessment of materiality. Secondly, and as a result of the aforementioned approach to materiality, there is now an established duty on doctors to engage in dialogue. Without dialogue between doctors and their patients, it would appear difficult, if not impossible, for a medical professional to comprehensively assess materiality for an individual.

Despite these clarifications the term "material risks" remains ambiguous to both legal and medical professionals. Post-Montgomery cases have been wide-ranging in nature and have done little to provide definitional clarity to "material risks." Such cases have frequently been dependent on factors beyond mere percentages of risk provided by expert evidence. Subsequently the test of materiality was further broadened as doctors were deemed to not be liable for every omission to which a patient subsequently complains.[20, 21] It seems reasonable to assume, that this uncertainty will be clarified as the common law position advances in the coming years. The prudent or reasonable person test, is currently open to interpretation. Until the test is clarified and refined, it may for a time obfuscate the approach to medical negligence cases. Although this uncertainty, combined with the paucity of such cases that currently find in favour of the plaintiff, is invariably of concern to practicing clinicians.

How then to proceed clinically? It is hard to imagine a valid means within medical practice of auditing the wishes of patient and population groups regarding disclosure of risk – consider for instance the challenge of simulating the position of the patient being given bad news or being offered surgery. *Montgomery* reinforced the current GMC guidance in relation to the nature of consent as a process, rather than an event.

Steps should be taken to reinforce and facilitate patient-led control of the amount of information they receive - (an exhaustive consent should not be mistaken for an informed consent.) The initial discussion with a clinician should be guided by the patient's wishes, but each patient should be provided other means of gathering information (such as through leaflets or websites) and they should be made aware that their consent can be revoked at any time prior to the procedure.

Mr. CG Leonard, ST7 in ENT, LLM Medical Law and Ethics and Mr. JG Toner, MA Medical Ethics and Law.

Department of Otorhinolaryngology – Head and Neck Surgery, Royal Victoria Hospital, Belfast

E-mail: mrcgleonard@gmail.com

REFERENCES

1. United Kingdom, Supreme Court. *Montgomery (Appellant) v. Lanarkshire Health Board (Respondent) (Scotland)*. Case ID UKSC AC 2013/0136. (11 Mar 2015). Available from https://www.supremecourt.uk/cases/uksc-2013-0136.html. [Last accessed November 2018].
2. Katz J. *The silent world of doctor and patient*. New York: Free Press; 1984
3. Murray PM. The history of informed consent. *Iowa Orthop. J*. 1990;10: 104-9
4. Southwick, AF. *The law of hospital and health care administration*. Ann Arbor. Michigan: Health Administration Press; 1988.
5. Percival T. *Medical ethics; or a code of institutes and precepts, adapted to the professional conduct of physicians and surgeons*. Manchester: S. Russell; 1803.
6. United Kingdom. English Reports. *Slater v. Baker and Stapleton*. 95 ER 860, 2 Wils. KB359; 1767.
7. United States. Supreme Court of Michigan. *Luka v. Lowrie*. July 11, 1912. 136 N.W. 1106, Michigan; 1912
8. United States. New York Court of Appeals. *Schoendorff v. Society of New York Hospital*. 211 N.Y. 215, 105 N.E. 92; 1914.
9. Caselaw: California. District Court of Appeal, First District Division 1, California. . 317 P.2d 170; 1957.
10. United Kingdom Queen's Bench Division 432. *Chatterton v Gerson*. QB 432; 1 All ER 257; 1981.
11. Kaufmann CL. Informed consent and patient decision making: two decades of research. *Soc Sci Med*. 1983; 17(21):1657-64.
12. United Kingdom. House of Lords. *Sidaway v Governors of Bethlem Royal Hospital*. 1 AC 871; 1985.
13. United Kingdom. Court of Appeal. Blyth v. Bloomsbury. AHA 4 Med LR; 1993.
14. United Kingdom. House of Lords. *Bolitho v. City and Hackney Health Authority*. AC 232; 1998.
15. United Kingdom. House of Lords. Appeal Court. *Chester v. Afshar*. UKHL 41 2004. , 1 AC 134; 2005.
16. General Medical Council. *Consent: patients and doctors making decisions together*. London: General Medical Council 2008. Available from: https://www.gmc-uk.org/-/media/documents/Consent___English_0617.pdf_48903482.pdf. [Last accessed November 2018].
17. United Kingdom. Supreme Court. *Montgomery (Appellant) v. Lanarkshire Health Board (Respondent) (Scotland)*. SC 11 [2015] 1 AC 1430; 2015
18. Sundar S. *Case based laws are turning into "emperors new clothes." Br Med J*. 2015. Available from: https://www.bmj.com/content/350/bmj.h1481/rr-23. [Last accessed November 2018].
19. Tyler F. *Supreme Court decision changes doctor-patient relationship forever*. Edinburgh: Balfour and Manson; 2015
20. United Kingdom. England and Wales High Court, Queen's Bench Division. *Spencer v. Hillingdon Hospital NHS Trust*. EWHC 1058; 2015.
21. United Kingdom. England and Wales High Court, Queen's Bench Division. *Mrs A v East Kent Hospitals University NHS Foundation Trust*. EWHC 1038; 2015.

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Guest Editorial

Our Digital Future -Encompass: Delivering Care Together

Dr Grace Cuddy, Dr Michael Quinn

Working as a junior doctor in Northern Ireland over the last five years I have been introduced to the interesting mix of systems we use to look after our patients.

From I first started working on wards on a F0 placement from Queen's University, Belfast, ringing GPs to clarify patients' medication lists, to spending an average of eight hours a week rewriting kardexes as an F1, the time consuming waste in the system was apparent. Initially I was an idealistic doctor, asking histories from patients before reviewing their voluminous chart as I was taught by senior clinicians, but the patients would often ask with disbelief 'Have you not looked at my notes?' Northern Ireland's Electronic Care Record (NIECR) was opened to F1s that year (2013), helping us understand a patient's history, medication and allergies, allowing a more informed discussion with patients and/or family where they could clarify rather than frustratingly tell anew. Although it had limitations, it was a vast improvement for information gathering and daily care, proving successful in a world where the best software can be poorly implemented.

As a junior doctor, every four-six monthly change of job is associated with weariness at the prospect of losing skills such as how to order, send and sign off investigations, what and where the local request forms and referral modes are and where to find filed notes. Not only are there expected variations between specialties but also between wards, hospitals and Trusts, which are sometimes difficult to understand. Whilst this variation may be justifiable in complex environments, for most patients and common conditions, the care pathways are similar and reduction in clinical variation tends to improve outcomes. Learning how your local clinical area works often takes more time and effort than caring for patients and it often feels that it reduces my efficacy as a doctor, despite constantly striving to gain clinical experience.

In F2 I was based on one of the first 'electronic' clinical areas in Northern Ireland. Now I could use clinical noting, read notes more easily, view nursing, pharmacy and allied healthcare professionals' notes in one record, use an across hospital task list and view referred patients on the 'take.' However, the entire note was printed on discharge and placed into a paper chart! In this small area of innovation clinics were redesigned, with small desks and cameras permitting fast 'single sign on' and the previous clinic letter used for background detail. However, when I moved to another clinical area, I could see from an alternative perspective how these different ways of working with patients could lead to frustration with this system, 'enforced' on them from elsewhere with little engagement or trial.

NIECR has enhanced the digital maturity of NI's healthcare environment, with improving functionality reaching over 18,000 users of which >96% find it acceptable. However, it is primarily a view only portal into multiple, disparate data silos. This system hides the many complexities of redundant and aging systems and allows HSCNI to keep moving. Many of these, including our patient administration systems, urgently need replacement, whilst NIECR itself will require re-procurement and platform upgrades after 2022. It cannot currently facilitate many of the recommendations of the Bengoa report, such as e-prescribing and telemonitoring[1].

Encompass is a HSCNI programme set up to facilitate procurement and implementation of a regional electronic health and care record. We will have one core solution which will allow care providers to note, prescribe, request, schedule and communicate in order to improve patient care, from the cradle to the grave. Clinicians will be able to order any test, referral or procedure anywhere in Northern Ireland, view and sign off investigation results, track task lists and handovers, document observations electronically from integrated devices, prescribe and administer medications and fluids (by bar code) and be aided by inbuilt clinical decision support.

This paper-lite environment will incorporate both acute and community sectors, enabling mobile working. Current systems within scope, not incorporated into NIECR, include theatre management, bed management and patient flow, pharmacy stock control, Child Health and maternity, emergency department notes, anaesthetics and ICU, mental health and social care. The vision would include allowing community pharmacists, dentists, opticians and independent care providers access to up to date patient information on encompass. The consistent coding and gathering of information will allow data reporting and analytics to improve and allow population health identification, screening and reporting.

The programme will run alongside infrastructure modernising, ensuring good governance and training, support and engagement of healthcare professionals. Engagement of end users is a vital factor for success, which the encompass programme has shown it's keen to do, including providing a fellowship post for NIMDTA's ADEPT clinical leadership

programme, involving both clinical and non-clinical professionals in inaugural Digital Care and Business Support Forums and a successful week of supplier demonstrations as part of procurement.

One of the most exciting features will be the patient portal, which will enable patient autonomy and encourage our HSCNI culture to become ever more citizen centred, consistent and cost effective. Our patients and clients will be able to manage their appointments and bookings, monitor referrals, view letters and results, manage medications, complete assessment forms and surveys, input health information from external technology i.e. blood sugars or fitness trackers. Relevant HSCNI appropriate educational lifestyle and disease-specific information will be available. Patient and public involvement has also been incorporated from an early stage in the process, including procurement, to ensure a satisfactory co-produced solution for all.

Make no mistake – this is different! This is not an optional system for the technologically interested or enabled user, encompass will be the primary solution for delivery of secondary and community care in Northern Ireland. Encompass seeks to deliver change in unison with all clinical staff in HSCNI, it is a way to accelerate the change in service delivery needed for HSCNI. Importantly, encompass is only an enabler for change, a facility with which clinical staff of all backgrounds reimagine and envision better ways to do their jobs in true partnership with engaged patients. Therein lies the challenge: encompass will succeed through direct involvement of the staff and patients who will ultimately use the system every day. We need you to help us design this system so get involved and help us in Delivering Care Together!

Dr Michael Quinn, Consultant Nephrologist, Belfast HSC Trust.

Dr Grace Cuddy, ADEPT Leadership Fellow, Health and Social Care Board.

Correspondence to: Dr Grace Cuddy, Grace.Cuddy@hscni.net

REFERENCES

1. Bengoa, R. *Systems, not structures: changing health & social care*. Department of Health Northern Ireland. Report number: 1, 2016. https://www.health-ni.gov.uk/publications/systems-not-structures-changing-health-and-social-care-full-report. Last accessed 5th December 2018.

LIST OF REFEREES FOR 2018

We pass on our sincere thanks to all our referees for 2018

Prof Tom Rogers	Dr Ian Menown	Mr Michael Harron
Mr Asif Oraksai	Dr Rory Convery	Dr Cian Collins
Dr Darren Monaghan	Mr Zola Mzimba	Dr Sanjeev Kamath
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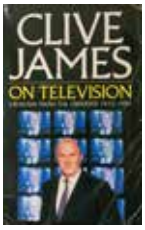
Dr Nicholas Hegarty	Dr Colin Prendergast	

Book Case

Professor Barry Kelly

CLIVE JAMES ON TELEVISION



Clive James. (Picador 1991. ISBN-13: 978-0330319744. Paperback OOP around £3.12)

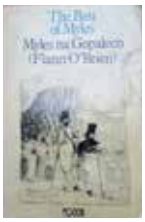
Between 1972 and 1982, Clive James was the Observer's Television Critic. This anthology is a compilation of his three earlier books of television criticism: *The Crystal Bucket; Visions before Midnight* and *Glued to the Box*. If you are old enough to remember the Three Day Week; Alias Smith and Jones; Nationwide; Dallas; The Liver Birds; Hadleigh; Sasha Distel; Little and Large; Morecambe and Wise and the whole cornucopia of three channel television, the memories will come flooding back. Reviewing one soap opera, he wrote, "I tuned in late as part of my usual preparation for tuning out early." Mr James reports both high and lowbrow culture with the same forensic gimlet eye but always accompanied by a raised amused eyebrow, describing Arnold Schwarzenegger as having a face that looked like "a condom full of walnuts" and Lisa Minelli as someone "who couldn't even walk up a flight of stairs sincerely". As the man himself said, 'I like to turn a phrase until it catches the light.'

FROM FIRST TO LAST

Damon Runyon. (Penguin Classics. New Edition 2001. ISBN-13: 978-0141184661. Paperback OOP around £5)

Runyon's beat was 1920's Broadway and its immediate precincts, in what he himself called 'The Hardened Artery' of New York. These are gloriously comic stories involving among other players, Hot Horse Herbie, Nathan Detroit, Sky Masterson, and Ambrose Hammer the theatre critic, as they try to win a buck, avoid the police and help the good guy get the girl (and vice versa). The stories are all told by the same anonymous narrator who always speaks in the present tense with a marvellous Runyonese lexicon. Typical gems include 'She has a laugh so hearty it knocks the whipped cream off an order of strawberry shortcake on a table fifty feet away, and 'I came to the conclusion long ago that all life is six to five against.' Men are 'Guys' and ladies, 'Dolls'. One of his best short stories *The Idyll of Miss Sarah Brown* became precisely that: *Guys and Dolls*. If Raymond Chandler had been designed by Groucho Marx, the result could well have been Damon Runyon. More than somewhat.

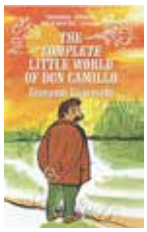
THE BEST OF MYLES



Flann O'Brien. (Harper Perennial Reissue Edition 2007. ISBN-13: 978-0007247189. Paperback RRP £9.99)

'The majority of the members of the Irish parliament are professional politicians, in the sense that otherwise they would not be given jobs minding mice at a crossroads.' Brian O'Nolan usually wrote under the pseudonym of Flann O'Brien, but for his Irish Times column, which ran between 1940 and 1966, he adopted the name Myles na gCopaleen, and his column was entitled *Cruiskeen Lawn* (The Little Full Jug). This book is a compilation of his finest work over many years and is quite simply a joy. In it, his virtuosity as a writer, wit, linguist and humorist is on full display. Creations such as The Brother, Keats and Chapman and The Cruiskeen Court of Justice. His column was serendipitously published in harmonious synchrony with J.B. Morton's *Beachcomber* in the Daily Express. Inventive, irreverent and gloriously funny he often insulted and pointed arrows at the adjacent columns, especially the editorials written by the long-suffering R.M. Smyllie. If that fictitious Ambassador ever ran out of Ferrero Rocher bon-bons and served up literary bon-mots instead, this is what he would use to spoil his guests.

THE LITTLE WORLD OF DON CAMILLO



Giovanni Guareschi. (Pilot Productions Ltd 2013. ISBN-13: 978-1900064071. Paperback RRP £11.99)

In the introduction, Guareschi tells us that this is a special place. "Here, the deep eternal breathing of the river freshens the air for both the living and the dead, and even the dogs have souls." These are the charming stories, set in Italy's post-war Po valley, where the priest, Don Camillo looks after his simple flock whilst waging perpetual war with his communist nemesis, the Mayor Peppone. Christ on the Cross in his little church watches over them all. However, gentle reader, know this: both fought together as partisans during the war and there is a bond between them that can never be broken. In his preface, Guareschi concludes, "And one final word of explanation before I begin my story. If there is a priest anywhere who feels offended by my treatment of Don Camillo, he is welcome to break the biggest candle available over my head. And if there is a Communist who feels offended by Peppone, he is welcome to break a hammer and sickle on my back. But if there is anyone who is offended by the conversations of Christ, I can't help it; for the one who speaks in this story is not Christ, but my Christ - that is, the voice of my conscience." Once you step into this little world, you will never wish to leave it.

THE COMPLETE SHORT STORIES OF AMBROSE BIERCE

Ambrose Bierce. (CreateSpace Independent Publishing Platform 2017. ISBN-13: 978-1975940164. Paperback RRP £9.98)

Bierce's work is generally divided into three: his Civil War stories; Ghost Stories and *The Devil's Dictionary*. The latter is every bit as irreverent as its name suggests. The Ghost stories are chilling and the Civil War stories harrowing, evocative, and graphic. Perhaps the most

famous is *An Occurrence on Owl Creek Bridge,* the story of a soldier who is about to be hanged when a sharpshooter cuts his noose and he dives off the bridge into a river, thus escaping. It's a really short story with a big twist; the sort of device for which Bierce is justifiably famous.

Bierce fought on the Union side and his contemporary Mark Twain, the Confederate. Twain remarked that he was eventually discharged "with exhaustion, brought on by persistent retreating." Both were haunted by the war, but Bierce's proximity to the carnage is graphically recalled in his stories. In *Chickamauga,* a baby crawls off into the woods away from his farm but when he returns, the farm has been burnt down and his parents are dead. The baby's descriptions of their remains, told with a toddler's inarticulate incomprehension, are heart-stoppingly graphic and ultimately heartbreaking. They also reveal that the author has seen these things for himself and can't forget them.

COSMOS

Carl Sagan. (Abacus New edition 1983. ISBN-13: 978-0349107035. Paperback RRP £12.99)

Cosmos the book was derived from the eponymous TV series that older readers doubtless remember. Sagan takes us on a journey from the origins of time and space through history, discoveries, human thought and folly. In a sense he 'pulls back the curtains' and beckons us to peek out with him into the vastness of the universe.

Carl Sagan was a polymath, but one with a singular gift for explanation. The concepts he presents are tricky to say the least, but he puts so much care into the choice of the perfect word for each occasion that the mists actually do clear. His descriptions of The Milky Way as 'The Backbone of Night' and humanity as 'One Voice in the Cosmic Fugue' are sheer poetry. Later in *Pale Blue Dot*, he describes our tiny earth, photographed by Voyager as it passed Saturn, as "A mote of dust, suspended on a sunbeam."

THE HITCH-HIKER'S GUIDE TO THE GALAXY

Douglas Adams. (Pan 2016. ISBN-13: 978-1509808311. Paperback RRP £8.99)

"I think you ought to know I'm feeling very depressed" moans Marvin the paranoid android. "Here I am, brain the size of a planet, and I'm parking cars." The five parts of this trilogy follow Arthur Dent and his old friend Ford Prefect (not from Guilford, as Arthur had been led to believe, but from a small planet in the vicinity of Betelgeuse) as they look for the ultimate answer to Life, the Universe and Everything. Our heroes leave earth, a small insignificant planet in the *unfashionable* western spiral arm of the galaxy, seconds before it is demolished to make way for a hyperspace bypass. Our heroes visit the legendary planet of Magrathea, meeting the mice, Slartibartfast, Zaphod Beeblebrox the two-headed galactic president and consummate wide-boy, Marvin and Tricia McMillan. As Arthur sighs wearily at one point, "Is there any tea on this spaceship?' If you haven't read this, it won't make sense. If you have, you'll be smiling already. *Don't Panic* and *Mostly Harmless* will never read the same. Just remember to bring your towel.

Game Changers

ADVANCES IN LAPAROSCOPIC PANCREATIC SURGERY

Mr Gareth Martel, Mr Gareth Kirk, Ms Claire Jones

Department of Hepatobiliary Surgery, Mater Hospital, Belfast BT14 6AB

Distal pancreatectomy involves removal of the tail and body of the pancreas, with or without the spleen. The number of distal pancreatectomies performed in Northern Ireland has been increasing over the last number of years, in no small part due to the increasing number of incidental lesions detected radiologically. Additionally there is now recognition of the potential for malignant transformation within certain cystic tumours.

Traditional distal pancreatectomy involves an open procedure with a laparotomy via rooftop incision. Recent developments in laparoscopic technology, in particular laparoscopic energy devices for dissection and staplers for dividing the pancreas, have enabled surgeons to develop techniques for performing distal pancreatectomy with a minimally invasive approach[1]. A Cochrane review found that the laparoscopic approach was associated with a 2.43 day reduction in length of stay (MD -2.43 days, 95% CI -3.13 to -1.73), with no other statistically significant differences, although it should be noted that this was based on observational studies [2].

Where laparoscopic distal pancreatetectomy was previously a novel approach, In Northern Ireland it is now first choice in all patients if technically feasible. Where to next? Around the world laparoscopic and robotic Whipples procedure is the new novel technique - watch this space!

1. National Institute for Health and Clinical Excellence. *Laparoscopic Distal Pancreatectomy*. 2007. http://www.nice.org.uk/guidance/IPG204

2. Riviere D, Gurusamy KS, Kooby DA, Vollmer CM, Besselink MGH, Davidson BR, van Laarhoven CJHM. Laparoscopic versus open distal pancreatectomy for pancreatic cancer. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD011391. DOI: 10.1002/14651858.CD011391.pub2.

WILL SGLT2 INHIBITORS PROVE TO BE A 'MULTIPLE' GAMECHANGER?

Authors: Dr Noel Sharkey, Prof Peter Maxwell

Regional Nephrology Unit, Belfast City Hospital, Belfast BT9 7AD

Type 2 diabetes (T2D) causes microvascular and macrovascular disease[1]. Diabetic kidney disease is the leading cause of end-stage renal disease worldwide and associated with significant cardiovascular morbidity and mortality[2].

The kidney plays an important role in glucose homeostasis. The proximal tubule employs two sodium glucose co-transporters for glucose reabsorption from glomerular filtrate – SGLT1 and SGLT2. SGLT2 accounts for 90% of glucose reabsorption and is markedly upregulated in T2D. This, along with other renal and extra renal mechanisms, contributes to the persistent hyperglycaemia seen in T2D, making SGLT2 a pragmatic drug target[3].

SGLT2 inhibitors (empaglifozin, canaglifozin, dapaglifozin) are approved for treatment of T2D. Improved glycaemic control is achieved by reducing renal glucose reabsorption with a resultant increase in urinary glucose excretion[3]. The US FDA has mandates that new oral T2D medications undergo clinical trials to assess cardiovascular safety[4]. The EMPA-REG OUTCOME trial demonstrated the cardiovascular benefits of empaglifozin (versus placebo) in patients with T2D with established cardiovascular disease[5].

SGLT2 inhibitors may have other benefits including weight loss, lower blood pressure, reduced levels of serum uric acid, improved lipid profiles, lower plasma volume and decreased albuminuria[3]. The EMPA-REG OUTCOME trial also reported long-term renal effects of empaglifozin in patients with T2D and established cardiovascular risk. Patients who received empaglifozin, in addition to standard care, had a significantly lower risk of progression to macroalbuminuria, doubling of the serum creatinine level and initiation of dialysis compared to placebo, although renal death and incidental microalbumunuria were not affected[4].

The renoprotective effects of SGLT2 inhibitors are attributed to their ability to reduce renal hyperfiltration, by vasoconstriction of the afferent arteriole resulting in reduced intraglomerular pressure[5]. The renal benefits seen in the EMPA-REG OUTCOME trial may be due to the combined reduction in intraglomerular pressures as a result of SGLT2 mediated vasoconstriction of the afferent arteriole and RAAS drugs vasodilating the efferent arteriole[4]. A subsequent trial, CANVAS-R has demonstrated the renal benefits of canaglifozin over placebo in patients with T2D and heart disease, albeit with an increased risk of amputation[6].

SGLT2 inhibitors have been shown to be safe. Genital and urinary infections are the most frequently reported adverse effects, associated with the increased urinary excretion of glucose[3]. SGLT2 inhibitors are not associated with significant hypoglycaemia[7]. Some cases of euglycaemic diabetic ketoacidosis have been reported, but this is less of a concern in T2D[3]. Nephrologists are studying whether SGLT2 inhibitors can slow progression of chronic kidney disease while cardiologists are interested in these drugs to improve heart failure outcomes. SGLT2 inhibitors may be a useful treatment of diverse medical conditions.

1. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;**375**:2215-22.

2. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, De Boer IH. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol*. 2013;**24**:302-8

3. van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, van Raalte DH. SGLT2 inhibition in the diabetic kidney—from mechanisms to clinical outcome. Clin J Am Soc Nephrol. 2017;12:700-10

4. Department of Health and Human Services, Food and Drug Administration. Guidance for industry: diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available at: hwww.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances. Last Accessed 27/4/18.

5. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J*. 2016;**37**:1526-34.

6. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;**377**:644-57.

7. Rosenstock J, Vico M, Wei LI, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care*. 2012;**35**:1473-8.

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Grand Rounds

Oesophageal Stents for Potentially Curable Oesophageal Cancer – A Bridge to Surgery?

Jennifer E Tham[1], Benjamin Tharian[2], Patrick B Allen[1], Gary Spence[1], Tony C Tham[1]

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ABSTRACT

For oesophageal cancer patients with potentially curative disease, treatment usually comprises neoadjuvant chemoradiotherapy followed by surgery. Several methods are currently used for nutritional support while patients are undergoing neoadjuvant treatment but these do not relieve dysphagia. Stenting as a bridge to curative surgery has been explored in several case series and a case control study. This is a review of the current literature on the topic. Some small series have shown it to be safe and effective in relieving dysphagia and malnutrition without adverse effect on surgical outcomes, perioperative complications or delay in surgical resection post neoadjuvant therapy. However, there are sufficient concerns about its adverse impact on oncological outcomes such as a reduction in the R0 resection rates, median time to recurrence and 2 - 3 year overall survival, to not currently recommend its routine use in resectable cancers.

INTRODUCTION

For patients with potentially curative oesophageal cancer, there is a risk that a compromised nutritional state can extend through the period of tumour staging to the commencement of neoadjuvant treatment, leading to treatment delays, poorer response and an adverse impact on the long term prognosis and surgical outcome[1].

Several methods are currently used for nutritional support. These include enteral feeding via nasogastric or nasojejunal tubes, percutaneous gastrostomy (PEG) and jejunostomy (PEG-J) tubes, parenteral nutrition via central venous access, as well as aggressive oral supplementation under dietetic review[1-4]. All of these methods have significant limitations as they do not relieve dysphagia, which decreases quality of life. In addition, there is the risk of aspiration pneumonia, surgical compromise of the stomach, dislodgement and risk of central line infection and thrombosis, thrombophlebitis, liver failure and prohibitive cost of parenteral nutrition[2].

The concept of employing stents (partially or fully covered self-expanding metal stents (SEMS) or plastic/biodegradable) as a *'bridge'* to curative surgery has been explored in several case series and a case control study[5-8]. The principle is that the stent will relieve or improve dysphagia allowing an increase in oral intake, an improvement in nutritional status and possibly surgical outcome. There is a general reluctance to stent operable candidates, possibly due to poor knowledge about outcome, which is why we decided to review the literature.

METHODS

We included only articles on the use of oesophageal stents in operable cancer in the main discussion, though references have been occasionally made to others when there was no relevant information available. Scientific papers published between 1990 and 2015 were searched for in PubMed, EMBASE, Cochrane Library and Medline; the key words were (o) esophageal stent, surgery, resectable cancer and (o)esophageal cancer. In addition, a search of the references within papers was made to identify other studies. English and non-English sources were reviewed, though the relevant studies included were all in English. Manual searching was also done. Grey literature including non-indexed journals, proceedings and posters from international meetings were also included in the initial review. Two independent reviewers (TCKT and JEJT) scrutinised all the studies with regards to the inclusion criteria and quality. The overall results were assessed by all authors for their robustness and conclusions were discussed to avoid any bias before arriving at a consensus.

RESULTS

We identified 15 studies that evaluated the role of stents as a bridge to surgery [3-5, 9-21]. Three systematic reviews were also available. There are several key questions to be addressed with regards to oesophageal stents being used as a bridge. We have tried to critically review these studies and discuss each question in this context.

WHAT IS THE EFFICACY OF OESOPHAGEAL STENTING IN RELIEVING DYSPHAGIA?

Dysphagia is the commonest indication for stenting this subgroup of patients, being the predominant indication in up to 95% of patients in some studies[5]. It is important to evaluate

1. Division of Gastroenterology and Surgery, Ulster Hospital, Belfast; Northern Ireland
2. University of Arkansas Medical Sciences, Little Rock, USA.

Correspondence to: Dr Tony Tham

E-mail: tctham1234@gmail.com

the efficacy of stenting from the point of view of procedural success, and relief of dysphagia. Most of the studies discussed below included subjective scoring of dysphagia at initial presentation, ranging from no dysphagia through solid, mixed and liquid dysphagia to total dysphagia.

Alder et al, conducted a prospective non-randomised study of 13 patients who underwent EUS (endoscopic ultrasound) followed by stent placement[15]. The dysphagia scores significantly improved post stent insertion. The study concluded that oesophageal stent insertion was safe and permitted adequate oral feeding though at the cost of risk of migration (6 in 13 patients, 43%). Martin, et al performed a small prospective study of 5 patients who received oesophageal stents prior to receiving neoadjuvant chemotherapy[16]. Stent placement was successful in all 5 cases (100%) with optimal calorific needs met within 2 hours.

Siddiqui et al performed a retrospective, non-randomised study of 6 patients with malignant strictures who underwent oesophageal stent placement before receiving neoadjuvant chemo radiation[21]. Of the 6 patients, stent placement was successful in 5 (83%). Pellen et al conducted a study of 16 patients who received a self-expanding removable metal stent (SERMS) during neoadjuvant therapy[10]. There was a significant fall in mean dysphagia score from 2.5 (range 1-4) to 1.1 (range 0-3) immediately preoperatively.

Langer et al conducted a study of 38 patients, who had stents inserted, before undergoing neo-adjuvant chemo radiotherapy [14]. 37 of 38 (97.4%) patients had immediate dysphagia relief. Brown et al prospectively evaluated the use of self-expanding plastic stents (SEPS) during neoadjuvant therapy[12]. Lopes et al conducted a study of 11 patients who received SEMS prior to neoadjuvant therapy[13]. Dysphagia significantly improved compared to baseline in both these studies.

Griffiths, et al[17] evaluated a cohort of 22 patients who received biodegradable oesophageal stents (BD SX –ELLA) of whom 9 had oesophageal malignancy. The insertion was successful in 21/22 (96%) of their patients with a significant improvement in dysphagia scores at a median of 47 days.

Park, et al[19] evaluated the clinical efficacy of temporary placement of a retrievable expandable metallic stent during preoperative neoadjuvant chemoradiotherapy. Stent placement was technically successful in all patients with 24 of 25 (96%) showing symptomatic improvement. Stents were removed electively 32 days after starting neoadjuvant chemoradiotherapy or after stent migration and exit through the anus. The dysphagia score improved from 3.1 by 3 days after stent placement to 1.3 and was maintained up to 1 month after stent removal.

Van den Berg, et al[20] included 10 patients who underwent biodegradable stent placement (BD – ELLA) before neoadjuvant chemoradiotherapy. Technical and clinical success rates were 100% each. Mean dysphagia score improved significantly, 3 to 1.13 pre and post stent insertion, $p < 0.001$.

A systematic review and meta-analysis conducted by Nagaraja, et al[22] found a substantial decrease in dysphagia scores (standard error 0.15, 95% CI, -1.1 to -0.51). This review included nine of our fifteen studies.

Are oesophageal stents effective in management of malnutrition?

Van den Berg et al showed that although biodegradable stent placement as a bridge to surgery prior to neoadjuvant treatment resulted in improved dysphagia scores, it appeared to hamper oral intake, resulting in significant weight loss, needing additional nutritional interventions[20]. In contrast Siddiqui, et al[4] showed that albumin levels and weight increased significantly with both plastic stent (PS) and surgical jejunostomy (JT). There were no significant differences between groups in the procedural success rates (PS 92% vs. JT 100%, P = 0.33), complication rates (PS 22% vs. JT 4%, P = 0.11), mean increase in weight (PS 4.4 kg vs. JT 4.2 kg, P = 0.59), and mean increase in serum albumin (PS 0.62 g/dL vs. JT 0.44 g/dL, P = 0.05). In a review of a prospective database by Bower, et al, the silicone stent group demonstrated greater mean improvement in albumin levels (0.14 g/dL vs. -0.39 g/dL vs. -0.45 g/dL, P<.001) and less percentage body weight loss (1.5% vs. 4.2% vs. 5.5%, P<.001) compared with the groups with feeding tubes and oral nutrition.

Nagaraja et al conducted a meta-analysis of the literature. They found a substantial increase in weight (SE 0.434, 95% CI, -0.261 to 1.442) and albumin (SE 0.271, 95% CI, -0.181 to 0.881) standard difference in means[22].

WHAT ARE THE COMPLICATIONS OF STENTING RESECTABLE OESOPHAGEAL CANCER?

Stent migration varied from 20% in the study by Martin, et al (removed without complication at the time of operation[16] to 60% in the study by Siddiqui, et al (all successfully removed endoscopically or at the time of surgery)[22]. Stent-related morbidity occurred in 4/16 (25%) patients and migration occurred in 7/16 (44%) in the study by Pellen, et al, though all were resolved endoscopically with no stent-related mortality[10]. A meta-analysis of stents for resectable oesophageal cancer concluded that stent migration occurred in 1 patient causing jejunal perforation (2.6%), tracheo-oesophageal fistula in 2 (5.2%) and significant bleeding 1 (2.6%); delayed complications occurred in three (7.89%) ie tracheo-oesophageal fistula and recurrent dysphagia[22].

Griffiths, et al reported of 9 patients who had biodegradable stents, one (11%) required reinsertion of a self expanding metal stent at 2 months and 2 (22%) required supplementary feeding via jejunostomy and a fine bore nasojejunal tube within 12 weeks of stenting. Van den Berg, et al[20] used biodegradable stents, with an adverse event rate of 70%. Retrosternal pain developed in 6 patients and persisted for a median of 12 days. Stent obstruction occurred in one patient because of necrotic tissue.

TABLE: SUMMARY OF THE RESULTS OF THE USE OF SELF EXPANDING STENTS AS A BRIDGE TO SURGERY IN OESOPHAGEAL CANCER

SEMS = Self expanding metal stent; SEPS = Self expanding plastic stent, BDS = Biodegradable stent, REMS = Retrievable expandable metallic stent

Author	*Year*	*Type of stent*	*Number of patients*	*Number who had surgical resection (%)*	*Number of stent related complications (%)*
Mariette[5]	2014	SEMS	38	38 (100%)	Not reported
Krokidis[4]	2013	SEPS	11	1 (9%)	5 (45%)
Pellen[10]	2012	SEMS	16	10 (63%)	8 (50%)
Siddiqui[11]	2012	SEMS	55	8 (15%)	19 (35%)
Brown[12]	2011	SEPS	32	20 (63%)	10 (31%)
Lopes[13]	2010	SEMS	11	2 (18%)	5 (45%)
Langer[14]	2010	SEMS-25, SEPS-13	38	20 (53%)	18 (47%)
Adler[15]	2009	SEPS	13	3 (23%)	6 (46%)
Bower[3]	2009	SEPS	25	14 (56%)	6 (24%)
Martin[16]	2009	SEPS	5	Not reported	1 (20%)
Siddiqui[4]	2009	SEPS	12	Not reported	4 (33%)
Griffiths[17]	2012	BDS	9	3 (33%)	3 (33%)
Kjaer[18]	2016	SEMS	63	All R0 (this was the group from which the patients who had stents were identified)	Not reported
Park[19]	2015	REMS	25	Not reported	Not reported
Van den Berg[20]	2014	BDS	10	7 (70%)	7 (70%)
Siddiqui[21]	2007	SEPS	6	100%	3 (60%)

The systemic review by Nagaragi et al noted the incidence of major adverse events including stent migration as 32% and chest discomfort as 51.4%[22]. The authors in this review recommend stents for dysphagia prior to or during neoadjuvant chemotherapy but seem to underestimate the impact of the complications and did not adequately assess the disadvantages of stenting preoperatively as they considered stent migration not to be a disadvantage but rather an indicator of tumour reduction. A review by Jones and Griffiths[23] came to the conclusion that there can be significant complications in a small proportion of patients which can compromise opportunity for curative surgery.

HAS STENTING BEEN COMPARED TO STANDARD OPTIONS SUCH AS NASOGASTRIC OR NASOJEJUNAL FEEDING AND GASTROSTOMY OR JEJUNOSTOMY?

Only two studies to date have compared stenting to standard treatments. Bower, et al conducted a retrospective study comparing nutritional support methods in patients undergoing neoadjuvant chemo radiotherapy[3]. This study compared the outcomes of oesophageal stenting, feeding tubes and oral diets. 25 patients received stents, 19 patients had feeding tubes inserted and 14 patients were maintained on oral diet only. The group of patients who received oesophageal stents had a lower rate of interruption of chemo radiotherapy (8% vs. 29% vs. 47%, P=0.011), greater mean improvement of albumin (0.14 g/dL vs. -0.39 g/dL vs. -0.45 g/dL, P<0.001), less percentage body weight loss (1.5% vs. 4.2% vs. 5.5%, P<0.001) and a reduction in major operative complications (20% vs. 47% vs. 43% among stent, feeding tube, and oral nutrition respectively (P=0.130). As mentioned earlier, Siddiqui, et al showed that plastic stents were a safe and effective alternative to surgical jejunostomy for maintaining nutrition in this subset of patients undergoing neoadjuvant chemo radiotherapy[4].

DOES STENTING COMPROMISE SUBSEQUENT SURGERY AND ONCOLOGICAL OUTCOMES?

Studies have shown that interval disease progression as a direct consequence of SEMS could adversely affect the treatment plan of 30 to 85%.[3,12,14] Mariette et al conducted a retrospective study of 2944 patients in a multicentre European cohort, who underwent oesophageal resection over a period of ten years[5]. They evaluated the oncologic impact of covered SEMS when used as a bridge to surgery. A total of 38 patients had SEMS inserted. SEMS insertion was complicated by perforation in 2 cases. The study also found that postoperative mortality (13.2% vs 8.6%) and morbidity rates (63.2% vs 59.2%) were increased in the SEMS group compared to the control group respectively. They found a significant reduction in the R0 resection rate (71% vs 85.5%; p=0.041), median time to recurrence (6.5 vs 9 months) and the 3-year overall survival (25% vs 44%) in the SEMS group compared to the control.

Griffiths, et al[17] found that in nine patients who had biodegradable stents, 6 (66%) did not proceed to surgery; 1 (11%) because of disease progression, two (22%) because of failure to gain weight and three (33%) because they became unfit for surgery. The additional 3 (33%) did progress to surgery but were not resected due to the recognition of disseminated disease. In the other biodegradable stent study by van den Berg[20], 4 of 10 patients did not undergo surgery because of fatal pneumonia, liver metastases, poor performance status and insertion of a self expanding metal stent for a post radiation stricture, respectively.

A retrospective cohort study from a prospectively maintained national database in Denmark identified all patients treated without neoadjuvant therapy that had an R0 resection[18]. Of these 63 patients had a stent as a bridge to surgery. The outcomes from these patients were compared to 211 who did not have a stent. The median survival in the stent group was significantly lower than the non-stent group by 11.6 months and 21.3 months respectively. Non-stent group exhibited a significantly better two year survival with a median recurrence free survival of 9.1 months for the stent group compared with 15.2 months for the non-stent group.

ARE THERE ANY DIFFERENCES DEPENDING ON THE TYPES OF STENTS USED?

Krokidis, et al conducted a prospective study to evaluate the use of biodegradable oesophageal stents in malignant oesophageal strictures as a bridge to surgery[9]. In this study 11 patients had a woven polydioxanone degradable oesophageal stent inserted. Stent deployment was successful in all patients. However, early complications occurred in 3 patients that resulted in failure to restore oral nutrition. Stent dysfunction occurred in 5 of 8 patients (62.5%). In 2 of the 5 patients this was due to a local inflammatory reaction and in the remaining 3, this was due to tumour ingrowth. Subsequently a new metallic stent was inserted in 4 of the 5 patients. At the end of follow-up only 3 of 8 oesophageal stents were patent. This study demonstrates that biodegradable oesophageal stents do not appear to have benefit in malignant strictures. Two other studies on biodegradable stents.[17,20] also do not show good outcomes in terms of surgical resection and stent related complications.

Five studies have evaluated self-expanding plastic stents (SEPS)[3,4,15,16,21] and three studies[10,11,13] have evaluated self-expanding metal stents (SEMS). One study combined both SEPS and SEMS[14]. There did not appear to be any differences in outcomes although there are no studies comparing these two. Two studies looked at the concept of removing stents prior to surgery with self expanding plastic stents[19,21] but there was no clear benefit.

WHAT ABOUT COST-EFFECTIVENESS?

To date, no studies have evaluated cost effectiveness as a bridge to neoadjuvant therapy and surgery in oesophageal cancers.

DISCUSSION

In summary, although stents are effective in relieving dysphagia in resectable tumours, significant complications are common such as perforation and fistula, with one study showing increased postoperative mortality and morbidity.

Although a systematic review[22] found that stents before neoadjuvant therapy result in an increase in weight and albumin, biodegradable stents appear to hamper oral intake resulting in weight loss needing additional nutritional interventions[20].

Stent insertion before surgery was found to be a predictor of poor prognosis after adjusting for confounding factors in the study by Mariette, et al[5]. The reasons suggested include peri-stent fibrosis secondary to expansive radial forces, compromising the normal planes of dissection and therefore the resectability[24,25]; fixating spurs causing micro perforations and dissemination[26]; inability to accurately restage tumours after stent insertion making it difficult to identify the tumours that progress and become unresectable. However this study has limitations. This retrospective study did not evaluate patients who underwent stent insertion and did not benefit from surgery due to tumour progression or stent-related fistula. In addition, it is a small study with only 38 cases of SEMS insertion. The findings from this study are supported by a larger similar study from Denmark[18] of 63 patients who underwent stenting prior to surgery. In this study, only patients who underwent an R0 resection were selected. They too found that the two year survival and recurrence-free survival was decreased in the stent group compared with those who did not have a stent.

Although stents appear to be effective in relieving dysphagia prior to surgery, there are major concerns about its adverse impact on oncological outcomes. The European Society of Gastrointestinal Endoscopy (ESGE) clinical guidelines[28] for the use of oesophageal stenting in benign and malignant disease do not recommend the use of stent placement as a bridge to surgery or prior to preoperative chemo-radiotherapy due to a high incidence of adverse events and the availability of safer feeding options.[29] . The review by Jones and Griffiths[23] also came to the same conclusion.

CONCLUSION

With the limited available data on this topic, we can conclude that although stenting appears to be effective in relieving dysphagia and addressing malnutrition prior to surgery, there are currently sufficient concerns about its adverse impact on oncological outcomes, to not recommend its routine use in resectable patients. Well-designed randomised prospective trials are required but are unlikely to happen because of concern about adverse oncological outcome. In our opinion, the use of oesophageal stents as a bridge to surgery should be confined to patients with dysphagia who cannot tolerate tube feeding or where a feeding gastrostomy or jejunostomy is contraindicated or not possible, or in the context of a clinical trial evaluating its role.

REFERENCES

1. Mariette C, De Botton ML, Piessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? *Ann Surg Oncol*. 2012;**19(7)**:2128–34.
2. Tessier W, Piessen G, Briez N, Boschetto A, Sergent G, Mariette C. Percutaneous radiological gastrostomy in esophageal cancer patients: a feasible and safe access for nutritional support during multimodal therapy. *Surg Endosc*. 2013;**27(2)**:633–41.
3. Bower M, Jones W, Vessels B, Scoggins C, Martin R. Nutritional support with endoluminal stenting during neoadjuvant therapy for esophageal malignancy. *Ann Surg Oncol*. 2009;**16(11)**:3161–8.
4. Siddiqui AA, Glynn C, Loren D, Kowalski T. Self-expanding plastic esophageal stents versus jejunostomy tubes for the maintenance of nutrition during neoadjuvant chemoradiation therapy in patients with esophageal cancer: a retrospective study. *Dis Esophagus*. 2009;**22(3)**:216–22.
5. Mariette C, Gronnier C, Duhamel A, Mabrut J-Y, Bail J-P, Carrere N, *et al*. Self-expanding covered metallic stent as a bridge to surgery in esophageal cancer: impact on oncologic outcomes. *J Am Coll Surg*. 2015;**220(3)**:287–96.
6. Duron V, Fadeku A, White R. Stent placement in esophageal cancer as a bridge to surgery: Short-term outcomes. *Chest*. 2011;**140(4 Suppl)**:830A.
7. Sabbagh C, Browet F, Diouf M, Cosse C, Brehant O, Bartoli E, *et al*. Is stenting as "a bridge to surgery" an oncologically safe strategy for the management of acute, left-sided, malignant, colonic obstruction? A comparative study with a propensity score analysis. *Ann Surg*. 2013;**258(1)**:107–15.
8. Vleggaar FP. Stent placement in esophageal cancer as a bridge to surgery. *Gastrointest Endosc*. 2009;**70(4)**:620–2.
9. Krokidis M, Burke C, Spiliopoulos S, Gkoutzios P, Hynes O, Ahmed I, *et al*. The use of biodegradable stents in malignant oesophageal strictures for the treatment of dysphagia before neoadjuvant treatment or radical radiotherapy: a feasibility study. *Cardiovasc Intervent Radiol*. 2013;**36(4)**:1047–54.
10. Pellen MGC, Sabri S, Razack A, Gilani SQ, Jain PK. Safety and efficacy of self-expanding removable metal esophageal stents during neoadjuvant chemotherapy for resectable esophageal cancer. *Dis Esophagus*. 2012;**25(1)**:48–53.
11. Siddiqui AA, Sarkar A, Beltz S, Lewis J, Loren D, Kowalski T, *et al*. Placement of fully covered self-expandable metal stents in patients with locally advanced esophageal cancer before neoadjuvant therapy. *Gastrointest Endosc*. 2012;**76(1)**:44–51.
12. Brown RE, Abbas AE, Ellis S, Williams S, Scoggins CR, McMasters KM, *et al*. A prospective phase II evaluation of esophageal stenting for neoadjuvant therapy for esophageal cancer: optimal performance and surgical safety. *J Am Coll Surg*. 2011;**212(4)**:582–8; discussion 588–9.
13. Lopes TL, Eloubeidi MA. A pilot study of fully covered self-expandable metal stents prior to neoadjuvant therapy for locally advanced esophageal cancer. *Dis Esophagus*. 2010;**23(4)**:309–15.
14. Langer FB, Schoppmann SF, Prager G, Tomaselli F, Pluschnig U, Hejna M, *et al*. Temporary placement of self-expanding oesophageal stents as bridging for neo-adjuvant therapy. *Ann Surg Oncol*. 2010;**17(2)**:470–5.
15. Adler DG, Fang J, Wong R, Wills J, Hilden K. Placement of Polyflex stents in patients with locally advanced esophageal cancer is safe and improves dysphagia during neoadjuvant therapy. *Gastrointest Endosc*. 2009;**70(4)**:614–9.
16. Martin R, Duvall R, Ellis S, Scoggins CR. The use of self-expanding silicone stents in esophageal cancer care: optimal pre-, peri-, and postoperative care. *Surg Endosc*. 2009 Mar;**23(3)**:615–21.
17. Griffiths EA, Gregory CJ, Pursnani KG, Ward JB, Stockwell RC. The use of biodegradable (SX-ELLA) oesophageal stents to treat dysphagia due to benign and malignant oesophageal disease. *Surg Endosc*. 2012;**26(8)**:2367-75.
18. Kjaer DW, Nassar M, Jensen LS, Svendsen LB, Mortensen FV. A bridging stent to surgery in patients with esophageal and gastroesophageal junction cancer has a dramatic negative impact on patient survival: A retrospective cohort study through data acquired from a prospectively maintained national database. *Dis Esophagus*. 2017;**30(3)**:1-7.
19. Park JH, Song HY, Shin JH, Kim JH, Kim YH, Kim SB, Kim JH. Preliminary results of temporary placement of retrievable expandable metallic stents during preoperative neoadjuvant chemoradiotherapy in patients with resectable esophageal cancer. *J Vasc Interv Radiol*. 2015;**26(6)**:883-8.
20. van den Berg MW, Walter D, de Vries EM, Vleggaar FP, van Berge Henegouwen MI, van Hillegersberg R, *et al*. Biodegradable stent placement before neoadjuvant chemoradiotherapy as a bridge to surgery in patients with locally advanced esophageal cancer. *Gastrointest Endosc*. 2014;**80(5)**:908–13.
21. Siddiqui AA, Loren D, Dudnick R, Kowalski T. Expandable polyester silicon-covered stent for malignant esophageal strictures before neoadjuvant chemoradiation: a pilot study. *Dig Dis Sci*. 2007;**52(3)**:823–9.
22. Nagaraja V, Cox MR, Eslick GD. Safety and efficacy of esophageal stents preceding or during neoadjuvant chemotherapy for esophageal cancer: a systemic review and meta-analysis. *J Gastrointest Oncol*. 2014:**5(2)**; 119-26
23. Jones CM, Griffiths EA. Should oesophageal stents be used before neo-adjuvant therapy to treat dysphagia in patients awaiting oesophagectomy? Best evidence topic (BET). *Int J Surg*. 12(2014): 1172-80
24. Sunde B, Ericson J, Kumagai K, Lundell L, Tsai JA, Lindblad M, *et al*. Relief of dysphagia during neoadjuvant treatment for cancer of the esophagus or gastroesophageal junction. *Dis Esophagus*. 2015;**29(5)**: 442-7.
25. Hirdes MM, van Hooft JE, Wijrdeman HK, Hulshof MC, Fockens P, Reerink O, *et al*. Combination of biodegradable stent placement and single-dose brachytherapy is associated with an unacceptably high complication rate in the treatment of dysphagia from esophageal cancer. *Gastrointest Endosc*. 2012;**76(2)**:267–74.
26. Hirdes MM, Vleggaar FP, de Beule M, Siersema PD. In vitro evaluation of the radial and axial force of self-expanding esophageal stents. *Endoscopy*. 2013;**45(12)**:997–1005.
27. Maruthachalam K, Lash GE, Shenton BK, Horgan AF. Tumour cell dissemination following endoscopic stent insertion. *Br J Surg*. 2007;**94(9)**:1151–4.
28. Spaander MC, Baron TH, Siersema PD, Fuccio L, Schumacher B, Escorsell À, *et al.* Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy.* 2016;**48(10)**:939-48.
29. Roy A, Kim M, Christein J, Varadarajulu S. Stenting versus gastrojejunostomy for management of malignant gastric outlet obstruction: comparison of clinical outcomes and costs. *Surg Endosc*. 2012;**26(11)**:3114–9.

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Case Report

Fifty Years of Ventricular Tachycardia in a Single Patient

Stephen Adams, Alastair Gray, Niall Herity

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Key Words: Arrhythmogenic Right Ventricular Cardiomyopathy, Dysplasia, Ventricular, Tachycardia

Abstract We report a patient who first presented during childhood in the early 1960's with several episodes of ventricular tachycardia (VT) and we describe her management which reflected the best medical knowledge at the time. She then presented more than 50 years later, again with VT, at which time a definitive diagnosis of the underlying cause was made. Her case illustrates the evolution in the understanding and management of VT over the past 50 years. This in turn reflects the clinical and technological advances in the management of cardiovascular disease over time.

CASE PRESENTATION

A 7-year old patient presented with symptoms of palpitations in April 1961. The medical notes at the time described symptoms coming on while dancing or during physical exertion at school. There was no loss of consciousness. An electrocardiogram (ECG) showed ventricular tachycardia (VT) (Figure 1). An ECG during sinus rhythm was reported to show right ventricular hypertrophy with strain (Figure 2). The conclusion at the time was that the episodes of VT were triggered by sympathetic over-excitement and she was commenced on oral quinidine and propranolol. In July 1969 a chest X-ray report stated that '…prominence has developed in the left heart border…could be consistent with myopathy'. In 1983, an echocardiogram demonstrated normal biventricular structure and function.

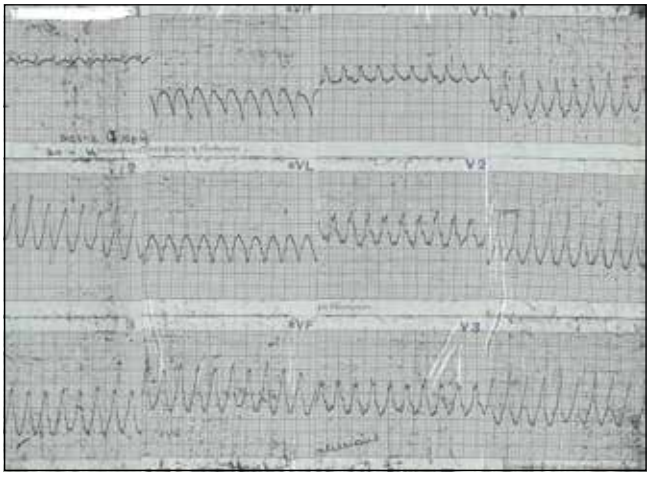

Fig 1. Electrocardiogram showing ventricular tachycardia

She remained under regular cardiology review and over a 10-year period, presented 15 times with symptomatic VT. Three episodes required DC cardioversion for haemodynamic instability; intravenous lignocaine was used on one occasion and spontaneous reversion to normal sinus rhythm occurred on other occasions.

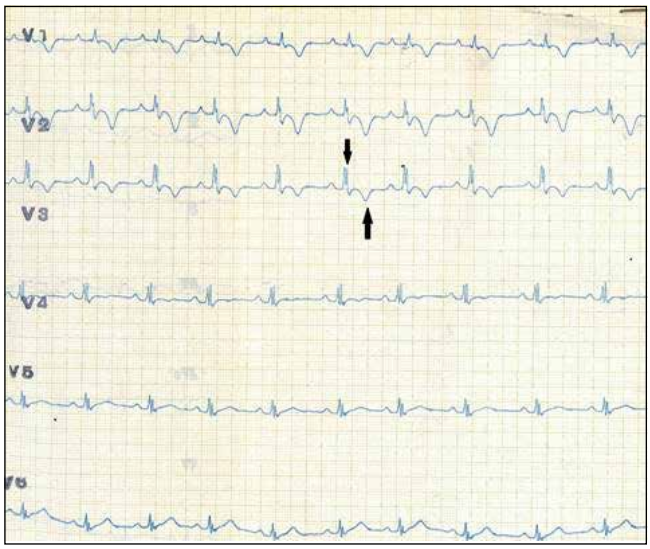

Fig 2. Electrocardiogram reported as showing right ventricular hypertrophy with strain pattern (arrows).

During the 1970's she came off her medication but remained asymptomatic until 2018, when she presented to the emergency department in VT, 57 years after her first admission (Figure 3). Following DC cardioversion for haemodynamic compromise, a 12-lead ECG showed right bundle branch block, anterior T-wave inversion, and an epsilon wave (Figure 4), features typical of arrhythmogenic right ventricular cardiomyopathy (ARVC).

An echocardiogram confirmed severe right ventricular dysfunction and aneurysmal dilatation and cardiac magnetic resonance imaging confirmed classic features of ARVC (Fig. 5).

A cardioverter defibrillator was implanted and she was referred to the Inherited Cardiac Conditions clinic for follow up and genetic screening. She has remained well since

Cardiology Department, Belfast HSC Trust
Correspondence to: Dr Stephen Adams
E-mail: stephenadams2301@gmail.com

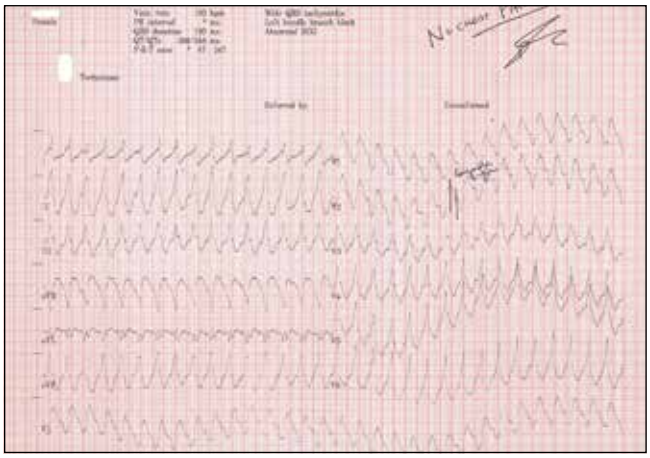

Fig 3. Electrocardiogram form 2018 showing ventricular tachycardia.

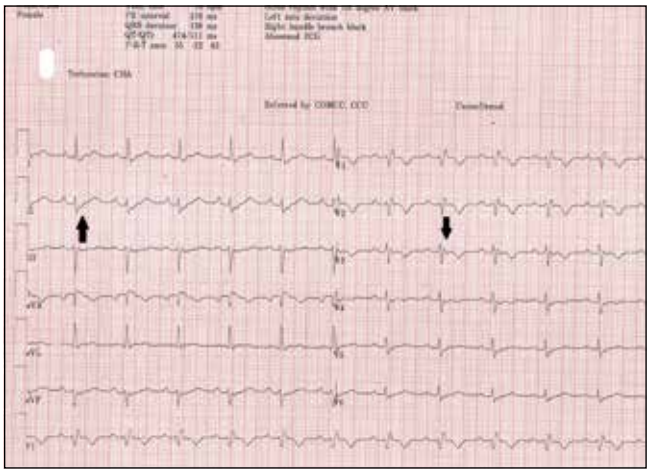

Fig 4. 12-lead electrocardiogram showing right bundle branch block, anterior T-wave inversion, and an epsilon wave (arrows).

DISCUSSION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) (also known as arrhythmogenic right ventricular dysplasia [ARVD]) is an autosomal dominant inherited cardiac disorder. It demonstrates incomplete penetrance with variable expression and is thought to be the result of a desmosomal abnormality arising from mutations in genes encoding desmoplakin and plakoglobin. [1] Characterised by fibro-fatty replacement of the ventricular myocardium, it predominantly affects the right ventricle but can also involve the left ventricle (LV) and rarely LV involvement can occur exclusively. [2,3]

Clinical presentation arises due to ventricular dysfunction and arrhythmia. Although symptoms may be non-specific they frequently include dyspnoea and palpitations. Arrhythmia or sudden cardiac death may be the first presenting feature. Diagnosis is challenging and may require several years of follow up and serial imaging investigations. A diagnostic task force was established in 1994 outlining diagnostic criteria which were updated in 2010. [4]

When this patient first presented with VT in 1966, ARVC had not been described formally and did not appear in cardiology textbooks. Of interest, in 1736, there had been descriptions of an Italian family who experienced right ventricular failure and cardiac death in four successive generations. It is reasonable to assume that the underlying cause was ARVC. The first modern description was in 1982 involving 24 adults with VT of left bundle branch block morphology. [5] In 1984 additional ECG findings including the epsilon wave were first recognised. [6]

This patient's clinical journey is a metaphor for the remarkable evolution in our understanding of VT and ARVC over the past 50 years. In particular it exemplifies how advances in cardiac imaging, electrophysiology and implantable device therapy, genetic analysis and the global and immediate availability of scientific information has transformed the diagnosis, management and prognosis of patients with complex cardiovascular diseases.

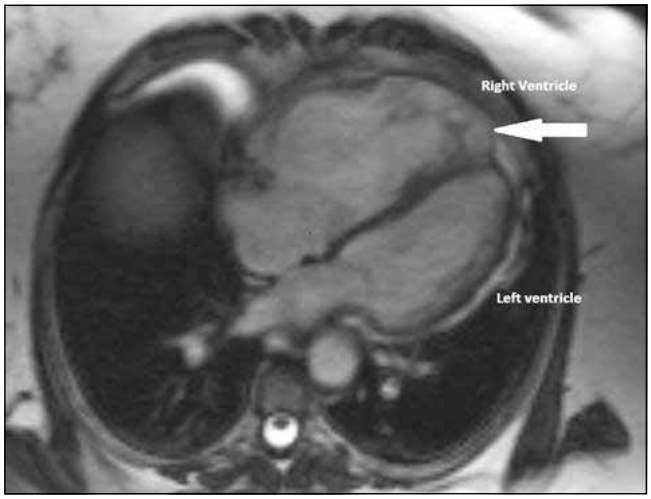

Fig 5. Cardiac magnetic resonance imaging showing a severely dilated right ventricle with multiple areas of wall thinning. There is aneurysm formation within the apical region (arrow). In contrast, the left ventricle is undilated.

REFERENCES

1. Cox M, van der Zwaag Paul, van der Verf C, van der Smagt J, Noorman M, Bhuiyan ZA. *et al*. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: pathogenic desmosome mutations in index-patients predict outcome of family screening: Dutch arrhythmogenic right ventricular dysplasia/cardiomyopathy genotype-phenotype follow-up study. *Circulation*. 2011;**123(23)**: 2690-700.
2. Saguner AM, Brunckhorst C, Duru F. Arrhythmic ventricular cardiomyopathy: a paradigm shift from right to biventricular disease. *World J Cardiol*. 2014;**6(4)**:154-74.
3. Corrado D, Buja G, Basso C, Thiene G. Clinical diagnosis and management strategies in arrhythmogenic right ventricular cardiomyopathy. *J Electrocardiol*. 2000;**33(Suppl):** 49-55.
4. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, *et al*. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121(**13**): 1533-41
5. Romero J, Mejia-Lopez E, Manrique C, Lucariello R. Arrhythmogenic right ventricular cardiomyopathy (ARVC/D): A Systematic Literature Review. *Clin Med Insights Cardiol*. 2013;7: 97-114
6. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malerque C, *et al*. Right ventricular dysplasia: a report of 24 adult cases. *Circulation*. 1982;65(**2**): 384-98

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Clinical Paper

The Preventative Effect of Hydrocolloid Dressings on Nasal Bridge Pressure Ulceration in Acute Non-Invasive Ventilation

Abigail Bishopp[1], Amy Oakes[1], Pearlene Antoine-Pitterson[1], Biman Chakraborty [2], David Comer[1], Rahul Mukherjee[1]

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Key words: Hydrocolloid, non-invasive ventilation, patient safety, pressure ulcer, wound care

ABSTRACT

Background: Non-invasive ventilation (NIV) is a valuable treatment in the management of acute hypercapnic respiratory failure. NIV is not without risks. One such adverse effect is the development of pressure ulcers over the nasal bridge which have an incidence of up to 20% of patients requiring NIV in this setting. The role of medical devices in the development of hospital acquired pressure ulcers has been increasingly recognised with 10-35% of all hospital acquired ulcers attributed to medical devices. Guidelines on acute NIV use suggest good skin care strategies. However, data on the magnitude of the problem of nasal bridge pressure ulceration and the effect of proactive preventative steps remains scant.

Method: A quality improvement project was designed to reduce the incidence of nasal bridge pressure ulcers during acute NIV. Hydrocolloid dressings were placed over the nasal bridge in all patients requiring NIV between 30th October 2015 and the 29th October 2016. Tissue viability was assessed daily with new pressure ulceration defined as grade 2 or above. Rates of nasal bridge pressure ulcers were compared to all patients requiring NIV in the 12-month period prior to intervention.

Results: In Group 1, there were 161 admissions and 9 grade 2 pressure ulcers from 666 NIV bed-days. In Group 2 there were 134 admissions and 0 pressure ulcers from 718 NIV bed-days. There was a statistically significant reduction in grade 2 pressure ulceration rates (p= 0.0013) in Group 2 compared to Group 1.

Conclusion: Application of an early prophylactic pressure-relieving hydrocolloid nasal dressing reduces the risk of developing grade 2 pressure ulcers in patients in patients requiring acute NIV.

INTRODUCTION

Non-invasive ventilation (NIV) is a valuable treatment for acute hypercapnic respiratory failure. Use of ward based NIV is increasing, with approximately 9000 episodes yearly within the UK[1]. Exacerbations of COPD remain the most common indication[2] with hypercapnic respiratory failure complicating up to 20% of acute admissions[3]. NIV has been shown to reduce mortality[4] and avoids the need for intubation thereby avoiding associated complications such as ventilator associated pneumonia. The use of NIV is not without risks. These range from relatively minor complications to more clinically significant effects, such as a heightened risk of aspiration, and untoward haemodynamic effects.[6] The impact of the device itself on the skin and the predisposition to skin breakdown in this context is now appreciated to be another clinically significant untoward effect of NIV.[6]

The role of medical devices in the development of hospital acquired pressure ulcers has been increasingly recognised over recent years. A variety of medical devices have been shown to increase the risk with patients 2.4 times more likely to develop a pressure ulcer if any medical device is used[7]. 10-35% of hospital acquired pressure ulcers are directly related to medical devices[7,8].

Nasal bridge pressure ulcers related to the use of NIV masks occur in 5-20% cases[5,6,9]. The development of pressure lesions can result in intolerance to NIV and potentially treatment failure. Patient comfort and enhanced compliance are key factors in determining NIV outcome. Lesions develop as a result of pressure exerted by the mask which can approach pressures of 70mmHg[10]. In the presence of shear forces, such as that generated between inspiratory and expiratory phases of ventilation, pressures of as low as 30mmHg may be sufficient to result in tissue damage within a few hours[11].

1. Department of Respiratory Medicine & Physiology, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS, UK
2. School of Mathematics, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

Corresponding author Dr Rahul Mukherjee.

E-mail: rahul.mukherjee@heartofengland.nhs.uk

Current guidelines regarding the management of NIV suggest ensuring best mask fit along with pressure relieving strategies. This includes regular breaks from the mask, alternating between two interface types or barrier dressings[9], however data regarding this is lacking. Our objective was to examine the effect of a proactive approach to reducing grade 2 or above nasal bridge pressure ulcers in patients requiring acute NIV. We aimed to reduce the incidence of pressure ulcers by using a hydrocolloid dressing placed over the nasal bridge throughout the episode of NIV.

Fig 1. Top – A typical full face mask used for acute non-invasive ventilation: the nasal bridge is the most prominent bony structure in contact with the mask cushion (white arrow); Bottom – Grade 2 Nasal bridge pressure ulcer (bordered arrow)

METHODS

Aim: We designed a quality improvement project to assess the effect of a proactive preventative approach towards nasal bridge pressure ulceration through the prophylactic use of a hydrocolloid dressing on the incidence of nasal bridge pressure ulcers in patients requiring acute non-invasive ventilation. This study is a report of a Quality Improvement Project (QIP) performed as a systematic, data-guided activity designed to bring about immediate improvements in health delivery. This QIP was registered on the audit database managed by the Clinical Standards Committee of the Heart of England NHS Foundation Trust, Birmingham, B9 5SS, UK. Data was collected from the continuous audit of all NIV admissions registered with the audit database of the Heart of England NHS Foundation Trust (audit registration number: 2399). Rates of development of nasal bridge pressure ulcers were compared to all patients requiring NIV in the 12-month period prior to intervention.

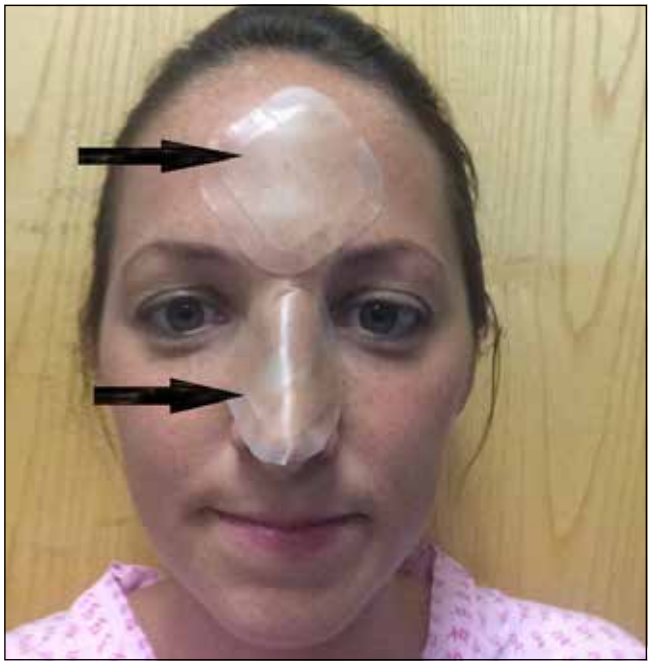

Fig 2. Application of hydrocolloid dressings to prevent nasal bridge ulceration (black arrows)

Subjects and intervention: We aimed to do a pre and post observational study following the introduction of the proactive preventative approach. Consecutive patients admitted to our dedicated physiotherapy-led, respiratory ward based NIV unit requiring NIV for acute hypercapnic respiratory failure between 30th October 2014 to -30th October 2015 were included. NIV was delivered in a ward-based setting using standard non-invasive ventilators in spontaneous-timed (ST) and volume-assured Pressure support modes via a FreeMotion RT040 (Fisher Paykel) oronasal mask sized according to manufacturer instructions. NIV settings were managed according to local protocols based on British Thoracic Society guidelines for the use of acute NIV.

Group 1 included all patients commencing NIV between 30th October 2014 and 29th October 2015, who received usual care. *Group 2* included all patients commencing NIV between 30th October 2015 and 29th October 2016. Group 2 received hydrocolloid dressings (BeneHold Bordered Hydrocolloid dressing 5cm x 5cm [Aspen Medical]) which were positioned in a diamond formation over the centre of the forehead with

Table 1:

Patient demographics and primary clinical indication for NIV

	Group 1 (161 episodes NIV)	Group 2 (134 episodes NIV)	P value
Male	70 (43.5%)	46 (34.3%)	0.109
Age (mean years)	69.7	69.2	0.610
Diagnosis COPD Obesity Musculoskeletal Other	 129 (80.1%) 11 (6.8%) 6 (3.7%) 15 (9.3%)	 110 (82.1%) 13 (9.7%) 3 (2.2%) 8 (6.0%)	 0.668 0.369 0.459 0.286

a further dressing positioned as a diamond over the nasal bridge. The NIV mask was placed over this. All other care, including NIV pressure changes and breaks off NIV, was given according to local protocols which remained unchanged between the time periods.

Data collection: Data regarding age, sex, admission diagnosis, co-morbidity, length of NIV use, IPAP, EPAP, and nasal bridge tissue viability grading was recorded. The nasal bridge was formally inspected daily by a nurse trained in skin and pressure ulcer grading. Inspection involved removing the hydrocolloid dressing and assessment using hospital guidelines adapted from NPUAP/EPUAP pressure ulcer classification system. A pressure ulcer was diagnosed when criteria for grade 2 pressure change (partial thickness skin loss involving epidermis, dermis or both) was observed. If there was no evidence of pressure change or grade 1 change only, a new hydrocolloid dressing was placed and NIV continued via oronasal mask.

Table 2:

Comorbidity in patient groups

Co-morbidity	Pre	Post	P value
Diabetes	52	36	0.293
Vascular disease	61	47	0.589
Chronic kidney disease	30	19	0.295
Chronic dermatological	2	0	0.502

Statistical analysis: Chi squared and Fisher exact tests were used for analysis of incidence of grade 2 pressure ulcers between groups and other categorical data. Mann Whitney U test was used to analyse all other variables.

RESULTS

A total of 295 patients were included, 161 in Group 1 (pre) and 134 in Group 2 (post). 1 patient in Group 1 had incomplete records regarding co-morbidities and was excluded from analysis of this parameter, but all other categories were complete and the patient was therefore included in the study. Demographics including sex and age, and diagnosis or reason for commencement of NIV did not differ significantly between groups (Table 1).

Pressure ulcer incidence: Pressure ulcer development differed significantly (p=0.001) between groups. For Group 1, 9 out of 161 episodes of acute NIV resulted in a grade 2 nasal bridge pressure ulcer during 666 NIV bed days. As for Group 2, none of 134 episodes of acute NIV resulted in a grade 2 nasal bridge pressure ulcer during 718 NIV bed days.

IPAP and EPAP used were not significantly difference between groups (IPAP p=0.110, Group 1 mean 19.8 [median 20, IQR 16-24], Group 2 mean 19.0 [median 18, IQR 16-22], EPAP p=0.100, Group 1 mean 6.1 [median 6, IQR 5-7], Group 2 mean 5.68 [median 6, IQR 5-6]).

Co-morbidity: Co-morbidities considered to have an association with an increased risk of pressure ulcers were not significantly difference between groups (Table 2).

Adverse effects: There were no local adverse effects (eg rash, contact dermatitis) related to dressings.

DISCUSSION

The use of prophylactic hydrocolloid dressings placed over the bridge of the nose effectively removed the risk of grade 2 nasal bridge pressure ulcers. Previous studies have shown the incidence of nasal bridge pressure ulcers during the use of acute NIV to be between 5-20%[5,6,9]. The incidence in our pre-intervention group was 6%. There were no ulcers evident in the intervention group.

The development of pressure ulcers related to NIV is due to a combination of pressure effects and shear forces exerted by the presence of the mask, pressure changes during different phases of ventilation, and mask strap tension[6,10,11]. The use of oronasal masks and increasing time spent on NIV increase the risk of pressure ulcers forming, as do patient factors including age, sensory impairment, chronic skin conditions, and hypotension amongst others.[5]

Previous studies into reducing NIV related pressure ulcers have examined the effect of dispersing pressure effects by changing the interface from an oronasal mask to a full face or helmet mask with a significant reduction in the incidence of pressure ulcers[13]. With regard to ventilation there is no evidence that any one interface is superior. Laboratory modelling suggested an increase in the internal volume of the interface may increase dead space and CO2 rebreathing[14],

however this has not been borne out in vivo[15]. Despite this, oronasal masks remain the most popular interface with a Europe wide survey showing them to be first choice in 70% of cases. Reasons given by respondents for their choice include reduced air leaks, patient comfort and cost[13].

Three previous studies examining the effect of dressings in reducing nasal bridge pressure ulcers were identified. Weng et al report a significant reduction in grade 1 nasal bridge pressure ulcers with both Tegasorb and Tegaderm dressings when compared to no intervention[17]. Callaghan et al support this finding, using Granuflex compared to usual care[18]. Evaluation of a protective solution by Pena-Otero et al found a trend towards a protective benefit with use of a solution of hyperoxygenated fatty acids but no improvement with either an adhesive thin polyurethane dressing or an adhesive foam dressing[19]. All of these studies were limited by small sample sizes with the largest containing only 40 patients per group.

There is a larger body of evidence that considers more traditionally recognised pressure ulcers or 'bedsores' rather than ulcers related to medical devices. Preventative measures including turning regimes, pressure redistributing devices e.g. appropriate mattresses, and optimisation of nutritional status are now well known. Pooled analysis of RCTs of preventative dressings within this field demonstrate an overall 79% risk reduction in the incidence of new pressure ulcers with use of dressings[20], although it was noted that the studies included in this analysis had a high risk of bias.

Our study is the assessment of a real-life quality improvement project. It is therefore limited in that its style it is a quasi-experimental 'before-and-after' study, lacking randomisation or blinding. There are a number of potentially confounding factors regarding the risk of developing pressure ulcers that were not systematically assessed, namely nutritional status and use of certain medications such as steroids. It does, however, provide real world data and is therefore easily transferrable to practice.

CONCLUSION

The current evidence base regarding both the incidence of nasal bridge pressure ulcers and the effect of preventative strategies is limited. We have demonstrated a strategy to reduce the incidence of grade 2 pressure ulcers associated with NIV, thereby reducing avoidable harm to patients and improving quality and safety of their care. We would therefore advocate the use of hydrocolloid dressings to prevent NIV related nasal bridge pressure ulcers.

REFERENCES

1. Juniper M, Ellis G, Smith NC, Protopapa KL, Mason M. Inspiring change: a review of the quality of care provided to patients receiving acute non-invasive ventilation. NCEPOD reports 2017. [Internet] London: National Confidential Enquiry into Patient Outcome and Death; 2017. Available from: http://www.ncepod.org.uk/2017niv.html [Accessed September 2018]
2. Davies M. British Thoracic Society. NIV Adult 2013 (national audit period 1 February – 31 March 2013). [Internet] London: British Thoracic Society; 2013. Available from: https://www.brit-thoracic.org.uk/document-library/audit-and-quality-improvement/audit-reports/bts-adult-niv-audit-report-2013/ [Accessed September 2018]
3. Roberts CM, Stone RA, Buckingham RJ, Pursey N, Lowe D, National Chronic Obstructive Pulmonary Disease Resources and Outcomes Project implementation group. Acidosis, non-invasive ventilation and mortality in hospitalised COPD exacerbations. *Thorax*. 2011;**66(1)**:43–8.
4. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*. 2000;**355(9219)**:1931-5.
5. Yamaguti WP, Moderno EV, Yamashita SY, Gomes TG, Maida AL, Kondo CS, *et al*. Treatment-related risk factors for development of skin breakdown in subjects with acute respiratory failure undergoing non-invasive ventilation or CPAP. *Respir Care*. 2014;**59(10)**:1530-6.
6. Gay P. Complications of Noninvasive Ventilation in Acute Care. *Respir Care*. 2009;**54(2)**:246-58.
7. Black JM, Cuddigan JE, Walko MA, Didier LA, Lander MJ, Kelpe MR. Medical device-related pressure ulcers in hospitalized patients. *Int Wound J*. 2010;**7(5)**:358-65.
8. VanGilder C, Amlung S, Harrison P, Meyer S. Results of the 2008–2009 International Pressure Ulcer Prevalence Survey and a 3-year, acute care, unit-specific analysis. *Ostomy Wound Manage*. 2009;**55(11)**:39–45.
9. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, *et al*. BTS/ICS guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax*. 2016;**71(Suppl 2)**:S1-S35.
10. Munckton K, Ho KM, Dobb GJ, Das-Gupta M, Webb SA. The pressure effects of facemasks during noninvasive ventilation: a volunteer study. *Anaesthesia*. 2007;**62(11)**:1126–31.
11. Dellweg D, Hochrainer D, Klauke M, Kerl J, Eiger G, Kohler D. Determinants of skin contact pressure formation during non-invasive ventilation. *J Biomech*. 2010;**43(4)**:652–7.
12. Worsley PR, Prudden G, Gower G, Bader DL. Investigating the effects of strap tension during non-invasive ventilation mask application: a combined biomechanical and biomarker approach. *Med Devices*. 2016;**9**:409–17.
13. Schallom M, Cracchiolo L, Falker A, Foster J, Hager J, Morehouse T, *et al*. Pressure ulcer incidence in patients wearing nasal-oral versus full-face noninvasive ventilation masks. *Am J Crit Care*. 2015;**24(4)**:349-56.
14. Schettino GP, Chatmongkolchart S, Hess DR, Kacmarek R. Position of exhalation port and mask design affect CO2 rebreathing during noninvasive positive pressure ventilation. *Crit Care Med*. 2003;**31(8)**:2178–82.
15. Fraticelli AT, Lellouche F, L'Her E, Taille S, Mancebo J, Brochard L. Physiological effects of different interfaces during noninvasive ventilation for acute respiratory failure. *Crit Care Med*. 2009;**37(3)**:939–45.
16. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. *Eur Respir J*. 2010;**36(2)**:362–9.
17. Weng M. The effect of protective treatment in reducing pressure ulcers for non-invasive ventilation patients. *Intensive Crit Care Nurs*. 2008:**24(5)**;295-9.
18. Callaghan S, Trapp M. Evaluating two dressings for the prevention of nasal bridge pressure sores. *Prof Nurs*. 1998;**13(6)**:361-4.
19. Otero DP, Domniguez DV, Fernandez LH, Magarino AS, Gonzalez VJ, Klepzing JV, *et al*. Preventing facial pressure ulcers in patients under non-invasive mechanical ventilation: a randomised control trial. *J Wound Care*. 2017:**26(3)**;128-36.
20. Moore ZE, Webster J. Dressings and topical agents for preventing pressure ulcers. *Cochrane Database Syst Rev*. 2013:**(8)**: CD009362.

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Clinical Paper

Renal and Ureteric Stone Composition: A five year retrospective study for Northern Ireland

Matthew Tyson[1], Nathen Grimes[2], Laura McAuley[1], Derek Hennessy[1], Ajay Pahuja[3], Michael Young[1]

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Key Words: Calculi, Renal, Ureteric, Stone, Calcium oxalate, phosphate, struvite, urate, Cystine

ABSTRACT

Introduction: The study aimed to present the types of renal and ureteric stones (calculi) present in the population of Northern Ireland. The data may help in future planning treatment of stone services, patient education and prevention.

Methods: Consecutive retrospective renal and ureteric stones analysed over 5.75 years (January 2008 – September 2013) in Northern Ireland. Exclusions included patients < 16 years, and calculi listed as bladder stone.

Results: Total of 1618 stones analysed. Male to female calculi ratio 1.93: 1. Age range 16 – 94 years (52.2 mean), most common age for stone analysis 31–60 years. From 2008 to 2012 the number of stones analysed increased by 132.9%. Calcium was demonstrated in 94.5% (1529) of stones, of which 2.5% (40) pure calcium oxalate. Calcium oxalate and phosphate 72.9% (1182) of all stones, male to female ratio 2.4:1. Stones containing uric acid 9.6% (156), with uric acid male to female ratio 4.83:1. Struvite 13.7% (222), male to female ratio 1:1.6. Pure cystine 1.1% (18) of stones, male to female ratio 1:1.3.

Conclusion: There is a high proportion (94.4%) of stones containing calcium oxalate in Northern Ireland; these patients should be aiming to produce 2L of urine a day to aid prevention. Most common age for stone analysis (31–60) is in keeping with most common age for presentation. The steep increase in calculi analysis of 132.9% must be met with personalised stone treatment and prevention strategies.

INTRODUCTION

Renal stones (calculi) have afflicted the human population for thousands of years, having been identified in Egyptian mummies, and even make up part of the classical Hippocratic Oath from the 4th century BC[3] Renal stones can be identified in 8% of the population[2], which translates to 148160 people living with renal stones in Northern Ireland. In the United Kingdom renal colic is common, with 12% of men and 6% of women having at least one episode of renal colic in their lifetime, with the annual incidence of 1-2 per 1000 and incidence peaking at 40-60 years of age for men and late 20's for women.[2,4] This translates to a potential 3752 patient presentation per year for renal colic in Northern Ireland, with potential for consuming Emergency Department time and resources. The difference between male and female risk is decreasing, this is likely due to the increase in obesity and western diet.[5] The overall incidence of renal stones is rising. In America, an incidence rate of 1 in 20 in 1994 has almost doubled to 1 in 11 when compared to year 2007-2010 data.[7] The risk of further stone development is high, with 30% to 40% chance of recurrence at 5 years.[5]

The aim of the study was to present the epidemiological data for renal stone composition for Northern Ireland. The data could aid planning of the urological service including treatment and prevention of patient's renal and ureteric stones. A retrospective review of 5.75 years of renal and ureteric stones submitted for analysis was conducted between 2008 and 2013, to allow for adequate numbers and an appreciation of the growing demand for the service. The European Association Urology (EAU) states that composition of the stone is important for future treatment and prevention strategies[1], hence the need for renal stone analysis. Stones are classified in many ways, the commonest is grouping by their biochemical constituents.

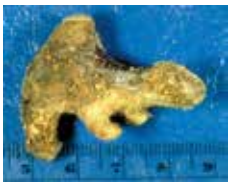
MATERIALS AND METHOD

The retrospective study period was from January 2008 to September 2013 inclusive. A consecutive list of urinary tract stones was generated by the central laboratory responsible for analysis. The majority of Northern Irish renal stones are sent for analysis at the same laboratory. During the study period all stones were analysed with wet chemistry methods. Exclusion and inclusion criteria are demonstrated in table 2.

1. Craigavon Area Hospital, 2.Altnagelvin Hospital, 3. Belfast City Hospital, Northern Ireland

TABLE 1.

Common Renal Calculi[2]

Stone Type	Percentage of all stones	Notes
Calcium-based calculi 	60-80% of all stones	Composed on Calcium oxalate, or more rarely calcium phosphate. Commonly contain oxalate and phosphate.
Struvite stones (Triple phosphate, infection stones) 	10 -15%	Composed of Calcium, magnesium and ammonium phosphate. Slightly more common in women
Uric Acid 	5-10%	Form in acidic urine, and common in patients with diet high in animal protein
Cysteine 	1%	Caused by hereditary Cystinuria.
Other	1%	Including drug stones, xanthine, carbonate.

(Images open access, BAUS)

TABLE 2:

Inclusion and exclusion criteria

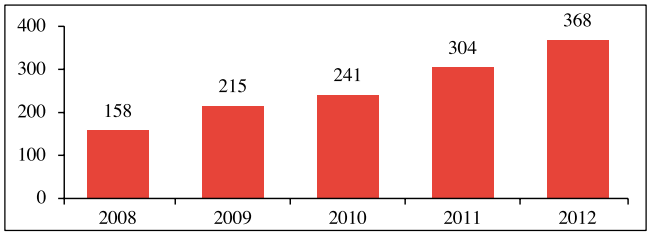
All urological stones submitted for analysis between 04/01/2008 and 18/09/2013	• Total 1808
Patient <16 excluded	• Total 47
Non labeled renal or ureteric stones excluded	• Total 82
Stones excluded for laboratory reasons	• Total 61
Total number of renal and ureteric stones in series	• 1618 renal and ureteric calculi

RESULTS

Between the 04/01/2008 to the 18/09/2013 a total of 1618 renal and ureteric stones were analysed. Overall, 1.93:1, male to female ratio. The number of stones analysed per year is demonstrated in Table 3, with an increase of 132.9% calculi analysed from 2008 to 2012 (most recent complete year).

TABLE 3

Number of Stones Analysed per year

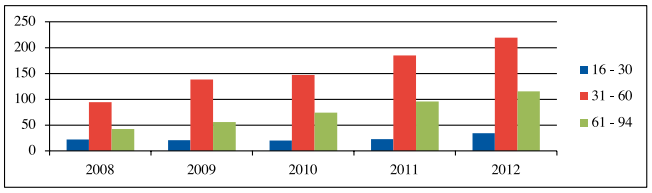


(2013 was an incomplete year in the series, demonstrating 332 stones analysed over 9 months of the year).

Overall distribution of patient age for stones analysed, table 4, noted age range of 16-94 years (mean 52.2 years).

TABLE 4

Number of Stones per Year per Age Group



Calcium containing stones totalled 94.5% (1529) of all stones analysed. Calcium oxalate mixed with varying concentrations of phosphate was 73.1% (1182) of stones. Pure calcium oxalate stones totalled 2.5% (40). No pure calcium phosphate stones were reported. Reviewing the written reports of the 1182 stones reported as calcium oxalate containing phosphate, there were 8 reports not specifying the type of calcium phosphate, otherwise apatite was listed, but not brushite.

Uric acid containing stones totalled 9.6% (156). There were no pure ammonium urate stones, but there were 1.1% which contained ammonium urate in part.

Overall 13.7% of stones were Struvite containing. Of these 99% contained some degree of calcium oxalate and 51.8% contained some dahilite (carbonate) in composition. Overall, as expected, 1.1% of analysed calculi were cystine based.

DISCUSSION

The number of stones being analysed has increased considerably year on year, for all age groups, during the study period (132.9%, 2008 year to 2012). The population of Northern Ireland is increasing,[8] as is the rate of obesity,[9] and so there will be a continued predicted increase in renal stone presentations. To ensure the most reliable results, the EAU recommend infrared spectroscopy or x-ray diffraction[1] over the wet chemistry method which was practised during this study period. Smaller samples are able to be analysed using infrared spectroscopy over wet chemistry, with a moderate increase in cost[16]. Whilst x-ray diffraction allows exact differentiation of all crystalline components, the high cost is often restricting[16]. It is unlikely that analysis by infrared spectroscopy or x-ray diffraction would see a significant shift in stone composition for Northern Ireland.

The 31-60 year old age group demonstrated the largest number of renal stones analysed each year of the study, in keeping with expected age of first calculi presentation.[2] However with an aging population,[8] the over 61 years group had the highest increase in stone analysed with a 173.8% increase (2008 to 2012 complete years).

Northern Irish calculi do not demonstrate any dramatic deviation away from the normal text book distribution for composition or epidemiological distribution.[2] There does appear to be a possible higher proportion of calcium oxalate calculi containing some degree of calcium phosphate, comprising 72.9% of calculi analysed. Mixed calcium oxalate and phosphate calculi are common,[2] tending to have a higher urinary pH then those with pure calcium oxalate stones, and demonstrate lower urinary citrate, hypercalciuria, and patients experience more frequent stone events.[10] Given the high proportion of calcium oxalate containing phosphate, this may be associated with incomplete distal tubular acidosis in the population.

Calcium phosphate in the form of brushite is a high risk for recurrence, but in the 5 year study only a possible 8 brushite calculi were identified, the remainder being calcium phosphate in the form of apatite.

Cysteine stones comprised 1.1% of stones analysed, in keeping with the expected number.[2] These stones are more likely to present in the paediatric population, where they comprise 6-8% of stones. Their management is multimodality, including paediatrics, renal, urology and dieticians,[11] and given the small numbers in Northern Ireland, may be best managed under a centralised team. The adult fluid urine output should aim to exceed >3L/day, with dietary restriction in methionine and salt intake no greater then 2g/day to reduce recurrence.[1]

The gold standard for adult identification of renal or ureteric

TABLE 5

Stones by composition, age and sex for Northern Ireland 2008 -2013

Stone composition	AGE 16-30 years		AGE 31-60		AGE 61+		Male to Female ratio	Overall total
	Male	Female	Male	Female	Male	Female		
Calcium Oxalate and Phosphate	76 (6.4%)	38 (3.2%)	530 (44.8%)	211 (17.9%)	230 (19.5%)	97 (8.2%)	2.4:1	1182 (73.1%)
Calcium Oxalate	0	0	19 (47.5%)	7 (17.5%)	7 (17.5%)	7 (17.5%)	1.86:1	40 (2.5%)
Uric Acid	0	0	26 (37.1)	6 (8.6%)	32 (45.7%)	6 (8.6%)	4.83:1	70 (4.3%
In Part Uric acid	0	1 (1.2%)	31 (36%)	12 (14%)	37 (43%)	5 (5.8%)	3.8:1	86 (5.3%)
Struvite	10 (4.5%	16 (7.2%)	39 (17.6%)	74 (33.3%)	35 (15.8%)	48 (21.6%)	1:1.6	222 (13.7%)
Cystine	3 (16.7%)	5 (27.8%)	5 (27.8%)	4 (22.2%)	0	1 (5.6%)	1:1.3	18 (1.1%)
Total	89	60	650	314	341	164	1.93:1	1618

calculi is a non-contrast CT KUB (Kidney, Ureter, and Bladder).[2] Since 94.5% of all calculi analysed contained some degree of calcium, this may aid calculi identification on plain X-ray KUB. Thus a plain x-ray KUB should be conducted the same day as identification of calculi on CT KUB if conservative or pharmacological management of calculi is planned.

The potential for a treatable cause of calculi production highlights the need for these patients to undergo at least a basic calculi workup, and can be undertaken prior to urological or endocrinology review. This must include medical history, drug history, prior renal calculi or family history, urinalysis (especially pH) and blood for renal function, calcium and uric acid. Primary hyperparathyroidism is responsible for an estimated 5% of calcium stone formation, with 20% of patients with primary hyperparathyroidism forming stones.[10]

Patients can potentially reduce their risk of calculi formation by undertaking general preventative measures. Such as fluid intake of 2.5-3.0 l/d (litres a day), aiming for a urine output of 2.0-2.5 l/d, normal calcium intake (1-1.2g/d), low salt (NaCl 4-5g/d), reduced animal protein (0.8-1.0 g/kg/d).[1] Obesity is on the rise with 61% of adults measured in Northern Ireland 2014, are either overweight (37%) or obese (24%),[12] but a BMI of 18-25 should be the aim to reduce risk of stones, as well as other health benefits.[1]

With the rise in obesity in Northern Ireland, the number of uric acid stones and also calcium oxalate stones may increase.[13] There would be the potential to treat more patients medically, with chemo-lysis of their uric acid stones, and thus avoiding potential surgery. The identification of stone composition is becoming more reliable with the use of diagnostic non-contrast CT, as well as reducing radiation dose.[14]

The data gives an extensive view of renal calculi composition with age and sex distribution throughout Northern Ireland. Data is incomplete from the Western Trust however, with the majority of their calculi sent to Birmingham for analysis. The addition of these calculi is unlikely to change the overall impression given the large numbers already involved in the study, covering a population of 1.63 million, from a total Northern Irish population of 1.876 million[17].

The stone burden for Northern Ireland is likely to increase, requiring an increase in surgery. The dramatic 173.8% increase in the 61 year old and beyond group could provide challenges to future surgery and increasing risk to the patient with an age related increase in co-morbidity.[15] To limit the burden on the health care system, preventative measures should be undertaken at a population level, tackling adequate hydration and obesity.

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REFERENCES

1. European Association of Urology. Urolithiasis. Available at: http://uroweb.org/guideline/urolithiasis/#3. Acessed 02.05.18
2. British Association of Urological Surgeons. Kidney Stones. Available at: https://www.baus.org.uk/patients/conditions/6/kidney_stones. Accessed 02.05.18
3. Tefekli A, Cezayirli F. The history of urinary stones: in parallel with civilization. Sci World J. 2013 Nov 20;2013:423964.
4. Bultitude M, Rees J. Management of renal colic. BMJ. 2012 Aug 29;345:e5499.
5. Best Practice Advocacy Centre New Zealand. *Managing patients with renal colic in primary care: know when to hold them. BPJ. 2014 60.*
6. *National Institute of Health and Clinical Excellence*. Renal or ureteric colic – acute. Available at: https://cks.nice.org.uk/renal-or-ureteric-colic-acute#!backgroundsub:2. Accessed 02.05.18
7. Romero V, Akpinar H. Kidnet Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors: Reveiws in Urology. 2010 (12) 86-96
8. *Northern Ireland Statistics and Research Agency*. Statistics, Population. Available at: https://www.nisra.gov.uk/statistics/population. Accessed 02.05.18
9. Northern Ireland Assembly Archive Site. Inquiry into Obesity – Institute of Public Health in Ireland. Available at: http://archive.niassembly.gov.uk/record/committees2008/HSSPS/090226_obesity.htm. Accessed 02.05.18
10. Potts, J. Essential Urology: A Guide to Clinical Practice. 2nd Ed. New York. Humana Press. 2012.
11. Ahmed K, Dasgupta P, Khan MS. Cystine calculi: challenging group of stones Postgraduate Medical Journal 2006;82:799-801.
12. Department of Health, Social Services and Public Safety Northern Ireland. A Fitter Future For All. Available at: http://www.northerntrust.hscni.net/pdf/FitfuturesforallObesityFrameworkNI2012.pdf. Accessed 02.05.18
13. Jeong JY, Doo SW, Yang WJ, Lee KW, Kim JM. Differences in Urinary Stone Composition according to Body Habitus. Korean J Urol. 2011 Sep;52(9):622-5.
14. Chaytor RJ, Rajbabu K, Jones PA, McKnight L. Determining the composition of urinary tract calculi using stone-targeted dual-energy CT: evaluation of a low-dose scanning protocol in a clinical environment. Br J Radiol. 2016 Nov;89(1067):20160408.
15. Chikuda H, Yasunaga H, Horiguchi H, Takeshita K, Sugita S, Taketomi S, et al. Impact of age and comorbidity burden on mortality and major complications in older adults undergoing orthopaedic surgery: an analysis using the Japanese diagnosis procedure combination database. BMC Musculoskelet Disord. 2013 May 28;14:173.
16. Basiri A, Taheri M, Taheri *F.* What is the State of the Stone Analysis Techniques in Urolithiasis? Urology Journal. 2012 April; 09;02.
17. Population UK, Northern Ireland Population 2018. Available at:
18. https://www.ukpopulation.org/northern-ireland-population/

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Clinical Paper

A Comparison of Inpatient and Outpatient-Based Chemotherapy Regimens for the Treatment of Acute Myeloid Leukaemia In The Elderly

A.B. Daly[1], R Cuthbert[1], D Finnegan[1], C Arnold[1], C Craddock[2], M.F. McMullin[1*]

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Key words: Acute Myeloid Leukaemia, non-intensive chemotherapy, treatment, outcomes, toxicity.

Abstract

Introduction: Acute myeloid leukaemia (AML) is an aggressive haematological malignancy which is more common in the elderly and has a poor 5-year survival. There are no established beneficial interventions to treat AML in elderly patients. It is unclear whether outpatient delivery of palliative chemotherapies could reduce the burden of disease and hospitalisation for this group.

Aims: To compare overall survival, response to treatment and supportive care needs between inpatient and outpatient-based treatments for AML in elderly patients.

Materials & Methods: We undertook a retrospective cohort study in the Haematology Department at Belfast City Hospital comparing overall survival (OS), treatment responses and supportive care needs between inpatient and outpatient treatments for AML in elderly patients. Consecutive entrants to outpatient and inpatient based clinical trials between February 2013 and January 2017 were included. Case notes, chemotherapy charts, clinic letters, blood bank and electronic care records were analysed.

Results: OS and rates of CR (complete remission), CRi (CR with incomplete count recovery) and PR (partial response) was not significantly different between inpatient and outpatient regimens with a median OS of 201 vs. 124 days, respectively. No response was observed in 35% of patients in the inpatient group compared with 65% of the outpatient group, however this did not reach significance. Of patients who achieved CR/CRi in the outpatient group, 75% relapsed at a median of 271 days, compared with 60% of the inpatient group at a median of 209 days. At least one grade 3-4 toxicity was experienced by 90% and 83.3% of inpatient and outpatient groups, respectively. There was no difference in six common grade 3-4 toxicities. Patients on the outpatient regimen spent fewer days in hospital but had a median packed red cell use of more than twice that of the inpatient group. No difference was noted in infections, days on antibiotics or platelet use.

Discussion: Our data suggests that outpatient chemotherapy is safe and can reduce hospitalisation for elderly patients with AML, without a decline in OS or response rates. These results provide an important rationale to test the comparative efficacy of outpatient chemotherapy. Chemotherapy related toxicities remain a significant source of morbidity in this population and highlight the need to develop novel, targeted therapies for this age group.

INTRODUCTION

Acute Myeloid Leukaemia (AML) is an aggressive group of haematological malignancies that are more common in the older population with a median age of onset at ~65years [1]. Despite recent therapeutic advances in younger patients, little improvement has occurred in the survival of older patients. Five year survival rates remain poor at ~5% in patients >60 years compared with up to 50% in younger patients [2,3]. It has been established that treatment of elderly patients with intensive chemotherapy is often futile, resulting in more early deaths and unacceptable toxicities compared with younger age group [4]. In addition, responses to chemotherapy are poorer and relapse rates are higher in older patients [5].

There are currently no established beneficial therapeutic interventions to treat AML in elderly patients and as such, enrolment in clinical trials investigating combinations of low dose chemotherapy is the recommended approach [3,6]. While determining the optimal chemotherapy regimens in the elderly has received much research interest, little attention

1. Department of Haematology, Belfast City Hospital, Belfast, N. Ireland. 2. Centre for Clinical Haematology, Queen Elizabeth Hospital, Birmingham

Corresponding author: Dr Aideen Daly

E-mail: adaly14@qub.ac.uk

has been paid to the clinical setting needed to support their delivery. It is unclear whether an outpatient delivery of such palliative regimens represents a treatment option which would potentially reduce the burden of hospitalisation and improve quality of life. To determine if chemotherapy regimens differ in efficacy or tolerability according to the clinical setting they are delivered in, we undertook a retrospective analysis of an outpatient based chemotherapy regimen (Phase II Randomised Trial of 5-Azacitidine versus 5-Azacitidine in combination with Vorinostat in patients with Acute Myeloid Leukaemia or High Risk Myelodysplastic Syndromes Ineligible for Intensive Chemotherapy- RAvVA trial) [7] and an inpatient based low dose chemotherapy regimen in patients with high risk MDS and AML unsuitable for intensive chemotherapy.

AIM & STUDY DESIGN

This was a retrospective cohort study carried out in the Haematology Department of Belfast City Hospital to compare overall survival, response to treatment and supportive care needs between inpatient and outpatient-based protocols for AML in elderly patients. Inpatient based treatment consisted of 4 cycles of low dose cytarabine (20mg BD subcutaneously, days 1-10) +/- another experimental drug at 28-42-day intervals as part of the AML- LI1 trial. Within the RAvVA outpatient trial, patients received either Azacitidine alone (75mg/m^2 days 1-9) or a combination of Azacitidine (75mg/m^2 days 1-9) + Vorinostat (300mg BD days 3-9 PO) for six 28-day cycles before assessment of response.

MATERIALS & METHODS

Patient selection

Inclusion criteria: Inpatient regimen included patients with newly diagnosed *de novo* or secondary AML (excluding Acute Promyelocytic Leukaemia; aPML) or high risk MDS (>10% blasts). Outpatient regimen included patients with *de novo* or secondary AML, including relapsed AML and able to undertake treatment on an outpatient basis. Inclusion criteria common to both groups include age >60, unfit for intensive chemotherapy and undergoing less intensive treatment within a clinical trial. All patients provided written informed consent.

Exclusion criteria: aPML or blast transformation of CML, previous cytotoxic chemotherapy or allogenic haematopoietic stem cell transplant for AML, concurrent active malignancy under treatment, pregnant or lactating, adults of reproductive potential not willing to use appropriate and effective contraception during the trial and specified time afterwards, serum creatinine of ≥175umol/L, AST ≥2.5 x ULN (Upper limit of normal) and/or ALP ≥2.5 x ULN, total bilirubin ≥1.5 x ULN unless due to Gilbert's syndrome, any active infection including fungal, bacterial and viral infections (HIV, Hepatitis), history of MI, unstable angina, cerebrovascular accident or TIA within 6 months. Further specific cardiac exclusion criteria were added for selected drugs used alongside low dose cytarabine in the inpatient regimen (Appendix 1).

Appendix 1:

Specific cardiac exclusion criteria for Ganetespib:

- Myocardial infarction within 12 months, uncontrolled angina within 6 months, current or history of congestive heart failure- New York Heart Association (NYHA) class 3 or 4 unless an echocardiogram or multiple gated acquisition scan performed either within 1 month prior to study screening or during screening results in a left ventricular ejection fraction that is >45% or institutional lower limit of normal value.
- Diagnosed or suspected long QT syndrome. Any history of clinically significant ventricular arrhythmia.
- Prolonged QTc interval on pre-entry ECG
- Uncontrolled hypertension
- Obligate need for a pacemaker
- Complete left bundle branch block
- Uncontrolled atrial fibrillation

Consecutive entrants to both trials between February 2013 and January 2017 were included. Baseline characteristics were compared across both groups. Co-morbidities were graded using the Haematopoietic Cell Transplant Comorbidity Index (HCT-CI) indicating severity of co-morbidity and risk of mortality (0= low risk, 1-2= intermediate risk, >2=high risk) [8]. Cytogenetic reports from Northern Ireland Regional Genetics Laboratory at Belfast City hospital were analysed using StarLims database and categorised into favourable, intermediate or poor cytogenetic risk.

Endpoints

Primary endpoint was overall survival (OS), measured from date of randomisation to trial as documented by Clinical Trials Nurse within patient notes, to date of death as documented on electronic care record (ECR). Alive patients were censored at date of analysis.

Response

Response to therapy was evaluated following each cycle of treatment on the inpatient regimen and after six cycles of the outpatient regimen. Response was categorised as Complete remission (CR), complete remission with incomplete recovery of neutrophils or platelets (CRi), partial remission (PR) or none. Patients who died during treatment before evaluation of response were classified as 'early deaths'[9]. Blood results of patients who experienced an 'early death' were analysed by a clinically trained researcher and further classified into 'Haematological Improvement' (HI) or 'no HI' depending on trends of blood counts during and following treatment. Duration of response was calculated from time of confirmed remission to date of relapse on bone marrow biopsies (blast count >5%).

Toxicity criteria

Data for reported toxicities was sourced from patient notes, clinic letters and discharge letters. Patients within the outpatient trial had chemotherapy charts in which toxicities

were documented and graded by trained nursing staff. All toxicities were graded for severity using a scale from 1-4 as per National Cancer Institute Common Terminology Criteria for Adverse Events; NCI CTCAE v4 [10].

Supportive care needs

Blood product use including platelets and packed red cells (units), number of hospital admissions, number of days spent in hospital, infections and antibiotic use were documented using patient notes, blood bank records and ECR.

Statistical Analysis

Comparisons of baseline characteristics and supportive care requirements between RAvVA and the outpatient regimen were undertaken using the Mann-Whitney test. Kaplan-Meier curves were generated to depict overall survival in each group and overall survival was compared using the log rank test. Contingency analysis using the Chi-Squared test was undertaken to compare rates of response and the occurrence of severe toxicities in each group. For the purpose of these comparisons patients who died before undergoing a bone marrow biopsy were excluded from the analysis. All p-values reported are two-tailed, a p-value of < 0.05 was considered statistically significant.

TABLE 1:

Baseline Characteristics

	RAvVA	Inpatient Regime
N	17	20
Gender (%)	M= 71	M= 60
	F= 29	F= 40
	Median (SD)	
Age (years)	72 (7.3)	72 (4.0)
Blast (%)	33 (31.2)	49.5 (30.1)
WCC on presentation (x10^9)	2.5 (14.0)	4.9 (14.3)
Platelets on presentation (x10^9)	34 (57.6)	29 (36.5)
Haemoglobin on presentation (g/L)	93 (11.4)	95 (20.8)
	Severity of co-morbidity: HCT CI score* (no of patients)	
0 (low)	5	4
1-2 (intermediate)	5	7
>2 (high)	7	9

**HCT-CI (Haematopoietic Cell Transplant- Comorbidity Index) comprises 17 different categories of organ dysfunction and indicates severity of co-morbidities and risk of mortality.*

RAvVA trial= Randomised Trial of 5-Azacitidine versus 5-Azacitidine in combination with Vorinostat in patients with Acute Myeloid Leukaemia or High Risk Myelodysplastic Syndromes Ineligible for Intensive Chemotherapy

RESULTS

Description of study cohort

From an initial sample of 40 patients, a total of 37 patients were included, all of whom had a diagnosis of AML or high risk MDS between February 2013 and January 2017. Reasons for exclusion include one patient with age below 60 years, and two patients who were initially enrolled on the inpatient regimen and subsequently entered the outpatient RAvVA trial following relapse. For these patients, analysis was limited to outcomes whilst on inpatient regimen only. Seventeen patients were part of the RAvVA outpatient-based trial, and 20 patients had or were undergoing treatment as an inpatient receiving low dose chemotherapy at the time of the study. Baseline characteristics are summarised in Table 1. There were no significant differences between any of the variables analysed. Evaluation of cytogenetic risks in the inpatient regimen revealed 9 and 10 patients in the poor and intermediate categories, respectively, compared with 4 and 13 patients in the outpatient group (p=0.71). One patient had incomplete cytogenetic analysis due to poor quality metaphases on cell culture.

Overall survival

There was no significant difference in overall survival between inpatient and outpatient delivered regimens (Figure 1), with a median no. of days of 201 vs. 124, respectively; p=0.3284. Overall percentage survival at 1 year was 19% and 5% at 2 years, which is consistent with findings from similar studies [1,11,12].

Response

In those who underwent bone marrow examination rates of CR, CRi and PR (31%, 8% and 8% vs. 13%, 13% and 0%, respectively) were not significantly different between inpatient and outpatient groups overall. There was a nominally greater rate of patients with no response to therapy in the outpatient group (73%, n=11) than the inpatient group (54%, n=7) but this failed to reach statistical significance (p= 0.28). There was a trend to more early deaths in the inpatient group than the outpatient group (n= 7; 35% vs. n=2; 12%

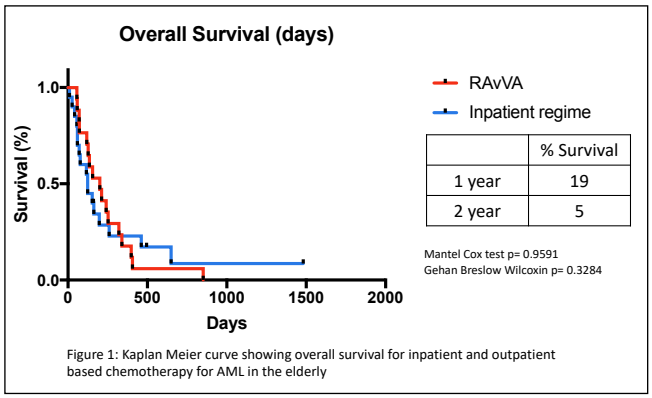

Figure 1: Kaplan Meier curve showing overall survival for inpatient and outpatient based chemotherapy for AML in the elderly

Fig 1. Kaplan Meier curve showing overall survival for inpatient and outpatient (RAvVA trial) based chemotherapy for AML in elderly

p=0.10). Further analysis of early deaths within both groups revealed a haematological improvement (HI) in one patient in both groups. It is possible that patients with early death and no HI may represent no response, therefore providing a potential explanation the lower rates of 'no response' in the inpatient group compared with the outpatient group. Of those who achieved CR or CRi in the outpatient group (n=4), seventy-five percent relapsed with an average time to relapse of 252 days (range 92-393). Sixty percent (n=3) of the patients who achieved CR or CRi in the Inpatient group relapsed with an average time to relapse of 236 days (range 170-330).

Toxicities

At baseline, 65.8% of all patients had a haemoglobin, white cell count or platelet count that would be classed as a grade 3 or 4 toxicity as per NCI common toxicity criteria. Further analysis was limited to non-haematologic toxicities, of which the majority were mild- moderate at grade 1-2 (73% and 59% of all reported toxicities in outpatient and inpatient regimen, respectively). Interestingly, 83.3% of patients in the outpatient and 90% of the inpatient group experienced at least one grade 3 or 4 toxicity which is defined as severe or life threatening. There were seven common grade 3 or 4 toxicities across both groups including sepsis, epistaxis, hypokalaemia, pulmonary oedema and fatigue (Table 2). There was no statistically significant difference between the two groups for any single grade 3/4 toxicity. Of note, over 50% of patients in both groups experienced life threatening sepsis.

Supportive Care Requirements

Unsurprisingly, patients treated on the outpatient regimen spent significantly less time in hospital with a calculated median number of days in hospital of 42 days compared with 80 days for inpatient group, including treatment days (p=0.0016). Both groups had a median of 2 hospitalisations, reflecting longer duration of in-hospital stay per admission on the inpatient regime. Despite this, packed red cell use was significantly higher in the outpatient group with a median of 26.5 units, compared with 12.5 units for the inpatient group (p=0.038). There was no difference between the outpatient and inpatient regimens for number of infections (median 3 vs. 2; p=0.96), days on antibiotics; (41.5 vs 41; p=0.54); or units of platelets required (15 vs 14, p=0.93), respectively.

TABLE 2:

Grade 3/4 Toxicities

Grade 3/4 Toxicity	IP regime	RAvVA
Sepsis	13	9
Epistaxis	3	2
Hypokalaemia	2	3
Pulmonary oedema	2	1
Hyponatraemia	2	1
Fatigue	1	1
Hypotension	1	1

DISCUSSION

We aimed to identify and characterise differences in outpatient and inpatient based chemotherapy regimens for elderly patients with AML. To our knowledge, this is the first study to compare clinical setting for delivery of palliative chemotherapy in this group. The average cost of treating elderly patients with AML has been estimated at around $42,000 in a US study [12]. Whilst treatment of AML has historically been associated with prolonged periods of hospitalisation, there has been much interest in shifting from inpatient to outpatient treatment to reduce medical resource utilisation and burden of hospitalisation [13]. Interestingly, a number of studies have been carried out which support early discharge of patients following intensive induction/ salvage chemotherapy for AML and suggest delivery of supportive care as an outpatient to be safe without negatively impacting on survival [14-16]. Similarly, the data presented here demonstrates no significant difference in the primary endpoint of overall survival or response to treatment between inpatient and outpatient delivery of chemotherapy (p= 0.3284). In keeping with the aim of reducing hospitalisation costs, there was a significant difference in the number of days spent in hospital with patients treated on the outpatient regimen spending on average less than half the time in hospital as patients on the inpatient regimen. Despite the observational nature of this study and baseline differences in patient characteristics, our work provides a rationale to explore the efficacy of this approach in interventional studies.

As with all types of chemotherapy, monitoring toxicity and prompt access to medical care is imperative. Analysis of toxicity and supportive care needs in this study revealed a high percentage of patients in both groups experiencing at least one life threatening or severe toxicity, with over half of the patients in both groups experiencing sepsis. Comparison between groups showed significantly more mild to moderate toxicities and higher packed red cell use in the outpatient group. Possible explanations for this include more reporting of toxicities as a result of close monitoring by day unit staff on a chemotherapy chart in the outpatient regimen, and also the preparation of 'standing orders' of packed red cells for patients receiving outpatient chemotherapy in a day unit. Furthermore, inclusion of 6 patients with relapsed AML in the RAvVA trial, and no participants with relapsed AML in the inpatient regimen may have constituted a subgroup of patients with more advanced disease and a higher requirement for blood product support. Nevertheless, this suggests that with delivery of an outpatient-based chemotherapy regimen, patient education on early recognition of chemotherapy related complications and sepsis is essential, as well as adequate facilities to provide supportive medical treatment as required.

This study has several limitations, including a small sample size and absence of a sample size calculation, reducing the external validity. We relied on accurate documentation of toxicities, blood product use and antibiotic duration on

discharge letters, patient notes and chemotherapy charts, many of which were not intended for research purposes. Different combinations of chemotherapy were a baseline confounding variable.

CONCLUSION

Survival of elderly patients with AML remains unfavourable even with advances in treatments over recent decades. Despite less intensive treatments with palliative chemotherapy, the burden of toxicities and hospitalisations for patients in this age group is still noteworthy. We postulate that there may be a role for outpatient-based chemotherapy in reducing hospitalisations and enhancing quality of life for elderly patients with AML without a decline in overall survival or response rates. A larger scale randomised controlled trial to compare inpatient and outpatient delivery of chemotherapy would be a suitable way to clarify this further.

CONFLICTS OF INTEREST

M.F McMullin has been on a speakers bureau and received funding for travel to Celgene Conference.

REFERENCES:

1. Thein MS, Ershler WB, Jemal A, Yates JW, Baer MR. Outcome of older patients with acute myeloid leukemia: an analysis of SEER data over 3 decades. *Cancer.* 2013;**119(15)**:2720-7.
2. Juliusson G, Antunovic P, Derolf A, Lehmann S, Möllgård L, Stockelberg D, *et al*. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009;**113(18)**:4179-87.
3. Krug U, Buchner T, Berdel WE, Muller-Tidow C. The treatment of elderly patients with acute myeloid leukemia. *Dtsch Arztebl Int*. 2011;**108(51-52)**:863-70.
4. Knipp S, Hildebrand B, Kundgen A, Giagounidis A, Kobbe G, Haas R, *et al*. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. *Cancer.* 2007;**110(2)**:345-352.
5. Krug U, Rollig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, *et al*. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet*. 2010;**376(9757)**:2000-2008.
6. Walter RB, Estey EH. Management of older or unfit patients with acute myeloid leukemia. *Leukemia*. 2015;**29(4)**:770-5.
7. Craddock CF, Houlton AE, Quek LS, Ferguson P, Gbandi E, Roberts C, *et al*. Outcome of azacitidine therapy in acute myeloid leukemia is not improved by concurrent vorinostat therapy but is predicted by a diagnostic molecular signature. *Clin Cancer Res*. 2017;**23(21)**:6430-40.
8. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, *et al*. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;**106(8)**:2912-9.
9. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, *et al*. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003;**21(24)**:4642-9.
10. National Cancer Institute. Safety Profiler: Common Terminology Criteria for Adverse Events *v4.0*. [Internet]. Available from: https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx . [Last accessed September 2018].
11. Buchner T, Berdel WE, Haferlach C, Haferlach T, Schnittger S, Müller-Tidow C, *et al*. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol*. 2009;**27(1)**:61-9.
12. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. *Arch Intern Med*. 2002;**162(14)**:1597-603.
13. Nerich V, Lioure B, Rave M, Recher C, Pigneux A, Witz B, *et al*. Induction-related cost of patients with acute myeloid leukaemia in France. *Int J Clin Pharm*. 2011;**33(2)**:191-9.
14. Walter RB, Taylor LR, Gardner KM, Dorcy KS, Vaughn JE, Estey EH. Outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia. *Clin Adv Hematol Oncol*. 2013;**11(9)**:571-7.
15. Saini L, Minden MD, Schuh AC, Yee KW, Schimmer AD, Gupta V, *et al*. Feasibility of outpatient consolidation chemotherapy in older versus younger patients with acute myeloid leukemia. *Am J Hematol*. 2012;**87(3)**:323-6.
16. Vaughn JE, Buckley SA, Walter RB. Outpatient care of patients with acute myeloid leukemia: Benefits, barriers, and future considerations. *Leuk Res*. 2016;**45**:53-8.

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Clinical Paper

All-Cause Mortality Amongst Patients Undergoing Above and Below Knee Amputation in a Regional Vascular Centre within 2014-2015

GEM Kennedy[1], K McGarry[1], G Bradley[2], DW Harkin[1]

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Keywords: Vascular Surgery; Amputation; All-Cause Mortality; Pulmonary Embolism; Deep Vein Thrombosis

Abstract

Background Major lower limb amputation remains a common treatment for patients with peripheral vascular disease (PVD) in whom other measures have failed. It has been associated with high morbidity and mortality, including risks from venous thromboembolism (VTE).

Methods A two-year retrospective cohort study was conducted involving 79 patients who underwent major lower limb amputation (below- or above-knee amputation) between January 2014 and December 2015 in a single tertiary referral centre. Amputation procedures were performed for reasons relating to complications of PVD and/ or diabetes mellitus. Patients were followed-up to investigate all-cause mortality rates and VTE events using the Northern Ireland Electronic Care Record database (mean follow-up time 17 months).

Results Of the 79 patients, there were 52 male and 27 female. Mean age at time of surgery was 72 years (range 34-99 years). Forty-six patients (58%) suffered from diabetes mellitus, 29 (35%) heart failure, 31 (39%) chronic kidney disease (CKD) and 10 (13%) chronic obstructive pulmonary disease (COPD). Twenty patients (25%) were on anticoagulant therapy, and 53 (67%) were on antiplatelet therapy.

Thirty-five patients (44%) died during follow-up; mean age at death was 74 years. No statistically significant association was found between mortality rate and the level of amputation (p=0.3702), gender (p=0.3507), or comorbid diabetic mellitus (p=0.1127), heart failure (p=0.1028), CKD (p=0.0643) or COPD (p=0.4987).

Two patients experienced radiologically-confirmed non-fatal pulmonary emboli and two patients developed radiologically-confirmed deep vein thrombosis.

Conclusions The results are in agreement with current literature that amputation is associated with significant mortality, with almost half of the study population dying during follow-up. Further work should explore measures by which mortality rates may be reduced.

INTRODUCTION

Peripheral Vascular Disease (PVD) affects up to one-fifth of patients over 75 years old[1], with higher global prevalence in diabetic patients[2]. Despite advances in revascularisation and endovascular procedures, major lower limb amputation remains a common treatment end-point.

Following major lower limb amputation, 30-day all-cause mortality has been reported as 8.6%, significantly worse for above-knee amputation (AKA) than below-knee amputation (BKA) (16.5% and 5.7% respectively, p<0.001)[3]. One- and 3-year mortality rates have been reported as high as 48% and 71% respectively[4]. Risk factors associated with increased 30-day mortality include age and comorbid cerebrovascular disease[5,6]. Additionally, diabetes mellitus has been associated with poorer five-year survival[3]. Other factors shown to be independent predictors of mortality include heart failure, chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD)[7].

[1]The Vascular Centre, Royal Victoria Hospital Belfast. Royal Victoria Hospital, Belfast Health and Social Care Trust, 274 Grosvenor Rd, Belfast BT12 6BA. N. Ireland

[2] Department of Paleontology. Faculty of Earth and Atmospheric Science. University of Alberta 1-26 Earth Sciences Building. Edmonton, Alberta T6G 2E3 Canada

E-mail: gkennedy15@qub.ac.uk

Correspondence to Ms Grace Kennedy

Vascular patients undergoing major lower limb amputation are also known to be at significant risk of Venous-Thromboembolism (VTE); namely Deep Vein Thrombosis (DVT) and Pulmonary Embolus (PE). Amputation patients frequently have several pre-operative VTE risk factors, which are increased by surgery and post-operative immobility [8]. VTE has been shown to affect over 10% of patients in the 2 months following amputation[9].

National Institute for Clinical Excellence (NICE) guidelines suggest that vascular patients undergoing lower limb amputation should be considered for *at least* seven days of low molecular weight heparin therapy and should receive mechanical VTE prophylaxis until they no longer have significantly reduced mobility relative to their anticipated mobility[10]. Thus, the optimum duration of pharmacologic VTE prophylaxis is not standardised.

This retrospective cohort study followed up patients who underwent major lower limb amputation between January 2014 and December 2015 in the Belfast Vascular Surgery Unit and assessed overall mortality rates, causes of death and incidence of VTE. Associations with amputation level, sex, and comorbid diabetes mellitus, heart failure, CKD and COPD are reported.

METHODS

A two-year retrospective cohort study was conducted in March 2017. All 79 patients representing 90 amputation procedures who underwent major lower limb amputation (defined as below- or above-knee amputation) between January 2014 and December 2015 in a single tertiary referral centre for vascular surgery (Royal Victoria Hospital, Belfast) were followed up. The primary aim of the study was to establish all-cause mortality within the cohort; the secondary aim of the study was to examine VTE incidence post-amputation. Only patients undergoing amputation for complications relating to PVD were included; patients undergoing amputation for trauma, tumours or other indications were excluded. Level of amputation was determined based on the clinical judgement of the attending surgeon. Mean time from date of amputation to point of data collection was 17 months (range 0–38 months).

Patients were followed up using the Northern Ireland Electronic Care Record (NIECR) database[11]. In cases where clinical details available on NIECR were unclear, inpatient notes were requested. NIECR was also utilised as a means of identifying relevant co-morbidities. DVT and PE occurrences were recorded from accessing ultrasound and computed-tomography perfusion pulmonary angiography (CTPA) reports on NIECR. Imaging was undertaken as per clinician judgement amongst patients displaying signs/ symptoms of VTE; no screening of asymptomatic patients was conducted throughout the study period. Throughout 2014-2015, practice within the Unit was that patients received pharmacological VTE prophylaxis in the form of prophylactic-dose enoxaparin throughout their inpatient stay unless contraindicated. No formal VTE risk-assessment was routinely conducted upon discharge.

Fisher's exact test[12] was carried out using 'GraphPad StatMate 2.00' and Kaplan-Meier Survival Graphs were created using 'Eureka Statistics'. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics are illustrated in **Table 1**.

TABLE 1.

Baseline patient characteristics.

Variable	Number of patients
Gender – Male	52 (66%)
Gender – Female	27 (34%)
History of diabetes	46 (58%)
History of heart failure	28 (35%)
History of renal impairment	31 (39%)
History of chronic obstructive pulmonary disease	10 (13%)
Known use of anticoagulant	20 (25%)
Known use of single or dual antiplatelet therapy	53 (67%)

There were 79 patients (52 male and 27 female) whose mean age at the time of lower limb amputation surgery was 72 years (range 34-99 years). All amputations were conducted for reasons related to PVD associated with ischaemia and/or infection or for complications related to diabetes mellitus. Of these, 37 (47%) procedures were categorised as 'elective', 37 (47%) as 'expedited' and 5 (6%) as 'urgent' as according to the National Confidential Enquiry into Patient Outcome and Death Classification of Intervention 2004[13].

Of the cohort, 46 patients (58%) were known to have diabetes (either insulin-dependent or non-insulin-dependent). Twenty-eight patients (35%) were known to have heart failure (as identified from NIECR documentation and/or pre-operative echocardiography demonstrating an ejection fraction less than or equal to 40%). Thirty-one patients (39%) were known to have CKD (as identified from NIECR documentation and/or review of peri-operative laboratory test results demonstrating an estimated glomerular filtration rate consistently below 60ml/min/1.73m^2). Ten patients (13%) were known to have COPD (as identified from NIECR documentation).

At time of follow-up, twenty patients (25%) were using anticoagulant therapy, and 53 (67%) were using single or dual antiplatelet therapy. Indications for anticoagulant therapy are detailed in **Table 2**.

Twenty patients (25%) were bilateral amputees at the time of follow-up. Ten patients (13%) had previously undergone contralateral limb major lower limb amputation prior to

TABLE 2.

Indications for anticoagulation usage amongst the cohort.

Indication	Number of patients
Indication unclear	1
Atrial fibrillation	12
Left ventricular thrombus	1
Post-operative PE	2
Pre-operative DVT	1
Recurrent DVT	1

the study period, nine (11%) underwent contralateral limb amputation during the study period and at the time of follow-up one (1%) underwent contralateral limb amputation after the study period. Only two patients (3%) underwent revision of below-knee amputation to above-knee amputation and both of these were conducted during the study period. For analysis purposes we have focused on the first procedure conducted during the two-year follow-up period.

Regarding all-cause mortality, 35 patients (44%) were found to be deceased at follow-up, as demonstrated in **Table 3** and **Figure 1**; mean age at death was 74 years (range 38-92 years).

Age of patients dying of any cause at the various time intervals is demonstrated in **Table 4**. Of those alive at the time of follow-up, mean age at time of surgery was 71 years (range 34-99 years) and mean age at time of follow-up 72 years (range 37-101 years).

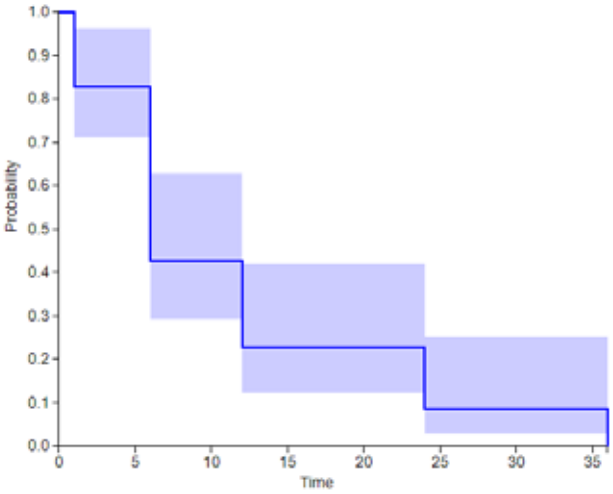

Fig 1. Kaplan-Meier survival graph considering all-cause mortality rates of 35 patients who were found to be deceased at follow-up, with 95% confidence intervals. Time is measured in months passed since operation.

TABLE 4.

Mean age of patients dying at the various time intervals.

Time interval following surgery	Mean age at time of death (years)
Within 30 days	85 years
30 days – 6 months	74 years
6 months - 1 year	74 years
1 year and 2 years	73 years
2 years and 3 three years	56 years

Mortality rates were determined by level of amputation, as demonstrated in **Figure 2.** Of the 41 patients who underwent BKA, 16 (39%) were deceased at follow-up, and of the 38 patients who underwent AKA, 19 (50%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and level of amputation (p=0.3702).

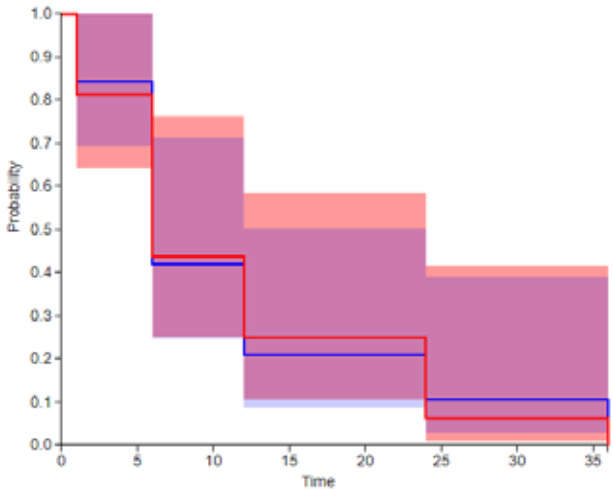

Fig 2. Kaplan-Meier survival graph for BKA (red) vs AKA (blue), with 95% confidence intervals (shaded areas). Time is measured in months passed since operation.

Of the 52 male patients, 21 (40%) were deceased at follow-up, and of the 27 female patients, 14 (52%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and

TABLE 3.

All-cause mortality rates at each of the given timeframes are demonstrated.

Timescale	Number of patients	% of those deceased (N=35)	% of overall cohort (N=79)
30-day	N=6	17%	8%
6-month	N=20	57%	25%
1-year	N=27	77%	34%
2-year	N=32	91%	41%
3-year	N=35	100%	44%

sex (p=0.3507).

Of the 46 diabetic patients, 24 (52%) were deceased at follow-up, and of the 33 non-diabetic patients, 11 (33%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and diabetic status (p=0.1127).

Of the 28 patients known to have heart failure, 16 (57%) were deceased at follow-up, and of those without known heart failure, 19 (37%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and heart failure (p=0.1028).

Of the 31 patients known to have renal failure, 18 (58%) were deceased at follow-up, and of those without renal failure, 17 (35%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and renal failure (p=0.0643).

Of the 10 patients known to have COPD, 3 (30%) were deceased at follow-up, and of those without COPD, 32 (46%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and diabetic status (p=0.4987).

Information was available on NIECR regarding the recorded primary cause of death for 13 of the 35 deceased patients (37%); inpatient records were accessed for the remaining patients to determine likely cause of death.

Causes of death were attributed to chest/ urinary sepsis (N=6), myocardial infarction (N=4), malignancy (N=4), cardiac arrest (N=3), cardiac failure (N=3), renal failure (N=3), cerebrovascular accident (N=2), ruptured common iliac artery aneurysm (N=1) and hypoxic brain injury following hyperkalaemic cardiac arrest (N=1).

Cause of death was unclear for the remaining eight patients. Of these, six deaths were documented as 'expected' and/ or the patient was receiving palliative care. However, no clinical information relating to the event of death was available for the remaining two patients.

Incidence of VTE was then determined as a secondary aim of the study. Two patients developed contralateral radiologically-confirmed DVT; one patient at two months post-amputation and the other at 15 months post-amputation. Two patients also developed radiologically-confirmed non-fatal PE within twenty days of surgery.

DISCUSSION

This study examined all-cause mortality rates amongst patients undergoing AKA and BKA within Northern Ireland's Regional Vascular Centre within 2014-2015.

The mortality rates reported reflect the frailty of the study population, with almost one-tenth of the cohort dying within one month post-operatively.

The overall 30-day mortality rate of 8% was comparable to that found by Aulivola et al[3], which is somewhat lower than rates of 22-30% demonstrated in other studies[5,6,14]. This may reflect differences in both patient demographics within the study groups and practice between the different centres, including exclusion criteria regarding high-risk patients, time from decision to amputate to surgery being conducted, and the use of amputation as a means of pain relief at the end stages of care.

In contrast to findings from Aulivola et al[3], no statistically significant association between mortality rate and level of amputation, that is, below- or above-knee, was found. Aulivola et al, however, studied a larger cohort of patients (N=788) for a longer period (11 years). Their cohort also contained a relatively higher proportion of patients undergoing BKA than ours, with 73.4% of their cohort having undergone BKA and 26.6% AKA, as opposed to 51.9% and 48.1% of our cohort undergoing BKA and AKA respectively. Fortington et al[6] also found no significant difference regarding level of amputation and we note that their ratio of AKA to BKA appears more equivocal to ours.

Similar to the findings of Fortington et al[6] and Tentolouris et al[15], but in contrast to Aulivola et al[3], no statistically significant association between mortality rate and diabetic status was found. This may represent differences between study populations but also in diabetic classification and management between centres. Although our numbers of patients are too small to make meaningful comparisons, we note 13% of the diabetic cohort as opposed to 0% of the non-diabetic cohort were deceased at 30-days. We believe that further study regarding the relationship between diabetes duration and mortality is advisable, as longer duration of diabetes has previously been associated with increased all-cause mortality post-amputation amongst diabetic patients[15].

Unlike Jones et al[7], who found heart failure to be an independent predictor of mortality following major lower limb amputation, we did not identify a significant association between the two variables. We note that Jones et al used data relating to a much larger cohort, and as not all patients routinely undergo pre-operative screening echocardiography within the Unit, patients with milder degrees of ventricular impairment may not have been identified. Furthermore, due to the small sample size, it has not been possible to examine the relationship between degree of severity of heart failure and all-cause mortality.

The findings of Aulivola et al[3], Fortington et al[6], and Jones et al[7], indicated an association between CKD and all-cause mortality following major lower limb amputation. Our results suggested a trend but this was not statistically significant. This may relate to differences in cohort size, but also to patient selection and definition of chronic kidney disease. Due to small numbers of dialysis-dependent patients it was not possible to examine differences in all-cause mortality between those with dialysis-dependent CKD and non-dialysis-dependent CKD. However, we feel that this represents an

area for future investigation with a larger cohort.

Only ten patients within the cohort were known to have COPD from NIECR documentation. Although the sample size was too small to make meaningful statistical analyses, our results would suggest that no association exists between COPD and all-cause mortality following major lower limb amputation. This finding is in keeping with that of Fortington et al[6] who did not identify an association between chronic lung disease and 30-day, one-year or five-year mortality rates. We also note that many of the cohort may have had undiagnosed COPD at the time of surgery, and that as pulmonary function tests were not readily available on NIECR we were relying on potentially incomplete information. Smoking status was not readily available on NIECR which may be associated with increased all-cause mortality due to compromised respiratory clearance mechanisms in patients with already compromised mobility.

Almost half of our cohort was deceased at three years. However, it must be remembered that limb amputation may prevent sepsis-related deaths and improve quality of life in patients affected by PVD not amenable to other treatment measures. From our data, no clear determinants of the three-year survivors were found but further investigation of this group is suggested. We also feel, given the profile of the causes of death seen, further work is warranted regarding the effects of pre-operative care and rehabilitation services on mortality.

As a secondary aim of the study, the incidence of VTE post-amputation was examined. Two patients developed radiologically-confirmed DVT and two patients developed radiologically-confirmed PE. However, PE could not be excluded amongst the three patients who died following sudden cardiac arrest (particularly as one of these patients developed bilateral PE whilst inpatient post-amputation) and amongst those for whom no cause of death was recorded.

In their prospective study following 49 patients undergoing amputation in 2007-2009, Struijk-Mulder et al[9] found that two of their patients developed confirmed DVT (one of whom was symptomatic), and six patients developed confirmed PE (four of which were symptomatic including two fatal PE). However, Struijk-Mulder et al[9] screened for DVT and PE at approximately two weeks post-procedure and did not follow-up their patients for VTE occurrence post-procedure. This meant that their work facilitated detection of asymptomatic VTE, whilst VTE events occurring at later dates remain unknown. Ultrasound screening for DVT at both one week and two weeks post-procedure has been reported in other studies but there is insufficient evidence for this in the literature to advise incorporation of this into routine clinical practice at present[16,17]. Given that these studies have not examined VTE incidence at later dates post-amputation, the optimal timing for screening remains unclear.

There is also no consensus in the literature regarding optimal VTE prophylaxis amongst this patient group. A recent Cochrane review[8] concluded that there is insufficient evidence regarding VTE prophylaxis in lower limb amputees as only two studies (Lastoria 2006, Williams 1978) met their inclusion criteria for analysis. Of these, Lastoria et al found no significant difference in DVT rates in those undergoing major lower limb amputation treated with low-molecular weight heparin as opposed to those treated with unfractioned heparin[16]. Williams et al, however, found no significant difference in VTE incidence in those treated with unfractioned heparin compared with placebo[18]. The patients in our cohort did not routinely receive VTE prophylaxis upon discharge from the Vascular Surgery Unit as per policy within the Unit within 2014 and 2015. The effects of a change in local policy whereby patients being discharged following amputation and deemed to be at increased risk of VTE receive a 30-day course of prophylactic-dose low molecular weight heparin remain to be seen.

Limitations of our study include the single-centre data and small cohort size. We also relied upon documentation on NIECR and in medical charts, which may not always be accurate. Formal review of autopsy/ coroner documentation was not undertaken. We also have not explored the effect of pre-amputation vascular intervention and the potential impact of undergoing ipsilateral/contralateral amputation before, during or after follow-up. Additionally, the effect of further hospital admissions during the study period was not analysed, which may alter VTE risk.

CONCLUSION

This study adds to the evidence that vascular amputation is associated with significant mortality in patients with poor baseline health status. No significant association between level of amputation, diabetic status or presence of heart failure, CKD or COPD and mortality was found, although a non-significant trend was observed in the case of CKD.

Although lower than demonstrated in other studies, 30-day all-cause mortality was 8% and three-year all-cause mortality was 44%. Further work should be undertaken to identify those who are most at risk and to establish methods to reduce mortality.

Several patients also experienced VTE events; therefore, we suggest that further work be conducted to establish optimal practice regarding VTE detection and prevention. The impact on mortality of the change in local policy regarding VTE prophylaxis upon discharge wherein patients receive 30-days prophylactic-dose enoxaparin post-procedure remains to be seen.

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Declarations of interest: None

REFERENCES

1. Shammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vasc Health Risk Manag*. 2007;**3(2)**:229–34.
2. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care*. 2003;**26(12)**:3333–41.

3. Aulivola B, Hile CN, Hamdan AD, Sheahan MG, Veraldi JR, Skillman JJ, et al. Major lower extremity amputation: outcome of a modern series. *Arch Surg*. 2004;**139(4)**:395–9.

4. Swaminathan A, Vemulapalli S, Patel MR, Jones WS. Lower extremity amputation in peripheral artery disease: improving patient outcomes. *Vasc Health Risk Manag*. 2014;**16(10)**:417–24.

5. Kristensen MT, Holm G, Kirketerp-Møller K, Krasheninnikoff M, Gebuhr P. Very low survival rates after non-traumatic lower limb amputation in a consecutive series: what to do? *Interact Cardiovasc Thorac Surg*. 2012;**14(5)**:543–7.

6. Fortington LV, Geertzen JHB, van Netten JJ, Postema K, Rommers GM, Dijkstra PU. Short and long term mortality rates after a lower limb amputation. *Eur J Vasc Endovasc Surg*. 2013;**46(1)**:124–31.

7. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J*. 2013;**165(5)**:809–15.

8. Robertson L, Roche A. Primary prophylaxis for venous thromboembolism in people undergoing major amputation of the lower extremity. *Cochrane Database Syst Rev*. 2013; **16 (12)**:CD010525.

9. Struijk-Mulder MC, van Wijhe W, Sze YK, Knollema S, Verheyen CC, Büller HR, et al. Death and venous thromboembolism after lower extremity amputation. *J Thromb Haemost*. 2010;**8(12)**:2680–4.

10. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline [NG89] Published date: March 2018. [Internet] Available from: https://www.nice.org.uk/guidance/ng89 [Accessed 07 August 2018]

11. NI Electronic Care Record [Internet]. [cited 2017 Jul 22]. Available from: http://www.ehealthandcare.hscni.net/niecr/niecr.aspx

12. Fisher, R. A. On the interpretation of χ 2 from contingency tables, and the calculation of P. *Journal of the Royal Statistical Society*. 1992; **85(1)**, 87-94.

13. NCEPOD Classification of Intervention 2004 [Internet]. [cited 2017 Jul 22]/ Available from: http://www.ncepod.org.uk/classification.html

14. Kald A, Carlsson R, Nilsson E. Major amputation in a defined population: incidence, mortality and results of treatment. *Br J Surg*. 1989;**76(3)**:308–10.

15. Tentolouris N, Al-Sabbagh S, Walker MG, Boulton AJM, Jude EB. Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study. *Diabetes Care*. 2004;**27(7)**:1598–604.

16. Lastória S, Rollo HA, Yoshida WB, Giannini M, Moura R, Maffei FHA. Prophylaxis of deep-vein thrombosis after lower extremity amputation: comparison of low molecular weight heparin with unfractionated heparin. *Acta Cir Bras*. 2006;**21(3)**:184–6.

17. Burke B, Kumar R, Vickers V, Grant E, Scremin E. Deep vein thrombosis after lower limb amputation. *Am J Phys Med Rehabil* 2000;**79(2)**:145-9

18. Williams JW, Eikman EA, Greenberg SH, Hewitt JC, Lopez-Cuenca E, Jones GP, et al. Failure of low dose heparin to prevent pulmonary embolism after hip surgery or above the knee amputation. *Ann Surg*. 1978;**188(4)**:468–74.

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Clinical Paper

Transformation of Heart Attack Care: A Primary Percutaneous Coronary Intervention Service for Northern Ireland

Niall Herity[1], Diane Corrigan[2], Albert McNeill[3]

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ABSTRACT Primary percutaneous coronary intervention (primary PCI) is the preferred immediate treatment for patients with acute ST elevation myocardial infarction. It is however, considerably more labour-intensive than the previous standard of care and requires an immediate response from consultant-led teams to deliver best outcomes. We describe the introduction of a comprehensive primary PCI service for Northern Ireland and suggest that the process by which it was designed, piloted, commissioned and benchmarked can serve as a prototype for other high-risk, time-sensitive clinical emergency services.

INTRODUCTION

Acute myocardial infarction (MI) is a common medical emergency with improving clinical outcomes reflecting a wealth of clinical trial evidence. Between the 1980's and the 2000's, 30-day mortality for MI in Denmark fell from 31.4% to 14.8%[1] and in the United Kingdom (UK) and Sweden 30-day mortality fell below 10% by 2010[2].

In this paper, we document the most recent evidence-based change in the management of acute MI in Northern Ireland (NI): a comprehensive primary percutaneous coronary intervention (PCI) service for patients with ST segment elevation MI (STEMI). The service combines pre-hospital diagnosis and clinical stabilisation, then direct transfer to one of two Heart Attack Centres for definitive, consultant-delivered coronary intervention on a 24-hour basis, 365 days a year (24/7/365). Consolidation of early specialised emergency care required the collaboration of all Trusts and is an approach that could benefit patients requiring emergency medical and surgical intervention.

TREATMENT OF MYOCARDIAL INFARCTION

While early forms of MI treatment aimed to limit the sequelae of acute coronary occlusion (heart failure, arrhythmias and reinfarction), a more definitive strategy emerged in the 1980's. Clinical trials proved that early restoration of coronary blood flow reduces mortality and this can be achieved safely by intravenous thrombolytic agents[3]. Thrombolytic therapy followed by rescue PCI for those who fail to reperfuse, or early convalescent coronary intervention for those who successfully reperfuse[4,5] rapidly became part of the standard of care for acute STEMI.

However thrombolytic therapy had many limitations: contraindications, failure to reperfuse, reocclusion after successful reperfusion and haemorrhagic complications including intracranial haemorrhage. These stimulated clinical trials of primarily mechanical as opposed to pharmacological coronary reperfusion. The procedure that evolved, eventually termed primary PCI, was highly effective[6] and in October 2008, the UK National Infarct Audit Project (NIAP) confirmed that it can be delivered safely and effectively beyond clinical trials[7] leading to a new standard of care for acute STEMI management in the UK.

THE BELFAST TRUST PILOT

Following this evidence base, small numbers of cases were undertaken during daylight hours in all PCI centres in NI but no centre had the resources to deliver a service on a 24/7/365 basis. In April 2007, the Review of Public Administration led to the merger of three adult cardiology services in Belfast into a single service within the newly-formed Belfast Health and Social Care Trust (BHSCT). By this time, the European Society of Cardiology (ESC) was recommending primary PCI as the preferred reperfusion option, but only if performed by experienced staff within 90 minutes of first medical contact[8]. The BHSCT merger delivered an interventional cardiology team of sufficient size and experience to deliver 24/7/365 primary PCI for a large number of patients with STEMI.

Following detailed preparation, a pilot project covering the greater Belfast area was undertaken. Planning involved many clinical teams and many logistical considerations (Table 1). The pilot service, launched on December 7 2009, proved that 24/7/365 primary PCI was feasible in NI, and outcomes compared well with appropriate benchmarks (Table 2). Treating several hundred patients over these early years enriched the expertise of many professionals who would form part of the NI-wide service and the annual procedural volume of the BHSCT pilot predicted the likely demand of a region-wide service (Table 3).

1. Belfast HSC Trust, 2. Public Health Agency, 3. Western HSC Trust
Correspondence to Dr Niall Herity
E-mail: Niall.Herity@belfasttrust.hscni.net

TABLE 1.

Logistical planning considerations prior to launch of the BHSCT primary PCI pilot

Staff	***Clinical protocols***
Daytime staffing arrangements	Inclusion and exclusion criteria
Out-of-hours on call rotas	ECG criteria to be used by NIAS
A primary PCI co-ordinator role	A care pathway
Staff accommodation	ECG transmissions and nurse-led interpretation
Training and CPD	Pharmacotherapy and equipment
Compensatory rest	Expected patient numbers
The patient journey	***Quality***
Direct admissions from NIAS	Clinical governance
Self-presenters at Emergency Departments	Education and research
Facilities for relatives	Benchmarking
Repatriation arrangements (nurse-led)	
	Communications
	Links with other clinical teams
	Public and media relations

A COMPREHENSIVE PRIMARY PCI SERVICE FOR NORTHERN IRELAND

Through the course of the BHSCT pilot, performance and outcome data were shared and a unified view emerged that a region-wide primary PCI service should be commissioned for NI. This consensus led to a formal commitment in the NI Programme for Government (2011-2015) which undertook to:

"*Expand cardiac catheterisation capacity to improve access to diagnostic intervention and treatment and further develop a new primary percutaneous coronary intervention (PPCI) service model to reduce mortality and morbidity arising from myocardial infarction (heart attack).*"

Under the direction of a Regional Cardiac Catheterisation Implementation Group (CCIG), it took less than 5 years to transform from having no systematic primary PCI service to one covering every patient with STEMI in NI with clinical outcomes as good as anywhere in the UK.

Planning and implementation

An early decision was to develop a two-centre regional primary PCI model between the BHSCT (Royal Victoria Hospital) and Western HSC Trust (Altnagelvin Hospital). The boundaries were defined by 60-minute travel times from each centre, following postcode regions to give greatest clarity to NIAS crews (Figure 1). They have required no modification since first drawn.

Fig 1. Postcode-based definition of the boundaries between the Eastern and Western primary PCI services. The use of postcodes ensures clarity for all and especially for NIAS crews

Experience from NIAP, the BHSCT pilot and international publications led to a set of assumptions from which the projected number of primary PCI activations was calculated. Three-quarters of patients with STEMI present outside office hours so most activations involve a team returning to the

TABLE 2.

Selected outcome measures from the Belfast Trust primary PCI service

	Number of primary PCI activations	Percentage admitted directly from NIAS	Median call-to-balloon time (minutes)*	Median door-to-balloon time (minutes)**
2010/11	257	37%	110	45
2011/12	256	47%	89	47
2012/13	279	47%	98	41
2013/14†	508	55%	104	36

*MINAP standard 150 minutes; **MINAP standard 90 minutes
†The BHSCT service extended its catchment area on 30 September 2013

Table 3.

*Projections of how many activations of a primary PCI service were expected across NI. *08.00 – 18.00, Monday to Friday*

Activity estimates								
1131 activations of the primary PCI service (including other causes of ST elevation on the ECG, likely to be 15 to 20%)								
305 in hours*			826 out of hours				**Total**	
			588 before midnight		238 after midnight		Altnagelvin	Belfast
76 Altnagelvin	229 Belfast		147 Altnagelvin	441 Belfast	60 Altnagelvin	178 Belfast	283	848
1.5 per week	4.4 per week		2.8 per week	8.5 per week	1.2 per week	3.4 per week	5.5 per week	16.3 per week

hospital from home. The projected activations are shown in Table 3: in 2015/16 there were 992 activations, indicating that we had overestimated the caseload by 14%.

Professional guidelines were integral to the strategy. In NI, National Institute for Healthcare and Clinical Excellence (NICE) guidance underpins commissioning strategy and funding of service developments. Cardiologists also aim to align with ESC recommendations and British Cardiovascular Intervention Society (BCIS) standards for UK primary PCI (PPCI) centres[9]:

> *All PPCI centres should provide a STEMI service 24 hours a day, 7 days a week, year-round*
>
> *All PPCI centres should undertake a minimum of 150 PPCI cases per year unless there is extreme geographical isolation to justify a lower volume service*
>
> *Services should be configured to achieve "call-to-balloon time" of <150 minutes in ≥ 75% of patients (excluding cardiogenic shock and out-of-hospital arrest)*
>
> *Optimal performance of the in-hospital service can be measured by a "door-to-balloon" time < 60 minutes in ≥ 75% of patients (excluding cardiogenic shock and out-of-hospital arrest)*

The imperative to deliver a seamless 24/7/365 service and the link between higher volume and lower mortality[10], underpinned the consolidation of expertise into the smallest number of centres that could deliver the required call-to-balloon time standards.

PRACTICE INNOVATIONS

Nurse-delivered electrocardiogram (ECG) interpretation was central from the outset. ECGs recorded at first medical contact (often in the patient's home) are sent electronically with a brief clinical description to the appropriate Heart Attack Centre. If defined criteria (Figure 2) are confirmed by the nurse, the interventional team is activated and the patient is transferred directly to the cardiac catheterisation laboratory.

In a recent internal quality improvement (QI) project, the calculated sensitivity, specificity, positive and negative predictive value of nurse-delivered ECG interpretation were 95%, 91%, 85% and 97% respectively, showing that the system inclines towards greater sensitivity to miss as few patients as possible. As a result, inappropriate activations (15%) are tenfold more common than inappropriate turn-downs (1.6%). Similar QI projects have also led to the acceptance of ECGs suggesting acute posterior MI and have strengthened recommendations that local cardiology teams review patients with borderline ECG changes (e.g. left bundle branch block or ST elevation <2 mm in anterior leads) or when a patient has been referred but not accepted for primary PCI (Figure 2). Such patients are often discussed directly with the primary PCI team if there is clinical suspicion of acute coronary occlusion. The purpose of these gradual protocol modifications has been to maximise sensitivity for the detection of acute coronary occlusion, while ensuring

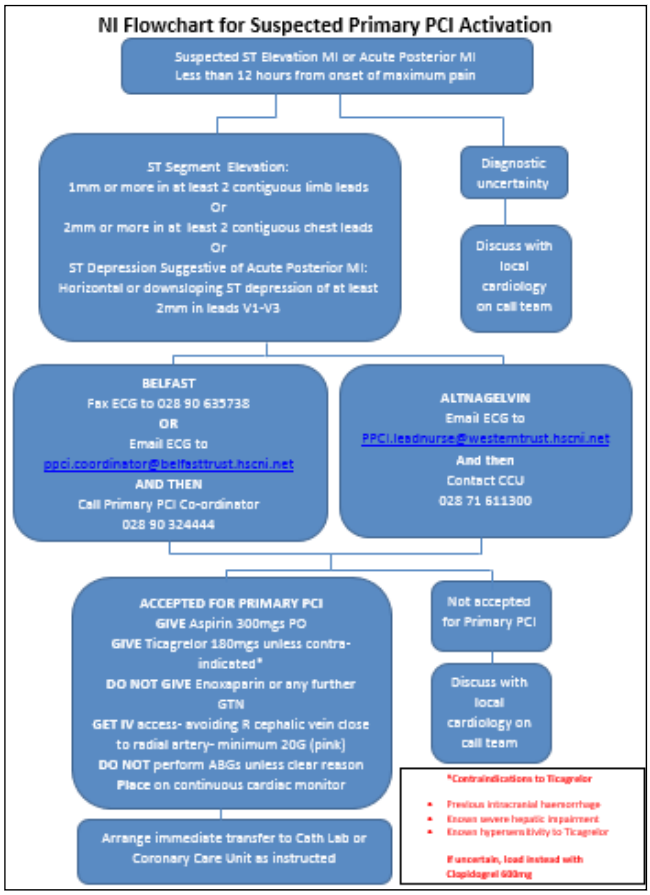


Figure 2. Regionally-agreed protocol for nurse-led primary PCI activation

TABLE 4.

*Key process and clinical outcome measures for the NI Eastern and Western primary PCI (PPCI) services from 2015/16, benchmarked against equivalent national figures from England and Wales (16). *2014 data for all UK – the last year for which 30-day mortality has been published to date*

	Eastern Heart Attack Centre (Belfast)	Western Heart Attack Centre (Altnagelvin)	England	Wales
Number of patients undergoing PPCI	680	168	19 216	1 001
PPCI rate per million population	451		354	323
Percentage of eligible patients undergoing PPCI	99.9%		99.3%	86.0%
Percentage admitted directly to Heart Attack Centre	61%	89%	78%	71%
Median call-to-balloon time (minutes)	109	114	117	127
Eligible patients who received primary PCI within 150 minutes of calling for help (call to balloon) including those admitted directly or transferred to Heart Attack Centre	78%	74%	75%	67%
Median door-to-balloon time (minutes)	34	29	40	41
Percentage of eligible patients who received primary PCI within 90 minutes of arrival at Heart Attack Centre	93.4%	84.7%	89%	87%
30-day mortality	6.2%	6.0%	6.9%*	

that the service remains sustainable by keeping inappropriate activations to a manageable level.

A fundamental component of the primary PCI pathway is a regionally-agreed repatriation protocol with transfer back to a local CCU at 6 hours post-procedure if the patient is stable and it is between the hours of 6am and 10pm. Primary PCI centres cannot deliver a responsive service without clear repatriation arrangements and it is in patients' best interests to have most clinical care and rehabilitation delivered close to home. The system also preserves teaching and training opportunities for staff and students in all CCU's.

Repatriation is managed by CCU nurses using clinical rather than operational criteria. Telephone calls to the host hospital and to NIAS at the time of admission are followed by a second call 6 hours later to confirm transport and to inform the host hospital that the patient is leaving. At no stage is it discussed whether a bed is available. The process shows that collaborative repatriation is achievable for any regionally-centralised service in NI.

The original NIAP report[7] highlighted that patients with STEMI who attend ED's or CCU's experience substantial time delays so the recommended model is pre-hospital diagnosis, then direct transfer to a cardiac catheterisation laboratory in primary PCI-capable hospitals, bypassing all other services. Tables 2 and 4 show that work is required to reduce the number of patients with STEMI attending ED's, particularly in the Eastern region.

The primary PCI service delivers prompt, high quality care for patients with STEMI across NI. The demanding nature of the work, coupled with a finite number of interventional cardiologists with primary PCI experience meant that working across Trust boundaries was essential. Other cross-Trust cardiology service developments, linked to primary PCI have included cardiac imaging, outpatient clinics and wider invasive cardiology services.

The Myocardial Infarction National Audit Project (MINAP) audits and publishes quality of care for patients with STEMI and non STEMI in England, Wales and NI, against NICE standards.[11-13] From their inception, the NI Heart Attack Centres have submitted MINAP data alongside English and Welsh Heart Attack Centres[14]. Performance measures show that both NI centres deliver high levels of performance and a 94% survival to 30 days (Table 4).

LESSONS LEARNED AND WIDER APPLICABILITY

Challenges to the primary PCI implementation project included many stakeholders, initial lack of consensus about the model and a need to balance other elective and urgent needs while transforming emergency care. The service which evolved sets a new standard in quality of care for a large number of patients who are seriously ill at presentation. The factors that we believe contributed to successful implementation are:

- A clear statement that the service change formed part of government policy
- Establishment of a regional Implementation Group with equal representation from all Trusts and a neutral Chair
- A shared, deliverable vision
- A focus on best quality, evidence-based care
- Expectation of cooperation across Trusts
- Sharing information across Trusts, identifying service gaps and examples of good practice
- Recognising the skills of NIAS staff and a lead role for nurses in managing patient pathways

Fig 3. Official launches of the Eastern (upper panel) and Western (lower panel) primary PCI services

- Open feedback in a 'no blame way'

Increasingly patients with high-risk conditions need services that bypass ED's to bring patients directly to a pre-activated specialist area – e.g. major trauma and stroke services. Common components include enhanced assessment skills by paramedics, diagnostic and triage tools and remote access to clinical advice. A supportive culture acknowledges the operational and clinical challenge for ambulance crews undertaking longer journey times with unstable patients. Concentrating specialist skills in fewer sites leads to concerns about clinical skills and staff recruitment; these can be allayed by cross-Trust working. Communication is key with agreed, widely disseminated protocols for incoming and repatriating patients. Finally, there must be willingness to review practice when the system does not work as planned.

The process by which a consolidated regional primary PCI service has been designed, piloted, commissioned, implemented, communicated and benchmarked should serve as a model for how services for other high-risk, time-sensitive clinical emergencies should be developed in NI.

ACKNOWLEDGMENTS

The evolution of the NI primary PCI service represents hundreds of person-years of dedication and hard work by people across the Health Service and its ongoing delivery demands just as much dedication and commitment. The service could not have happened without every one of these people. All involved should be proud of what they have achieved for patients to date, and what they continue to achieve every day

REFERENCES

1. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ*. 2012; **344**: e356.
2. Chung S-C, Sundström J, Gale CP, James S, Deanfield J, Wallentin L, *et al*. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. *BMJ*. 2015; **351**: h3913.
3. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994; **343(8893)**: 311-22.
4. Bonnefoy E, Steg PG, Boutitie F, Dubien PY, Lapostolle F, Roncalli J, *et al*. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J*. 2009;**30(13)**:1598-606.
5. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, *et al*. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;**368(15)**:1379-87.
6. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361(9351)**: 13-20.
7. Department of Health Vascular Programme Team. Treatment of Heart Attack National Guidance. Final Report of the National Infarct Angioplasty Project (NIAP). London: Department of Health; 2008.
8. Bassand J-P, Danchin N, Filippatos G *et al*. Implementation of reperfusion therapy in acute myocardial infarction. A policy statement from the European Society of Cardiology. *Eur Heart J* 2005; **26**: 2733–41.
9. MacCarthy PA, Blackman DJ, Hildick-Smith D, Banning AP. Primary percutaneous coronary intervention for ST elevation myocardial infarction. Position statement for facilities and emergency medical staffing. [Internet] London: British Cardiovascular Intervention Society; 2016.
10. Zahn R, M Gottwik M, Hochadel M, Senges J, Zeymer U, Vogt A, *et al*. Volume–outcome relation for contemporary percutaneous coronary interventions (PCI) in daily clinical practice: is it limited to high-risk patients? Results from the Registry of Percutaneous Coronary Interventions of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). *Heart*. 2008; **94(3)**: 329-35.
11. National Institute for Health and Care Excellence Quality Standard 68. Acute coronary syndrome in adults. NICE 2014. https://www.nice.org.uk/guidance/qs68/resources/acute-coronary-syndromes-in-adults-pdf-2098794360517
12. NICE Clinical Guideline; 172. Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease. [Internet] London: National Institute for Health and Care Excellence Clinical Guideline; 2013. Available from: https://www.nice.org.uk/guidance/cg172 [Accessed September 2018].
13. NICE Clinical Guideline; 167. Myocardial infarction with ST-segment elevation: acute management. [Internet] London: National Institute for Health and Care Excellence Clinical Guideline; 2013. Available from: https://www.nice.org.uk/guidance/cg167 [Accessed September 2018].
14. Weston CF, Reinoga KL, Dubos RF, Demian V. Myocardial Ischaemia National Audit Project. Heart attack in England, Wales and Northern Ireland. Annual Public Report April 2015 – March 2016. [Internet] London: National Centre for Cardiovascular Preention and Outcomes (NICOR); 2017. Available from: http://www.ucl.ac.uk/nicor/audits/minap/documents/annual_reports/minap-2015-16-annualreport. [Accessed September 2018].

Curiositas *(General Surgery)*

UNDERGRADUATE QUIZ

Jaundice is a yellow discolouration of the skin and soft tissues due to the presence of excessive amounts of circulating bilirubin. The causes of jaundice can be divided into pre-hepatic, hepatic and post-hepatic categories. It is important that patients presenting with jaundice undergo appropriate investigations to determine the underlying cause, since urgent treatment may be required.

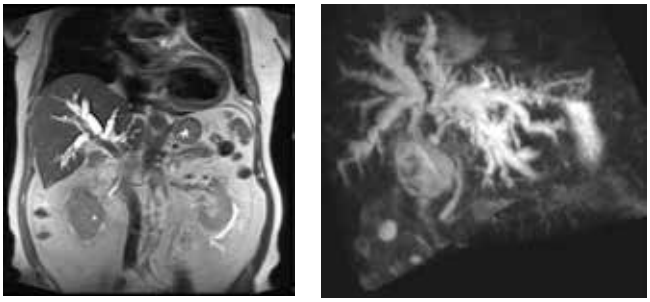
1. Create a table outlining the causes of jaundice by category.
2. In a newborn with abdominal distension and jaundice lasting more than 2 weeks, what diagnosis must be ruled out?

    a. Breastmilk jaundice
    b. Physiological jaundice
    c. Biliary atresia
    d. Infection
    e. Congenital hypothyroidism

Dr Ian Bickle, Consultant Radiologist, Chesterfield Royal Hospital, Derbyshire; Sandra Messiha and Melissa Tso (Medical Students, Queen's University Belfast).

POSTGRADUATE QUIZ

A 74-year-old male presents with a short-term history of anorexia, weight loss and jaundice. Blood results reveal the following: total bilirubin 166 μmol/L, GGT 1919 U/L, ALP 952 U/L, AST 120 U/L and ALT 134 U/L (all results are above the reference ranges).



A representative image from his magnetic resonance cholangiopancreatography (MRCP) study and a maximum intensity projection (MIP) are shown:

1. What are the most striking abnormalities?
2. What other investigations would you complete and why?

Dr Ian Bickle, Consultant Radiologist, Chesterfield Royal Hospital, Derbyshire; Sandra Messiha and Melissa Tso (Medical Students, Queen's University Belfast).

HISTORICAL QUIZ

The picture below represents one of the most dangerous infectious diseases to plague mankind. The first definitive outbreak of this disease occurred in 1647 on the island of Barbados. Symptoms of this condition include pyrexia, chills, nausea, muscle pain, abdominal pain and jaundice.

1. What condition does the image represent?
2. Where did it originate?
3. What is the method of transmission?

Sandra Messiha and Melissa Tso (Medical Students, Queen's University Belfast).

AND FINALLY…

Image credit: By Mdf - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=4106444

What is this bird, and how is it linked to the cases above?

Sandra Messiha (Medical Student, Queen's University Belfast).

ANSWERS See overleaf

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

Curiositas: Answers

UNDERGRADUATE QUIZ

1. Important causes of jaundice are listed in the table below:

Pre-hepatic
Haemolytic anaemia
Gilbert's Syndrome
Criggler-Najjar Syndrome
Hepatic
Alcoholic liver disease
Viral hepatitis
Drug-induced
Hereditary haemochromatosis
Autoimmune hepatitis
Primary sclerosing cholangitis
Primary biliary cirrhosis
Post-hepatic
Gallstones
Cholangiocarcinoma
Biliary strictures
Drug-induced cholestasis
Pancreatic cancer
Abdominal masses

2. All of the above causes are associated with prolonged jaundice however, in this scenario involving a newborn baby, biliary atresia is the most important diagnosis to rule out. Delayed diagnosis can lead to a poorer prognosis. The condition usually presents with prolonged jaundice, dark urine and pale stools. Examination may reveal abdominal distension and hepatomegaly. The procedure for curing biliary atresia is the Kasai procedure and there is a better prognosis if the surgery is performed before 8 weeks of age.

Dr Ian Bickle, Consultant Radiologist, Chesterfield Royal Hospital, Derbyshire; Sandra Messiha and Melissa Tso (Medical Students, Queen's University Belfast).

POSTGRADUATE QUIZ

1. The coronal MR images demonstrate severe diffuse intrahepatic ductal dilatation down to the porta hepatis, with an abrupt cut off. The common hepatic and bile ducts are of normal calibre. The concern in this case is an underlying cholangiocarcinoma.

2. The next most helpful investigation would be an endoscopic retrograde cholangiopancreatography (ERCP). This would allow a biopsy of the mass to be taken, which would in turn facilitate histological confirmation. It would also be important to order further imaging tests to check for metastatic deposits. Urgent investigations are necessary since cholangiocarcinomas are classed as highly malignant tumours and have a 15% overall 5-year survival rate.

Dr Ian Bickle, Consultant Radiologist, Chesterfield Royal Hospital, Derbyshire; Sandra Messiha and Melissa Tso (Medical Students, Queen's University Belfast).

HISTORICAL QUIZ

1. This image represents yellow fever. It depicts André Mazet tending to patients suffering from the disease in Barcelona.

2. Yellow fever most likely originated from East or Central Africa where it is thought that there was an initial transmission from non-human primates to humans. The viral disease than spread to South America through the slave trade during the 17th century.

3. The condition is transferred by the bite of an infected female mosquito and is mainly seen in Africa.

Sandra Messiha and Melissa Tso (Medical Students, Queen's University Belfast).

AND FINALLY…

This is a photograph of an adult male Baltimore oriole (*Icterus galbula*). Baltimore orioles are in a family of birds known as Icterids, whose name derives from the Greek word 'ikteros' meaning 'a yellow bird'. From 'ikteros' we get the term 'icterus', another term for jaundice. In some traditions it was believed that seeing a bird such as this would cure jaundice, but at the expense of the bird's death.

Sandra Messiha (Medical Student, Queen's University Belfast).

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James Logan Prize Essay

The Challenge of Cancer Pain Assessment

Christopher Cluxton

Accepted: 22nd November 2018

PREFACE

James Alexander Logan, a second-year medical student at the Barts and The London School of Medicine and Dentistry, died in February 2001 after a painful illness. A Trust was set up in his name in 2003 to promote education in the recognition and treatment of cancer pain and it provided funds for an annual essay prize, open to those undergraduate medical students of Queen's University, Belfast, who had completed their fourth year palliative care teaching. The first competition took place in 2010 and the winning entry appeared in the Ulster Medical Journal in 2011. The Trust itself was dissolved in 2014 but the essay prize continues and the Trust's website can still be accessed at http://www.jameslogantrust.org.uk .

INTRODUCTION

It is estimated that up to 80% of cancer patients experience disease related pain, and an estimated 65-80% of cancer patients with advanced disease suffer pain so severe that it negatively impacts their activities of daily living, disrupts their sleep pattern, depresses their mood and interferes with normal social functioning and relationships.[1-3] Furthermore, uncontrolled pain delays healing and recovery, leading to poorer outcomes for cancer patients.[4] Cancer pain can be well controlled in up to 90% of cases[5], but current evidence suggests that almost half of cancer patients in the developed world receive sub-optimal pain management.[1] The leading barrier to well controlled cancer pain is its inadequate assessment and reassessment.[6] Despite this being widely understood, cancer pain remains a prevalent problem.

In this essay I will examine the leading challenges of cancer pain assessment including the complex nature of cancer pain, barriers to patient reporting, ineffective communication of pain and physician and systematic failures. In doing so, I aim to identify how cancer pain assessment can be improved in the future.

CANCER PAIN: A COMPLEX PHENOMENON

Cancer pain is difficult to define due to the complexity of its origins and the biological, psychological, social and cultural influences on its perception.[6,7] In 1972, Margo McCaffery, a registered nurse and pioneer of pain management nursing, defined pain as 'whatever the experiencing patient says it is, and exists whenever he/she says it does'.[8] This definition describes the subjective nature of pain and the importance of the patient's experience of pain.

In 1964, Dame Cicely Saunders defined 'total pain'[9] as a phenomenon that encompasses the physical symptoms, mental distress, social problems and emotional difficulties of pain [10]. She also recognized, for the first time, the spiritual suffering associated with physical pain[11]. Perhaps the key aspect of Dame Saunders' observations was, however, the biographical quality of pain and the importance of the patient's story and experience.[9] Similarly, this approach to pain highlighted the need for multiple interventions for the effective management of pain. This concept of pain as a multi-modal experience together with the subjective and individualistic nature of pain underline the complexity of assessing pain for patients in the cancer setting.

Cancer pain further incorporates a range of aetiological factors, with about 75% of pain caused by the cancer itself, and the remainder caused by diagnostic procedures and treatments.[6,12] Tumours cause pain by compressing or invading healthy innervated tissue, triggering inflammation or infection, or releasing chemicals that make normally non-painful stimuli painful.[12] Accordingly, cancer pain is often classified as somatic, visceral or neuropathic in origin.[13] In advanced cancer, multiple mechanisms of pain often occur simultaneously at different sites. Each mechanism and anatomical site requires focused investigation. For example, a patient with advanced cancer may experience liver capsule pain from liver metastases, back pain from spinal metastases and neuropathic pain from systemic chemotherapy regimens. Management of such pain may require corticosteroids, radiotherapy and anti-epileptics for the liver, bone and neuropathic pain, respectively.[14] In such a case, pain would be inadequately managed if each source of pain was not carefully considered and assessed.

Not all cancer patients will experience all modalities of cancer pain, but for optimal cancer pain assessment and control all potential modalities of pain must be considered for each patient and addressed appropriately.

HOW DO WE CURRENTLY ASSESS PAIN IN CANCER PATIENTS?

As with all pain syndromes, accurate, thorough, and systematic assessment of cancer pain is crucial to identifying the underlying aetiology and developing a treatment

Correspondence to: Christopher Cluxton, 4th-year QUB medical student

E-mail: ccluxton01@qub.ac.uk

plan.[15] In all patients experiencing pain, a full pain history, general and focused physical examinations and complete psychosocial assessment should be performed.[16] There is often, however, variability in the overall impression of pain between healthcare professionals due to the subjective nature of these assessment methods.[17] There is also a reported lack of appropriate documentation of pain assessment with these methods leading to inaccurate monitoring of pain and pain control [18]. As such, the development of standardised assessment tools have reduced variability in pain reporting and improved documentation of pain assessment.[18] A variety of tools have been designed to assess pain in cancer.[19]

Pain intensity scales are unidimensional and include the 11-point numeric rating scale, a verbal descriptor scale (mild, moderate or severe) or a visual analogue scale (a line of increased severity).[20] There are also scales that use drawings of faces to facilitate patients who cannot easily use the above tools. These are very useful for confirming the presence of pain, gaining some basic information about that pain, tracking the course of pain over time and determining the efficacy of pain management. Multidimensional tools, including the Brief Pain Inventory and the McGill Pain Questionnaire, are clinically useful in cancer patients as they assess not only the location and severity of pain but evaluate impairment due to pain.[20] The use of multidimensional scales including the Edmonton Symptom Assessment Scale and the Distress Thermometer that include the most common symptoms (e.g. depression, pain, fatigue) may help in identifying symptom clusters and may also assess psychological, practical and spiritual aspects to pain in a systematic manner.[20]

Such scales used together can assist doctors and other caregivers to standardise pain assessment and to monitor pain appropriately and objectively. They also facilitate the development of guidelines for pain management on the ward that can be utilised by less experienced staff.

IDENTIFYING AND OVERCOMING CHALLENGES OF CANCER PAIN ASSESSMENT

Despite cancer pain being widely treatable, it is often undermanaged due to poor pain assessment. The barriers to effective assessment and management can be broadly characterised by factors relating to the patient, healthcare professional and healthcare system.

PATIENT FACTORS: OPTIMISING COMMUNICATION

The assessment of pain relies heavily on patient reporting.[21] The most significant patient-related barriers are the patient's reluctance to report pain and adhere to treatment recommendations.[22] Patients may, in some instances, under-report pain for a variety of reasons including the belief that cancer pain is inevitable and should be tolerated, that reporting pain may distract from treatment of the primary disease and fears that pain may indicated progression of disease.[23] Cancer and pain are not synonymous, and not all cancer patients experience pain.[1] Addressing fears and false beliefs is the responsibility of the attending physician and should be performed early in the diagnosis. Patients should also be fully educated about different presentations of pain, their meaning and the efficacy of available treatment options.[21] Patients may also harbour fears regarding the analgesics themselves and their efficacy [24]. Many patients fear that early pain control will promote tolerance and impede control later in the disease.[25] Patients are also often hesitant to take opioid analgesia because of stigma and concerns with dependence.[25] Concerns about side effects can further prevent cancer patients from reporting pain and seeking appropriate care.[24] These issues must be borne in mind by doctors and other healthcare providers when treating all cancer patients and relevant information giving should be provided to patients upon diagnosis to allay fears and false beliefs.

Pain is considered a 'mind-body' experience with the 'mind' encompassing the perception and interpretation of pain while the 'body' encompasses the pathways and processing of pain.[26] It is for this reason that self-reporting is central to the assessment of pain. In non-communicative patients, the mind-body experience cannot be articulated through self-reporting.[26,27] Non-verbal cancer patients can include those at the extremes of age, comatose or unconscious patients, the critically ill and the cognitively impaired. The International Association for the Study of Pain (IASP) states, "The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment".[27] Clinicians must therefore tailor pain assessment to non-verbal patients and this has been a significant challenge in the field. Current evidence indicates that the best predictors of pain in non-verbal patients are physiological parameters, including blood pressure and pulse rate, and behavioural indicators.[28] Physiological measures are, however, indicators only and are not sensitive screening tools.[28] As such, tools like the Behavioural Pain Scale and Checklist of Non-Verbal Pain Indicators (CNPI) have been developed to assess pain by scoring observable behaviours including facial expressions, movement of upper limbs and vocalisation.[29,30] As with verbal patients, pre-emptive pain assessment using a valid tool and timely intervention can accurately identify pain and facilitate its management.

HEALTHCARE PROFESSIONAL FACTORS: IMPROVING KNOWLEDGE, SKILLS AND ATTITUDES

Poor assessment of pain and inadequate knowledge on the part of clinicians have been identified as major barriers to cancer pain treatment.[31] Medical graduates will ultimately undertake the task of identifying, assessing and treating patients with cancer pain. Thus, the IASP has emphasised the importance of undergraduate teaching in pain management and have developed an undergraduate curriculum. Despite this, the topic of pain, and indeed cancer pain, is currently inadequately addressed according to various studies.[32,33] Additionally, the development of positive attitudes and conduct in relation to cancer pain management has also been shown to be sub-

optimal.[34,35] Accordingly, Briggs et al.[36] found pain education to be "fragmented, inadequately assessed and inconsistent between universities." In practice, clinicians inexperienced in cancer pain may not have the skills to perform the relevant pain assessment, resulting in inaccurate diagnosis of pain. Anxiety about the use of regulated drugs, concerns regarding the side effects of strong analgesics and the fear of the patient developing tolerance to analgesia have also been reported as significant factors in inadequate assessment and control of cancer pain.[21,37] There is, therefore, a proven need for improved education in cancer pain assessment and management at all levels of professional education to provide clinicians with the knowledge, experience and confidence to appropriately treat cancer pain.

SYSTEMATIC FACTORS: PROVISION OF SERVICES AND STANDARDISATION OF CARE

The most significant systematic barriers to achieving adequate cancer pain assessment are the healthcare setting and the lack of standardised methodology. Over the last decade, cancer care has been defragmented with the development of purpose-built cancer centres. This has helped to streamline cancer services in secondary care.[38] Oncology patients are, however, treated more and more often in the community for their pain. The European Prospective Investigation into Cancer and Nutrition (EPIC) study[39] revealed that 1 in 5 patients in the community with cancer pain were not treated with analgesia while over 1 in 4 patients treated with analgesia reported pain as greater than 5 on the Numerical Rating Scale (NRS). A Marie Curie study of 1000 GPs also revealed that 6 in 10 GPs believed that the majority of their terminally ill patient's pain was not adequately controlled.[40] This report suggests that without additional resources and/or the development of modern technology to improve patient-doctor communication cancer pain will continue to be undertreated.[40] Furthermore, the lack of a universally accepted methodology/tools impedes cancer pain assessment at all levels.[41] Indeed, there are various fit-for-purpose tools but evidence of their efficacy in all groups is lacking. The development or acceptance of one method and its implementation as a standard measure would enable the development of more concrete pain assessment guidelines that could be readily introduced in all healthcare settings.[41]

CONCLUSIONS

Cancer pain is a complex, devastating experience for patients when it is under-assessed and under-treated by healthcare professionals. The consequences extend far beyond the uncomfortable physical experience of pain, impacting all aspects of a patient's life. In non-terminal cancer patients, it hinders recovery and can develop into chronic pain syndromes that can last a lifetime. For terminal cancer patients, the finals months, weeks and days of their lives are spent in discomfort with depressed mood and impaired functioning. This is cruel to the patient and cruel to their families, who watch their loved ones suffer with a devastating illness. It is therefore imperative that we do not consider cancer pain the responsibility of the palliative care team or the oncologist, but the responsibility of every doctor, nurse and healthcare worker involved with that patient's care. With more thoughtful consideration of the suffering of cancer patients, together we can work to eradicate a proven eradicable condition and improve the lives of many thousands of patients.

REFERENCES

1. Hanna M, Zylicz Z. *Cancer pain*. London: Springer; 2013.
2. Marcus DA. Epidemiology of cancer pain. *Curr Pain Headache Rep*. 2011;**15(4)**:231-4.
3. Sheinfeld Gorin S, Krebs P, Badr H, Janke EA, Jim HS, Spring B, et al. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. *J Clin Oncol*. 2012;**0**:539-47.
4. Nersesyan H, Slavin KV. Current aproach to cancer pain management: Availability and implications of different treatment options. *Ther Clin Risk Manag*. 2007;**3(3)**:381-400.
5. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician*. 2010;**56(6)**:514-7.
6. Portenoy RK. Treatment of cancer pain. *Lancet*. 2011;**377(9784)**:2236-47.
7. Peacock S, Patel S. Cultural Influences on Pain. *Rev Pain*. 2008;**1(2)**:6-9.
8. McCaffery M, Ferrell BR. Nurses' knowledge of pain assessment and management: how much progress have we made? *J Pain Symptom Manage*. 1997;**14(3)**:175-88.
9. Saunders C. The evolution of palliative care. *J R Soc Med*. 2001;**94(9)**:430-2.
10. Ong CK, Forbes D. Embracing Cicely Saunders's concept of total pain. *BMJ*. 2005;**331(7516)**:576.
11. Brunjes GB. Spiritual pain and suffering. *Asian Pac J Cancer Prev*. 2010;**11 (Suppl 1)**:31-6.
12. von Gunten CF. Pathophysiology of pain in cancer. *J Pediatr Hematol Oncol*. 2011;**33 (Suppl 1)**:S12-8.
13. Regan JM, Peng P. Neurophysiology of cancer pain. *Cancer Control*. 2000;**7(2)**:111-9.
14. Raphael J, Hester J, Ahmedzai S, Barrie J, Farqhuar-Smith P, Williams J, *et al*. Cancer pain: part 2: physical, interventional and complimentary therapies; management in the community; acute, treatment-related and complex cancer pain: a perspective from the British Pain Society endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners. *Pain Med*. 2010;**11(6)**:872-96.
15. Caraceni A. Evaluation and assessment of cancer pain and cancer pain treatment. *Acta Anaesthesiol Scand*. 2001;**45(9)**:1067-75.
16. Cancer pain assessment and treatment curriculum guidelines. Ad Hoc Committee on Cancer Pain of the American Society of Clinical Oncology. *Support Care Cancer*. 1993;**1(2)**:67-73.
17. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol*. 2008;**19(12)**:1985-91.
18. Weinstein SM, Romanus D, Lepisto EM, Reyes-Gibby C, Cleeland C, Greene R, et al. Documentation of pain in comprehensive cancer centers in the United States: a preliminary analysis. *J Natl Compr Canc Netw*. 2004;**2(2)**:173-80.
19. Anderson KO. Assessment tools for the evaluation of pain in the oncology patient. *Curr Pain Headache Rep*. 2007;**11(4)**:259-64.
20. Haefeli M, Elfering A. Pain assessment. *Eur Spine J*. 2006;15 Suppl 1:S17-24.

21. Sun V, Borneman T, Piper B, Koczywas M, Ferrell B. Barriers to pain assessment and management in cancer survivorship. *J Cancer Surviv*. 2008;**2(1)**:65-71.

22. Jacobsen R, Liubarskiene Z, Møldrup C, Christrup L, Sjøgren P, Samsanaviciene J. Barriers to cancer pain management: a review of empirical research. *Medicina (Kaunas)*. 2009;**45(6)**:427-33.

23. McPherson CJ, Hadjistavropoulos T, Lobchuk MM, Kilgour KN. Cancer-related pain in older adults receiving palliative care: patient and family caregiver perspectives on the experience of pain. *Pain Res Manag*. 2013;**18(6)**:293-300.

24. Graczyk M, Borkowska A, Krajnik M. Why patients are afraid of opioid analgesics: a study on opioid perception in patients with chronic pain. *Pol Arch Intern Med*. 2018;**128(2)**:89-97.

25. Paice JA, Toy C, Shott S. Barriers to cancer pain relief: fear of tolerance and addiction. *J Pain Symptom Manage*. 1998;**16(1)**:1-9.

26. Simons LE, Elman I, Borsook D. Psychological processing in chronic pain: a neural systems approach. *Neurosci Biobehav Rev*. 2014;**39**:61-78.

27. McGuire DB, Kaiser KS, Haisfield-Wolfe ME, Iyamu F. Pain assessment in noncommunicative adult palliative care patients. *Nurs Clin North Am*. 2016;**51(3)**:397-431.

28. Chen HJ, Chen YM. Pain assessment: validation of the physiologic indicators in the ventilated adult patient. *Pain Manag Nurs*. 2015;**16(2)**:105-11.

29. Feldt KS. The checklist of nonverbal pain indicators (CNPI). *Pain Manag Nurs*. 2000;**1(1)**:13-21.

30. Young J, Siffleet J, Nikoletti S, Shaw T. Use of a Behavioural Pain Scale to assess pain in ventilated, unconscious and/or sedated patients. *Intensive Crit Care Nurs*. 2006;**22(1)**:32-9.

31. Nuseir K, Kassab M, Almomani B. Healthcare providers' knowledge and current practice of pain assessment and management: how much progress have we made? *Pain Res Manag*. 2016;**2016**:8432973 Epub 2016 Nov 4.

32. Ali N, Thomson D. A comparison of the knowledge of chronic pain and its management between final year physiotherapy and medical students. *Eur J Pain*. 2009;**13(1)**:38-50.

33. Watt-Watson J, Hunter J, Pennefather P, Librach L, Raman-Wilms L, Schreiber M, et al. An integrated undergraduate pain curriculum, based on IASP curricula, for six health science faculties. *Pain*. 2004;**110(1-2)**:140-8.

34. Schreiner U, Haefner A, Gologan R, Obertacke U. Effective teaching modifies medical student attitudes toward pain symptoms. *Eur J Trauma Emerg Surg*. 2011;**37(6)**:655-9.

35. Murinson BB, Gordin V, Flynn S, Driver LC, Gallagher RM, Grabois M, et al. Recommendations for a new curriculum in pain medicine for medical students: toward a career distinguished by competence and compassion. *Pain Med*. 2013;**14(3)**:345-50.

36. Briggs EV, Carr EC, Whittaker MS. Survey of undergraduate pain curricula for healthcare professionals in the United Kingdom. *Eur J Pain*. 2011;**15(8)**:789-95.

37. Dineen KK, DuBois JM. Between a rock and a hard place: can physicians prescribe opioids to treat pain adequately while avoiding legal sanction? *Am J Law Med*. 2016;**42(1)**:7-52.

38. Wiseman T, Lucas G, Sangha A, Randolph A, Stapleton S, Pattison N, et al. Insights into the experiences of patients with cancer in London: framework analysis of free-text data from the National Cancer Patient Experience Survey 2012/2013 from the two London Integrated Cancer Systems. *BMJ Open*. 2015;**5(10)**:e007792.

39. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr*. 2002;**5(6B)**:1113-24.

40. Adam R, Murchie P. Why are we not controlling cancer pain adequately in the community? *Br J Gen Pract*. 2014;**64(626)**:438-9.

41. Hjermstad MJ, Gibbins J, Haugen DF, Caraceni A, Loge JH, Kaasa S, EPCRC, European Palliative Care Research Collaborative. Pain assessment tools in palliative care: an urgent need for consensus. *Palliat Med*. 2008;**22(8)**:895-903.

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Medical History

International Contributions toward the Conquest of Polio

John Hedley-Whyte, M.D., F.A.C.P., F.R.C.A., Debra R. Milamed, M.S.

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INTRODUCTION

In October 1986 Paul Mellon flew his own jet to Aldergrove, thence to Ulster-American Folk Park near Omagh. To Mellon's surprise, he was met by a delegation headed by Park Director Denis MacNeice. Paul Mellon was then escorted to Camp Hill Cottage, where his grandfather, Thomas Mellon had been born in 1813. His grandfather left in 1817 for Baltimore, Maryland (memoir published privately 1885). The visages of Grandfather Thomas and Paul, both in their 70s are remarkably similar[1] (Fig. 1).

Fig 1. Paul Mellon, oil on canvas, by William Franklin Draper (1912-2003), 1974, 48.25 x 40.12 inches, image no. 183.75.1, from the collections of the U.S. National Gallery of Art, Washington, DC, and reproduced with permission. Paul Mellon wrote, "While flying [in his jet] on the return journey from Belfast to Heathrow my thoughts continually reverted to my grandfather. Would he have seen me as an effete wastrel or as the son of a sensible son"[1]. The Mellon family having moved from Ulster to Pittsburgh, in 1948 they funded the founding of the University of Pittsburgh School of Public Health to support Jonas Salk. They also supported Eric Ashby in the founding of Clare Hall and the maintenance of Clare.

THE GOLDEN YEARS

The recruitment of noted virologist George Williamson Auchinvole Dick by Eric Ashby[2,3,4], Paul Mellon's friend and beneficiary, led to vital improvements in the production and safety of polio vaccine (Fig. 2). Dick was to be awarded by Johns Hopkins University the title "Hero of Public Health"[5]. Eric Ashby became Lord Ashby of Brandon[4].

Fig 2. Lord Ashby of Brandon (1904-92), oil on canvas by Ruskin Spear, CBE, RA (1911-1990) 1960. From the Queen's University Belfast Art Collection, and reproduced with their permission. Eric Ashby, Kt, Ph.D., F.R.S., Vice Chancellor, President and Chancellor of the Queen's University, Belfast, entered the City of London College in 1916 and proceeded to Imperial College and the University of Chicago. In 1931, Ashby returned to Imperial College to marry Helen Farries. At Imperial College "They came together in an entirely appropriate manner for two plant scientists –collaborating in the use of an incinerating system "[4].

David S. Sheridan Professorship in Anaesthesia and Respiratory Therapy, Harvard University, 1400 VFW Parkway, Boston, MA 02132-4927 USA

john_hedley-whyte@hms.harvard.edu

Correspondence to Prof. John Hedley-Whyte

In 1929 Eric Ashby and Robert Maynard Hutchins came to the University of Chicago. Ashby was 24 and Hutchins 29 years of age[4,6]. Ashby was a Harkness Commonwealth Scholar from Imperial College, London[4]. Hutchins came from a youthful decanal professorship at Yale Law School[6].

Twenty-nine-year-old Hutchins was determined as the new Head of the University of Chicago, to redefine and by example to improve Research Universities. Ashby was determined to improve the practice and teaching of Ecology and Plant Pathology. Hutchins lectured frequently on University Governance and himself chose and vetted the Professoriate, University of Chicago staff, and architects. Ashby listened and learned. In 1932 Ashby returned to the Faculty of Imperial College. Polio was rampant in both the United States and Northern Ireland and would so remain[7,8,9,10] (Table 1, Table 2). The effect of polio on agricultural ecology and urban life was profound. Ashby was successively Professor of Botany at the Universities of Bristol and Sydney. From Sydney in World War II, the Australian Government sent Ashby as Scientific Liaison Officer to Moscow. Ashby thought Lysenko an opportunist but not a charlatan[4]. Introduced to Stalin and many of the Soviet Scientific Establishment, Ashby later returned to Sydney where he was offered the leadership of the University of Sydney and sequentially the National University in Canberra. The Ashbys decided to return to the United Kingdom[4].
Supported by the now semi-legendary Hutchins of Chicago, Ashby accepted the Vice-Chancellorship of Queen's University, Belfast, where he succeeded David Lindsay Keir who had such a leading role in the development and organization of Orthopaedics for the World War II Allies[11].

Ashby decided to follow Hutchins' teaching and precepts. According to the Royal Society, of all Ashby's Queen's Scientific Professorial appointments made, all when they were in their 30s, all were elected to Fellowships of the Royal Society[4]. Ashby served as the Vice-Chancellor of Queen's for the middle decade of the Twentieth Century. One of Ashby's most consequential appointments was George Dick whose recruitment of Lieutenant Colonel David Dane of Clare College, Cambridge led to a classic sequential trio of papers in the British Medical Journal[12,13,14].

DEVELOPMENT OF ANTI-POLIO VACCINES: KOPROWSKI, SABIN, ENDERS, SALK, DICK AND THEIR TEAMS

In 1953, my* tutor at Clare, Michael P. Stoker, told me that polio was "Antigenicity versus Infectivity". That in order to have hope of an academic career, I should study the history of the vaccines and their funding[15], starting with Paul Mellon and FDR[16]. In 1955 I moved to Barts and Michael Stoker to Glasgow as the first British Professor of Virology.

KOPROWSKI ATTENUATED POLIO VIRUS

Warsaw native Hilary Koprowski received a medical degree from the University of Warsaw in 1939, concurrently studying music at the Warsaw Conservatory. After the German invasion, Koprowski left Warsaw with his family for Rome, where he continued his musical studies. He then relocated to Rio de Janeiro and a position with the Rockefeller Foundation's Yellow Fever Research Service. The Koprowskis emigrated to the United States in 1944 where Dr. Koprowski obtained a position at Lederle Laboratories in Pearl River, New York[17].

TABLE 1.
POLIOMYELITIS CASES WITH MORTALITY IN NORTHERN IRELAND

YEAR	CASES NOTIFIED	NORTHERN IRELAND DEATHS	N.I. DEATH RATE/10^5 POP	U.S. DEATH RATE/10^5 POP
1938	11	2	0.2	0.4
39	12	3	0.2	0.6
40	4	4	0.3	0.8
41	20	12	0.9	0.6
42	21	9	0.7	0.4
43	13	6	0.5	0.9
44	13	2	0.2	1.0
45	36	14	1.1	0.9
46	22	7	0.5	1.3
47	208	30	2.2	0.4
48	17	2	0.1	1.3
49	40	4	0.3	1.8
50	272	25	1.8	1.3
51	80	10	0.7	1.0
52	142	7	0.5	2.0
53	290	15	1.1	0.9
54	54	4	0.3	0.8
55	52	0	0	0.6
1956	49	5	0.4	0.3

TABLE 2.
POST-VACCINE DEPLOYMENT POLIOMYELITIS CASES WITH MORTALITY IN NORTHERN IRELAND

YEAR	CASES NOTIFIED	NORTHERN IRELAND DEATHS	N.I. DEATH RATE/10^5 POP	U.S. DEATH RATE/10^5 POP
1957	297	9	0.6	0.1
58	55	5	0.4	0.1
59	19	0	0	0.3
60	12	1	0.1	0.1
61	16	3	0.2	0
62	35	1	0.1	0
63	1	1	0.1	0
64	0	0	0	0
65	4	0	0	0
66	1	0	0	0
1967	1	0	0	0

During the late 1940s, Hilary Koprowski and his team at Lederle Laboratories in Pearl River, New York, set out to attenuate polio type 2 virus through monkeys and cotton rats (*Sigmodon hispidus*). He achieved attenuation of neurovirulence after cotton rat and monkey to monkey transfer. In January 1948, Koprowski ingested the resultant vaccine himself[17] and then in 1950, with the physician-in-

* This and other first- person references are to the first author.

chief of twenty mentally disabled children at Letchworth Village, Rockland County, New York, they all drank the vaccine[18]. Safety and immunogenicity were demonstrated and the Koprowski vaccine was approved and successfully used in the Soviet Union[18,19].

Later Koprowski, with the support of Nobel-Prize winner John F. Enders of Harvard, rejuvenated the Wistar Institute of Philadelphia as Director and became a Professsor at the University of Pennsylvania[17,19]. Progress in development and refinement of vaccines continues at the University of Pennsylvania.

GEORGE DICK AND THE BELFAST LABORATORY

George William Auchinvole Dick (1914-1997) was a son of the Manse in The Gorbals[3,20]. Dick was educated in Glasgow before medical studies at the University of Edinburgh. After becoming a Colonel in the RAMC he served in the Colonial Medical Service until 1951. He then was awarded a Rockefeller Fellowship to their University in New York, which was followed by a year at Johns Hopkins from where he was recruited to the British Medical Research Council. In 1954 Dick accepted Ashby's offer of a Professorship of Microbiology at Queen's Belfast[3,20]. His group with Clare-educated Dane[21,22] and Florence McKeown[23,24,25] formed a virus research group and institute supported by Vice Chancellor Ashby and Dean John Henry Biggart[26]. Sir Hugh Casson designed the Microbiology Building[27]. In January 1957, the George Dick group published the three previously noted consecutive papers[12,13,14]. The first showed that Koprowski's TN type II attenuated poliovirus vaccine caused paralysis in monkeys, after passage through the intestinal tracts of vaccinated humans, so that "the laboratory characteristics of attenuation shown by TN type II virus which made it appear suitable for trial as a vaccine are not maintained after multiplication in human gut[12,17,28,29,30]" . Similar results were obtained using Koprowski's SM type I virus vaccine[13,14]. Many lives were saved by the more stringent standards required as a result of this trio of Dick, Dane and McKeown papers[14,28].

JOHN ENDERS AND THE NOBEL PRIZE: HARVARD UNIVERSITY

John Franklin Enders (1897-1985) (Fig. 3) was educated in Hartford, Connecticut where his father was head of the Hartford National Bank. From Hartford, in 1912, John Enders was further educated at St. Paul's Boarding School in Concord, New Hampshire. In 1915 Enders entered Yale. In 1917 he became a U.S. Navy pilot. Subsequently he served as a lieutenant flight instructor. He returned to Yale post World War I and graduated BA in 1920. In 1922 as an English teacher he received an MA from Harvard. For the next three years he taught philology[31]. In 1927 he married and entered a doctoral program in Bacteriology under Harvard's famous Hans Zinsser[32]. Enders was a Harvard Instructor from 1930 to 1935 and then Assistant Professor until 1942. Late in 1939 with Harvard Medical student Thomas H. Weller and Dr. A.E. Feller, Enders cultivated vaccinia virus in roller cultures of chicken tissues. In 1940 Hans Zinsser died. Enders' wife, Sarah Frances, died of acute myocarditis in 1943[31]. Enders expanded his own research on mumps. In 1946, Dr. Charles H. Janeway, previously of Harvard's 5th General Hospital during World War II[33], and Dr. Sidney Farber asked Enders to set up a laboratory at Boston Children's Hospital and become Head of the Research Division of Infectious Diseases at that institution.

In 1947 Dr. Thomas Weller commenced biological studies on infections. Next year Dr. Frederick C. Robbins joined the Enders laboratory and started work on a strain of mumps virus that they propagated *in vitro* for the first time. In March 1948 Weller tried with varicella virus propagation using human embryonic skin and muscle. "A few unused cultures were spiked with polio virus, Lansing strain"[34]. After three weeks of culture and three changes of medium, injection into mice produced paralytic polio. Enders suggested to Robbins that he use "cultures of intestinal tissue obtained at the autopsy of a premature human infant"[31,34].

Fig 3. John Franklin Enders, NAS, FRS. Oil on canvas, 60" x 44" by Janis Lejins (1899-1990), 1960. From the collection of Boston Children's Hospital and the Harvard University Portrait Collection and reproduced with their permission.

In the Yale Archives there are just over twenty years of correspondence during the years 1946-1967 between John Enders (Fig. 3) and Hilary Koprowski during the latter's stay at Lederle Laboratories, and later at the Wistar Institute, Philadelphia[35]. Enders supplied advice and tissues for the Koprowski-Lederle anti-polio vaccine which was at first successful. Then George Dick and his laboratory at Queen's

Belfast showed in their BMJ consecutive trilogy that human alimentary passage of the polio virus increased its virulence[12,13,14].

As a result of the ramification and later U.S. confirmation of the Dick team's studies of polio vaccines, the UK avoided the fiascos of the Cutter incident[28] which led to sixty separate civil lawsuits[28]. The resolution of the first, *Gottsdanker v. Cutter Laboratories*[36], set a precedent for a finding of breach of product warranty[28]. The Salk killed polio vaccine was approved in the UK on April 25, 1955[37,38]. In the same month of April, a quarter of a million U.S. children had been given a defective Salk polio vaccine. Forty thousand of these children developed polio; within days 200 children were paralysed and ten died[28]. The first U.S. mass vaccination programme against polio was promptly abandoned. Salk's protocol for formaldehyde inactivation of poliovirus in the vaccine produced by two companies had failed. Enders, Sabin, Dick and their research groups criticized Salk[28].

The United States courts found that Cutter Laboratories had not been negligent in failing to kill all the live allegedly non-toxic polio viruses of Jonas Salk's Mellon funded University of Pittsburgh vaccine. Unfortunately the ruling that the vaccine manufacturer should be held responsible for post-vaccine disability and vaccine-associated death led to drug companies not producing vaccine supplies and halting of funding for vaccine production.

The Enders laboratory showed type 1 polio virus could be propagated using excised human foreskins[39].

I had the opportunity to meet John Enders when his second wife Carol (Carolyn) was admitted seriously ill to the Massachusetts General Hospital. She needed controlled ventilation but recovered completely. My wife Tessa was, at the time, Electron-Microscopist in the Enders Building at Children's Hospital, Boston, and occasionally consulted for image verification.

John Enders, Fred Robbins, and Tom Weller had received the 1954 Nobel Prize in Physiology and Medicine[40]. Aged 80, Enders retired from virology therapeutics. John Enders died suddenly and unexpectedly while reading T.S. Eliot to his wife Carol (Carolyn) and daughter[31].

Robbins had left Boston for Cleveland shortly after winning his share of the Nobel Prize. Tom Weller, who after wartime service in the U.S. Army Medical Corps, in 1947, joined Enders in his new, Research Division of Infectious Diseases at Harvard Medical School's Children's Hospital Medical Center, was appointed Assistant Director in 1949. The Harvard Medical School's Department of Comparative Pathology and Tropical Medicine was transferred to the Harvard School of Public Health and renamed the Department of Tropical Public Health. In July 1954, Weller was appointed Richard Pearson Strong Professor of Tropical Public Health and Head of the Department[41,42]. Weller was a superb consultant to the nearby Beth Israel Hospital's Respiratory Surgical Intensive Care Unit; Max Finland[43]by night and Weller by day were consultants. Professor Sir Michael Stoker, when he came to Boston, said to me he hoped I had learned more from Weller than I had from himself as my tutor at Clare. Apparently Eric Ashby smiled when told of this.

MELLON SUPPORT OF SALK'S RESEARCH

Jonas Salk was, or seemed to be, the only person John Enders disliked[44]. Salk worked at the University of Pittsburgh. Paul Mellon was responsible for financing the extension and conversion and modification of the Salk group's laboratories. Paul Mellon's money came from his father, Andrew Mellon, Secretary of the U.S. Treasury for three presidents, before FDR, partly crippled by polio, was instrumental in founding the March of Dimes. Previously Andrew Mellon (1855-1937) had been the most financially successful U.S. businessman of the 19th Century and the leading citizen of Pittsburgh[45]. The Mellons in the 20th Century were to give away well over 1,000 million Pounds Sterling of which several hundred million went to Paul's college, Clare, and to the founding of Clare Hall and the very generous Mellon fellowships both ways between Clare and Yale University.

Paul Mellon was awarded three Bronze Medals as a Major in World War II for Bravery under Wild Bill Donovan, head of OSS, precursor of the CIA[1]. After World War II Mellon money and influence was used to attract Francis F. Foldes as Head of Anaesthesia at Mercy Hospital in Pittsburgh from the Massachusetts General Hospital, and later supported the appointment of Foldes as Professor at Albert Einstein College of Medicine in New York City[46].

Born of an English mother, Paul Mellon (1907-1999) was baptised in St. George's Chapel at Windsor Castle. He majored in Literature at Yale and then proceeded to Clare College, Cambridge for two years of further study. An excellent rower and horseman he left Clare in 1931 and returned home to Pittsburgh. When I was at Clare from 1952-1955 the Master of Clare used to regale us with descriptions of his luxurious flights in the Mellon Gulfstream II Jet which was decorated with work by George Braque, Paul Klee and Ben Nicholson. Paul Mellon presented the U.S. National Gallery and its holdings on behalf of his late father and himself to President FDR on March 17, 1941; FDR accepted this gift on behalf of the American people[1,47]. Later Paul Mellon chose I.M. Pei as the architect of the East Building of the U.S. National Gallery, originally planned by his father Andrew to house the expanded collections of the future, with groundbreaking ceremony in 1971[47].

For the Museum of British Art in New Haven, Connecticut, Paul Mellon chose architect Louis Kahn[48]. In turn Jonas Salk chose Louis Kahn on Paul Mellon's recommendation to design the Salk Institute in La Jolla, California[1,44,48]. For Clare and Clare Hall, Paul Mellon was an indispensable advisor to Eric Ashby, Master of Clare and to A. Brian Pippard as the founding Master of Clare Hall[49,50].

LEGAL CONSEQUENCES OF POLIO SEQUESTRATION

The legal consequences of the Cutter trials are still such that generally the drug companies have to organize reimbursement for patient injury from vaccine injuries and consequent deaths. The result is few if any drug companies are interested in vaccine development without government guarantees. Very few legislators or insurance companies are willing or able to step into this role. To some extent the Gates Foundation is filling this void. In the second decade of the 21st century polio has, through vaccination almost been eliminated from our world[51,52,53,54], but late sequelae are still a world-wide burden [55,56,57].

ALBERT B. SABIN

Born in Bialystok, Poland, then part of the Russian Empire, in 1906, Albert B. Sabin arrived in New Jersey with his family in 1921 after an 18-month journey. Fluent in Yiddish, Hebrew, Russian and German, only after intensive tutoring in English by his Americanized cousins, was he ready at age fifteen to enroll in Paterson, New Jersey's Public High School. He excelled and graduated after two years. With the support of a dentist uncle he enrolled at New York University with the initial goal of studying dentistry. After two years he found himself enthralled by the study of infectious diseases. Inspired by Dr. William H. Park, his professor of Bacteriology, Sabin determined to change course[58] Dr. Park, also Director of the Public Health Laboratories of the City of New York, helped Sabin obtain scholarships for medical school as well as lodging at Harlem Hospital in exchange for "chores" in the Pneumonia Laboratory. There he developed a method for rapid typing of pneumococci before his 1931 graduation from New York University's Medical School[59]. Before settling into an internship at Bellevue Hospital, he returned to Dr. Park's Bacteriology Laboratory just as a severe polio epidemic began in July 1931. Here, Park instructed Sabin to confirm Claus Jungeblaut's earlier immunological studies of the polio virus at Columbia University[60]. When Sabin was unable to do so, Park, Sabin and Jungeblut collaborated and published the revised finding that no one, without previous infection, was naturally immune to polio[61]. Thus began Sabin's campaign to control poliomyelitis[58,61].

After a two-year internship and residency at Bellevue Hospital, Sabin applied for a National Research Council Fellowship which enabled him to study virology during 1934 at the Lister Institute of Preventive Medicine in London. In 1935 he returned to New York with an appointment in the virus research laboratory of Dr. Peter Olitsky at the Rockefeller Institute for Medical Research; in 1936 Sabin and Olitsky established that poliovirus could be grown in human tissue cultures[58].

The National Foundation for Infantile Paralysis had been founded in 1938 by FDR, with Basil O'Connor serving as president. O'Connor recruited Dr. Thomas Rivers of the Rockefeller Institute, who enlisted the aid of his Rockefeller colleague, Albert Sabin, who, in turn, was offered a five-year appointment funded by the National Foundation, later renamed March of Dimes, to work exclusively on poliomyelitis at Rockefeller. In 1939, Sabin chose instead to develop a polio research program at the Children's Hospital Research Foundation at the University of Cincinnati. In a 1941 paper, co-authored with Dr. Robert Ward, Sabin demonstrated the transmission of poliovirus through the digestive tract, and that this pathogen was seldom found in the nasal passage[62].

In 1939, while in Cincinnati, Sabin was appointed a civilian advisor to the Army Epidemiological Board, and eventually enlisted in the U.S. Army as a commissioned officer at the rank of Major in February 1943[58]. During the war he researched diseases affecting the military and developed vaccines for a South Pacific variety of dengue fever and for Japanese encephalitis. After the war he returned to his Cincinnati laboratory.

In 1951, aware that Koprowski had attempted to develop an attenuated live polio vaccine, Sabin had contacted Dr. John F. Enders at Harvard and also sent an assistant to Salk's Pittsburgh laboratories to study tissue culture techniques[18]. Sabin continued this Cincinnati-based work on attenuated live vaccine[63,64,65]. The 1955 Cutter Incident[28] increased interest. At Children's Hospital, University of Cincinnati, Sabin developed his live attenuated virus polio vaccine from polio virus that Hilary Koprowski had attenuated[66,67].

During the late 1950s the Sabin vaccine was tested in field trials in Mexico, Chile, Holland, Sweden, Japan, Singapore, Czechoslovakia and the UK[58] . The most noteworthy field trial was Sabin's work with the Soviet Union's Dr. Mikhail P. Chumakov in which the vaccine was tested initially in over ten million persons[58]. By 1960 more than 90 million persons had received Sabin anti-polio vaccine[68].

ASHBY

In his post-Clare Mastership Lectures and conversations, Ashby was wont to say that his recruitment of young Professors to Queen's Belfast ranked first in importance in his own career[4]. George Dick and Clare-educated David S. Dane had saved Britain and the United States from future polio catastrophes like the Cutter incident. Second in order was the admission of women to Clare and third was his role in the Mellon funding of Clare Hall with Arthur Brian Pippard as founding Master[49]. Pippard had returned to Clare in 1947 as director of studies in Physics. In 1955 Pippard married Charlotte Dyer and immediately thereafter they left for their next year at the University of Chicago to join the Fermi Laboratories and work on Fermi surfaces of copper. Fermi himself had died of cancer of the stomach the previous November 28th [69].

In the early 1970s, I was referred to Brian Pippard by Eric Ashby. I had tried to get a Harvard post-doc in my Department, Albert J. Saubermann, a Visiting Fellowship to accompany his training position in the Cavendish

Laboratory[50]. Ashby said 'No' to Clare. Brian Pippard said 'Yes' and asked me to lunch. We decided that Mellon money should be involved, and that the long-term goal should be an eponymous chair at Einstein Medical College in New York City, preferably to be held by our trainee, Albert J. Saubermann[50].

After the Mastership of Clare, in 1976 Ashby was called to the Walgreen Visiting Professorship at the University of Michigan. Charles R. Walgreen, founder of the drugstore chain, had previously in 1935 sued President Robert Hutchins and the University of Chicago for indoctrinating his niece with communist ideology. Hutchins had supported the academic freedom of his faculty to teach as they wished[6,70]. Hutchins by dint of "character, knowledge and charm" persuaded Walgreen to drop the suit, and later to endow a series of lectures on democracy[6]. One of the duties of Ashby, as Walgreen visiting Professor in1976, was to lecture at Harvard where "Individual members of the teaching faculties have full control over and responsibility for their methods of teaching"[71]. As a result of Ashby's Tanner Lecture at Harvard, the Charter originally written in Seventeenth Century Puritan English, approved in 1650 and subsequently revised over the years, remained in effect[71]. Ashby later told Alfred Brian Pippard, Master of Clare Hall, that in Cambridge, Massachusetts he had been questioned about the Mellons' substantial support of Clare, Clare Hall and Jonas Salk's Pittsburgh anti-polio research.

EPILOGUE

Some dozen years later, in April 1988, the plan to install our former trainee Albert J. Saubermann in a named professorship in Anaesthesiology at Einstein in New York was underway, succeeding within a decade. Francis Foldes, former Chair of Anaesthesiology and now Professor Emeritus was present at the celebratory dinner party in the restaurant at the top of the World Trade Center, Windows on the World, located on the 106th and 107th floors: the dinner was to celebrate Foldes' 1988 Award for Excellence in Research[72]. At the last minute my wife found she could not accompany me, so I brought my mother instead without informing our hosts. As my mother reached the receiving line, Professor Foldes kissed her hand and said, "Nancy, we last met in 1938 in Budapest. How is Sir Ian Fraser and how are the Surgical Travellers? We helped them recover from Vienna?"[73] My mother replied that both were flourishing.

At dinner my mother said to Professor Foldes that she and I had gone to see Paul Mellon's Mill Reef at the National Stud at Newmarket. Foldes said that the Mellons had been very helpful when he, Francis Foldes, had been Head of Anaesthesia at Mercy Hospital, Pittsburgh[74]. Fifty years had passed since 1938 when he, my mother and the Ian Frasers had helped the Surgical Travellers in Budapest[73].

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REFERENCES

1. Mellon P, Baskett J. *Reflections in a Silver Spoon. A Memoir*. New York: William Morrow and Co. ;1992. p.17-24, 297-320, 377-92.
2. Walker BM. *A Degree of Excellence: The Story of Queen's Belfast 1845-1995*. Belfast: Institute of Irish Studies; 1994. p.91-3.
3. Frogatt R. George Dick (1914-1997): Physician and virologist. In: Dictionary of Ulster Biography. Belfast: Institute of Irish Studies, Queen's University of Belfast. Available from: www.newulsterbiography.co.uk/index.php/home/viewPerson/1766 [Last accessed November 2018.]
4. Heslop-Harrison J. Eric Ashby, Baron Ashby, of Brandon, Suffolk, Kt, 24 August 1904-22 October 1992. *Biogr Mems Fell R Soc*. 1995;**41**:2-18.
5. George W.A. Dick, MB ChB, MPH. Baltimore: Johns Hopkins Bloomberg School of Public Health; 2016. Available from: https://www.jhsph.edu/about/history/heroes-of-public-health/george-w-a-dick.html [Last accessed November 2018.]
6. University of Chicago Centennial Catalogues, Special Collections Research Centre, The University of Chicago Library. Robert Maynard Hutchins 1929-1951. Chicago: University of Chicago. Available from: https://president.uchicago.edu/directory/robert-maynard-hutchins [Last accessed November 2018.]
7. Historical data provided by Mr. Paul Woods based on: Northern Ireland. Statistics and Research Agency. Registrar General Historical Reports. 1938-1967. https://www.nisra.gov.uk/statistics/registrar-general-annual-report/registrar-general-historical-reports (Accessed 26 December 2017).
8. Historical data provided by Mr. Paul Woods based on: Northern Ireland. Public Health Agency. http://www.publichealth.hscni.net (Accessed 26 December 2017).
9. Simpson NJY. Poliomyelitis in Northern Ireland—1947 with special references to epidemiology. *Ulster Med J*. 1948;**17(1):**67-80.
10. U.S. Department of Health, Education and Welfare. Public Health Service. *Vital Statistics of the United States*. Annual volumes. 1938-1967. https://www.cdc.gov/nchs/products/vsus.htm (accessed 13 December 2017).
11. Hedley-Whyte J, Milamed DR. Orthopaedic surgery in World War II: military and medical role of Northern Ireland. *Ulster Med J*. 2016; **85(3):**196-202.
12. Dane DS, Dick GW, Connolly JH, Fisher OD, McKeown F, Briggs M, *et al*. Vaccination against poliomyelitis with live virus vaccines. 1. A trial of TN type II vaccine. *Br Med J*. 1957;**1(5010)**:59-65.
13. Dick GW, Dane DS, Fisher OD, Connolly JH, McKeown FM, Briggs B, *et al*. 2. A Trial of SM Type 1 Attenuated poliomyelitis virus vaccine. *Br Med J*. 1957; **1(5010)**:65-70.
14. Dick GWA, Dane DS. 3. The evaluation of TN and SM virus vaccines. *Br Med J*. 1957;**1(5010):**70-4.

15. Taylor-Papadimitrou J. Michael George Parke (Sir) Stoker. Royal College of Physicians: Lives of the Fellows. Munks Roll Details Volume XII. Available from: http://munksroll.rcplondon.ac.uk/Biography/Details/6695 [Last accessed November 2018].
16. Hedley-Whyte J, Milamed DR. FDR and American military deployment: "My" Armed forces and their health. *Ulster Med J*. 2018;**87(1)**:39-45.
17. Fox M. Hilary Koprowsi, Who Developed First Live-Virus Polio Vaccine, dies at 96. *New York Times*. [Internet]. 2013 Apr 21 p. A18.
18. Oshinsky DM. *Polio: an American story*. Oxford, UK: Oxford University Press; 2005. p.133-7, 247-50.
19. Plotkin SA. In memoriam: Hilary Koprowski, 1916-2013. *J Virology*. 2013;**87(15)**:8270-1.
20. Tyrrell D. George Williamson Auchinvole Dick. Royal College of Physicians: Lives of the Fellows. Munks Roll Details Volume X. Available from: http://munksroll.rcplondon.ac.uk/Biography/Details/1254 [Last accessed November 2018].
21. Zuckerman AJ. David Maurice Surrey Dane. Royal College of Physicians Lives of the Fellows. Munks Roll Details Volume XI. Available from: http://munksroll.rcplondon.ac.uk/Biography/Details/4976 [Last accessed November 2018].
22. Barbara JA. David Surrey Dane 1923-1998. *Vox Sang*. 1998;**75(3)**:177.
23. Elizabeth Florence McKeown. Royal College of Physicians. Lives of the Fellows. Munks Roll Details Volume XII. Available from: http://munksroll.rcplondon.ac.uk/Biography/Details/6086 [Last accessed November 2018].
24. McKeown F. *Pathology of the Aged*. London: Butterworth & Co Publishers Ltd.;1965.
25. Crane J. Annual Oration. Medical education in the future: lessons from the past. Royal Victoria Hospital, September 2013. *Ulster Med J*. 2015;**84(2)**:124-8.
26. Biggart D. *John Henry Biggart: Pathologist, Professor and Dean of Medical Faculty, Queen's University, Belfast*. Belfast: Ulster Historical Foundation; 2012.
27. Builders. Bricks and Mortar Boards. The Architecture of Queen's University 1845-2005. Belfast: Queen's University of Belfast; 2005. Available from: http://www.qub.ac.uk/directorates/EstatesDirectorate/FileStore/BuildersBricksandMortarboards/Filetoupload,638011,en.pdf#search=HUGH%20CASSON [Last accessed November 2018].
28. Offit PA. *The Cutter Incident: How America's first polio vaccine led to the growing vaccine crisis*. New Haven, CT: Yale University Press; 2005. p. 125-7, 132-53.
29. Dick GW, Dane DS. Vaccination against poliomyelitis with live virus vaccines. 4. A review of the present position. *Br Med J*. 1958;**2(5106)**:1184-6.
30. Dane DS, Dick GW, Briggs M, Nelson R. Vaccination against poliomyelitis with live virus vaccines. 5. Neutralizing antibody levels one year after vaccination. *Br Med J*. 1958;**2(5106)**:1187-8.
31. Weller TH, Robbins FC. John Franklin Enders. *Biogr Mem Nat Acad Sci*. 1991;**60:**46-65. Available from: http://www.nap.edu/catalog/6061.htm [Last accessed November 2018].
32. Zinsser H. *Rats, lice and history: being a study in biography, which, after twelve preliminary chapters indispensable for the preparation of the lay reader, deals with the life history of typhus fever.* New York: Blue Ribbon Books; 1935.
33. Hedley-Whyte J. Epidemic jaundice: Harvard's 5th General Hospital at Musgrave Park in World War II. *Ulster Med J*. 2005; **74(2)**:122-5.
34. Enders JF, Weller TH, Robbins FC. Cultivation of the Lansing Strain of poliomyelitis virus in cultures of various human embryonic tissues. *Science*. 1949;**109(2822):**85-7.
35. Letter of June 8, 1946, Dr. Hilary Koprowski (HK) to Dr. John F. Enders (JFE); letter of June 13, 1946, JFE to HK, letter of June 16, 1952 HK to JFE; letter of January 29, 1953 HK to JFE; letter of February 12, 1953 HK to JFE; letter of July 8, 1954 HK to JFE; letter of November 22, 1954 HK to JFE; letter of July 31, 1957 JFE to HK; letter of August 12, 1957, letter of Miss M.H. Platzer, secretary to HK to JFE; letter of August 18, 1967, JFE to Miss M.H. Platzer, secretary to HK; letter of January 6, 1958 JFE to HK; letter of May 4, 1966 JFE to HK; letter of September 23, 1966 HK to JFE; letter of October 19, 1966, JFE to HK; letter of November 22, 1966 HK to JFE; letter of January 20, 1967 JFE to HK. Yale University Library. Manuscripts and Archives. Enders (John Franklin) papers. MS 1478, Series No. 1, Box No. 41, Folder No. 980. [Last accessed November 2018].
36. Vaccine Law. Case compliments of Versuslaw. Early vaccine injury case – Cutter incident vaccine. Gottsdanker v. Cutter Laboratories, 182 Cal.App.2d 602, 6 Cal.Rptr.320, 79 A..R.2d 290 (Cal.App. 1 Dist. Jul 12, 1960). Anne Elizabeth Gottsdanker, a Minor, Etc. et al., Plaintiffs and Appellants, v. Cutter Laboratories (a Corporation), Defendant and Appellant. James Randall Phipps, a Minor, Etc., et al., Plaintiffs and Appellants, v. Cutter Laboratories (a Corporation), Defendant and Appellant. Available from: https:biotech.law.lsu.edu/cases/vaccines/GOTTSDANKER.htm [Last accessed November 2017].
37. Medical Notes in Parliament. The Salk Vaccine in Britain. *Br Med J*. 1955;**1(4921)**:1099-1100.
38. UK Parliament. Commons Sitting. Poliomyelitis vaccine. HC Deb 25 April 1955, vol 540 cc620-4. London: Hansard; 1955. Available from: http://hansard.millbanksystems.com/commons/1955/apr/25/poliomyelitis-vaccine-1 [Last accessed November 2018].
39. Weller TH, Robbins FC, Enders JF. Cultivation of poliomyelitis virus in cultures of human foreskin and embryonic tissues. *Proc Soc Exp Biol Med*. 1949;**72(1):**153-5.
40. Enders JF, Robbins FC, Weller T. The cultivation of the poliomyelitis viruses in tissue culture. Nobel Lecture, December 11, 1954. Stockholm, Sweden: The Nobel Prize Organisation; 2018. Available from: https://www.nobelprize.org/nobel_prizes/medicine/laureates/1954/enders-lecture.html [Last accessed November 2018].
41. Enders JF, Robbins FC, Weller T. Thomas H. Weller – Biographical. The Nobel Prize in Physiology or Medicine 1954. Stockholm, Sweden: The Nobel Prize Organisation; 2018. Available from: https://www.nobelprize.org/nobel_prizes/medicine/laureates/1954/weller-bio.html [Last accessed November 2018].
42. Thomas H. Weller, Nobel Laureate and Professor Emeritus, dies. News Release Tuesday, August 26, 2008. Available from: https://www.hsph.harvard.edu/news/press-releases/thomas-weller-nobel-laureate-professor-emeritus-dies/ [Last accessed November 2018].
43. Hedley-Whyte J, Milamed DR. Lobar pneumonia treated by Musgrave Park physicians. *Ulster Med J*. 2009;**78(2):**119-28.
44. Carter R. *Breakthrough: the saga of Jonas Salk*. New York: Trident Press; 1966; p.86-90.
45. Cannadine D. Epilogue. A fortune in history. In *Mellon: An American life*. New York: Alfred A. Knopf; 2006. p.583-621.
46. Foldes FF. An autobiography, with contributions by ES Siker. In: Fink BR, McGeldrick KE, eds. Careers in anesthesiology: two posthumous memoirs. Park Ridge, IL: The Wood Library-Museum of Anesthesiology; 2000. p.121-271.
47. National Gallery of Art. Highlights of the History of the National Gallery of Art. Timeline. London: National Gallery of Art; 2017. Available from: https://www.nga.gov/research/gallery-archives/nga-history-timeline.html [Last accessed November 2018].
48. Lesser W. *You Say to Brick: The Life of Louis Kahn*. New York: Farrar, Straus and Giroux; 2017.

49. Longair MS, Waldram JR. Sir Alfred Brian Pippard.7 September 1920-21 September 2008. *Biog Mems Fell R Soc*. 2009;**55**:201-20.

50. Saubermann AJ, Echlin P. The preparation, examination and analysis of frozen hydrated tissue sections by scanning transmission electron microscopy and x-ray microanalysis. *J Microsc* 1975;**105(2):**155-91.

51. World Health Organization (WHO). Polio fact sheet. Available from: http://www.who.int/mediacentre/factsheets/fs114/en/ [Last accessed November 2018].

52. World Health Organization (WHO) Polio Vaccines: WHO position paper – March, 2016. *Wkly Epidemiol Rec*. 2016; **91(12**):145-68.

53. World Health Organization (WHO) Immunization Fact Sheet. Available from: http://www.who.int/mediacentre/factsheets/fs378/en [Last accessed November 2018].

54. World Health Organization (WHO). Global Polio Eradication Initiative (GPEI). Available from; http://polioeradication.org/ [Last accessed November 2017].

55. Raymond CA. Decades after polio epidemics, survivors report new symptoms. *JAMA*. 1986;**255(11)**:1397-1404.

56. Haldstead LS. A brief history of postpolio syndrome in the United States. *Arch Phys Med Rehabil*. 2011;**92(8)**:1344-9.

57. Atwal A, Giles A, Spiliotopoulou G, Plastow N, Wilson L. Living with polio and postpolio syndrome in the United Kingdom. *Scand J Caring Sci*. 2013;**27(2)**:238-45.

58. Jiménez, MR. Albert B. Sabin.1906-1993 *Biogr Mem Nat Acad Sci*. 2014. Available from: www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/sabin-albert.pdf [Last accessed November 2018].

59. Sabin AB. "Stained Slide" microscopic agglutination test. Application to (1) rapid typing of pneumococci, (2) determination of antibody. *Am J. Public Health*. 1929:**19**:1148-50.

60. Jungeblut CW. An accelerated febrile reaction in monkeys upon reinoculation with poliomyelitis virus. *J Exp Med*. 1931;**53(2):**159-69.

61. Sabin, A B, Park, W H, Jungeblut, C W. Nature of skin reactions produced by heat inactivated poliomyelitis virus. Reaction of persons convalescing from poliomyelitis and of normal persons to intracutaneous injections of the heat-inactivated virus. *Arch Int Med*. 1933;**51(6):**878-89.

62. Sabin AB, Ward R. The natural history of human poliomyelitis. II. Elimination of the virus. *J. Exp Med*. 1941;**74(6):**519-29.

63. Sabin AB. Immunization of chimpanzees and human beings with avirulent strains of poliomyelitis virus. *Ann NY Acad Sci* 1955**;61(4):**1050-6.

64. Sabin AB. Behavior of chimpanzee-avirulent poliomyelitis viruses in experimentally infected human volunteers. *Br Med J* 1955;**2(4932)**160-2.

65. Sabin AB. Behavior of chimpanzee avirulent poliomyelitis viruses in experimentally infected human volunteers. *Am J Med Sci* 1955; **230(1)**:1-8.

66. Sabin AB. Properties and behavior of orally administered attenuated poliovirus vaccine. *J Am Med Assoc* 1957;**164(11)**:1216-23.

67. Sabin AB. Present position of immunization against poliomyelitis with live virus vaccines. *Br Med J*. 1959;**1(5123)**:663-80.

68. Chumakov MP, Voroshilova MK, Drozdov SG, Dzagurov SG, Lashkevich VA, Mironova LL, e*t al*. Some results of the work on mass immunization in the Soviet Union with live poliovirus prepared from Sabin strains. *Bull World Health Organ*. 1961;**25(1)**:79-91.

69. Enrico Fermi – Biographical. The Nobel Prize in Physics, 1938. Stockholm, Sweden: The Nobel Prize Organisation; 2018. Available from: https://www.nobelprize.org/nobel_prizes/physics/laureates/1938/fermi-bio.html [Last accessed November 2018].

70. Ashby E. Consequences of Success: Review of *Some Observations on American Education,* by Robert M. Hutchins (Cambridge, UK: Cambridge University Press, 1956). *Nature*. *Suppl*. 1957;**179(4562)**:722.

71. Morison SE. Introduction. Government and Administration. In Morison SE, editor. *The Development of Harvard University since the Inauguration of President Eliot 1869-1929*. Cambridge, MA: Harvard University Press; 1930. p.xxxviii.

72. Siker ES. Special Announcement. ASA Award: Francis F. Foldes. *Anesthesiology* 1988;**69(4):**448-50.

73. Hedley-Whyte J, Milamed DR. Surgical Travellers: Tapestry to Bayeux. *Ulster Med J* 2014;**83(3):**171-7.

74. UPMC, Mercy: A chronology. Pittsburgh Post-Gazette. 2006: Sept 21. https://www.post-gazette.com/business/businessnews/2006/09/21/UPMC-Mercy-A-chronology/stories/200609210367

Letters

A 10-YEAR REVIEW OF UNSTABLE THORACOLUMBAR SPINAL FRACTURES FROM NORTHERN IRELAND: THE ASSOCIATED INJURIES

Editor,

Trauma is the leading cause of death in young people (aged <50years) and a recent study showed that 10% of these patients have spinal injuries. [1]

Looking at it from the other side; thoracolumbar spinal fractures managed with surgical stabilisation in our regional unit are often associated with other significant injuries. An awareness of these associated injuries aids early diagnosis and management. In these cases, any delayed or missed diagnoses could result in significant morbidity and mortality.

Our unit is the regional trauma centre with around 90 inpatient fracture beds, there is often up to 50% bed occupancy with spinal patients. Our spinal referrals are increasing at a rate of approximately 10% per year.

We aimed to identify the prevalence of associated injuries in patients admitted with unstable thoracolumbar fractures.

The fracture outcome research database was interrogated to identify all surgically managed thoracolumbar spinal admissions to our unit over a 10-year period. A sample of 210 cases spanning that time period was identified and all early imaging was retrospectively reviewed and additional injuries were recorded.

Of the 210 cases reviewed, 80 (38%) had an associated injury. Of those 80, 46 (58%) had a single additional injury, 20 (25%) had 2 additional injuries and 14 (18%) had 3 or more additional injuries

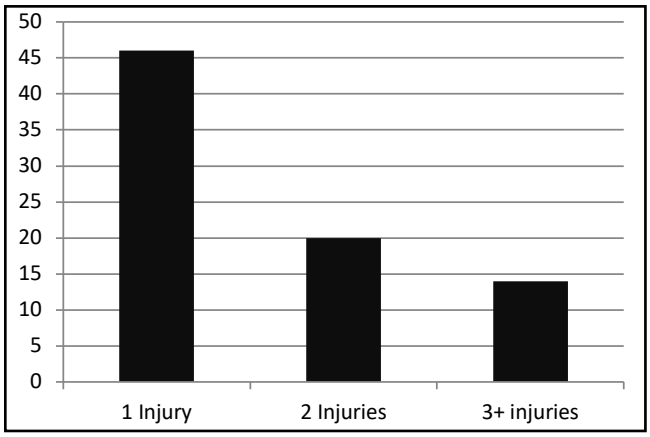

Fig 1.

From our sample other injuries were common, with 17% of patients having a further spinal injury, 16% other orthopaedic injury, 16% rate of thoracic trauma, 6% abdominal trauma and much rarer were facial trauma and brain/ neurological trauma at only 2% each.

Looking in more detail at some of the more common injuries.

Thoracic trauma was one of the more common pathologies with 11% having rib fractures, 6% having either a pneumo or haemothorax, sternal fractures were found in 4% with a further 1% having an aortic injury.

Abdominal trauma was far less common with 2% having splenic injuries, liver, renal, mesenteric and small bowel injuries having only a 1% incidence respectively.

The other orthopaedic injuries were varied and made up of upper limb injuries (6%), foot injuries (5%), os calcis or pelvic injuries (4% each) and tibia or femur injuries only 2% each.

All of these associated injuries are serious with potentially life changing implications.

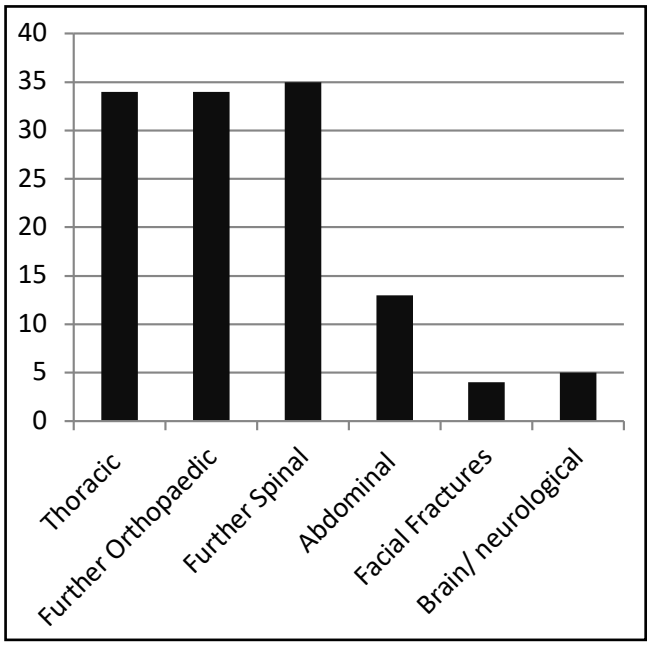

Fig 2.

We have shown that a significant number of unstable thoracolumbar fractures have additional injuries especially chest trauma, further spinal fractures and other orthopaedic injuries.

Further studies should be performed looking at the classification of these fractures and any associated injuries as well as where these patients are managed as we feel a High Dependency setting may be most appropriate.

We conclude that a high index of suspicion is required in the assessment of these patients and a multispecialty as well as multidisciplinary approach is required in their management.

Thomson S, Julian H, McLorinan G, Verzin E, Hamilton A, Eames N

Royal Victoria Hospital, Belfast, Grosvenor Road, Belfast, Northern Ireland

Correspondence to: Stacey Thompson

E-mail: staceylthomson@hotmail.co.uk

REFERENCES

1. Hasler RM, Exadaktylos AK, Bouamra O, Benneker LM, Clancy M, Sieber R. Epidemiology and predictors of spinal injury in adult major trauma patients: European cohort study. *Eur Spine J*. 2011;**20(12)**:2174–.80.

2. Prime M, Al-Obaidi B, Safarfashandi Z, Lok Y, Mobasheri R, Akmal M. Major trauma patients with spinal fractures have more complex injuries than non-major trauma patients. *Bone Joint J. 2015 97-B(2):235-9*.

AN UNUSUAL GASTROINTESTINAL COMPLICATION FOLLOWING HEART TRANSPLANTATION.

Editor,

A 29-year-old man underwent uncomplicated cardiac transplantation for advanced heart failure secondary to hypertrophic cardiomyopathy. Nine days post-operatively he required aggressive escalation of immunosuppression for 3 days with methylprednisolone due to an episode of severe cell-mediated rejection which promptly resolved. A routine chest radiograph a further 6 days later unexpectedly demonstrated free sub-diaphragmatic air. On subsequent assessment he admitted to only very mild abdominal discomfort. On examination his abdomen was distended and tympanic with active bowel sounds and no signs of peritonism. Inflammatory markers and lactate were normal. Due to concern regarding the possibility of gastro-intestinal perforation secondary to high dose steroid therapy an abdominal CT scan was undertaken. This confirmed the presence of pneumoperitoneum and also demonstrated extensive gaseous infiltration of the bowel wall and the omentum from the caecum extending as far as the distal descending colon with sparing of the sigmoid (Figure 1a and b) in keeping with a diagnosis of pneumatosis intestinalis. There was no radiological evidence of bowel ischaemia. Cytomegalovirus was not detected in blood or faeces. He was managed conservatively with 5 days of intravenous amoxicillin and metronidazole with complete resolution. He remains well 1 year later.

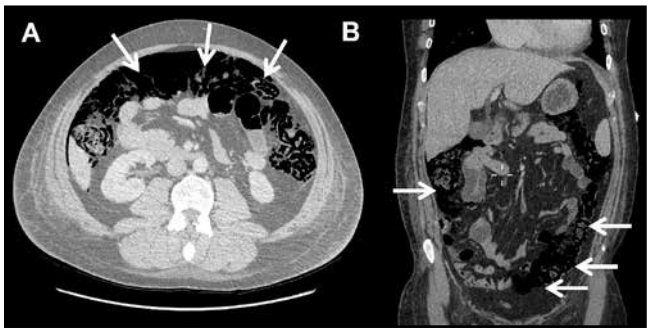

Fig 1. Axial (1A) and coronal (1B) views from a contrast computed tomography scan of the abdomen demonstrating extensive pneumatosis intestinalis of the large bowel. The dark areas (arrowed) represent extensive submucosal gas.

Pneumatosis intestinalis is a radiological diagnosis and occurs when the gastrointestinal wall becomes disrupted and infiltrated by intra-luminal gas[1]. It can have a benign or life-threatening course, largely dictated by the underlying aetiology, and has a reported association with a variety of conditions including bowel ischemia, intestinal obstruction, inflammatory bowel disease, connective tissue disorders and chronic obstructive pulmonary disease[2]. It is best diagnosed with CT and has rarely been reported following renal, lung and liver transplantation[2] and even less so following heart transplantation[3]. It has been speculated that pneumatosis intestinalis in the post-transplant setting may be related to multiple effects of immunosuppression including hyperactivity of the colonic flora as well as steroid-induced atrophy of Peyer patches and the gastro-intestinal mucosa with consequent invasion of the submucosa by intra-luminal gas[4]. From the limited literature regarding post-transplantation pneumatosis intestinalis, the large bowel seems to be more commonly affected than the small bowel and the majority of cases fully resolve with careful monitoring and conservative management alone[3,5]. Our patient had required prolonged treatment with high dose methylprednisolone due to an episode of allograft rejection which was the likely a major causative factor. This case reduces the paucity of literature on a rare complication of heart transplantation. It appears to be associated with a benign course in the majority of cases; however, care must be taken to exclude the coexistence of more malignant processes underlying this presentation, such as cytomegalovirus related colitis, in post-transplant patients.

Keywords: heart transplant, immunosuppression, pneumatosis intestinalis

Alison I Smyth, Advanced Heart Failure Fellow [1] Joanna Osmanska, Core Medical Trainee [1] Stefanie Lip, Advanced Heart Failure Fellow [1] Peter S Chong, Consultant Colorectal Surgeon [2] Jonathan R Dalzell, Consultant Cardiologist [1]

[1] Scottish National Advanced Heart Failure Service, Golden Jubilee National Hospital, Glasgow, G81 4DY, UK [2] Department of General Surgery, Glasgow Royal Infirmary, Glasgow, G31 2ER, UK.

Correspondence: Dr Alison Smyth

Scottish National Advanced Heart Failure Service, Golden Jubilee National Hospital, Glasgow, G81 4DY, UK

Email: alisonsmyth@doctors.net.uk

REFERENCES

1 Treyaud MO, Duran R, Zins M, Knebel JF, Meuli RA, Schmidt S. Clinical significance of pneumatosis intestinalis - correlation of MDCT-findings with treatment and outcome. *Eur Radiol*. 2017;**27(1)**:70-9.

2 Ho LM, Paulson EK, Thompson WM. Pneumatosis intestinalis in the adult: benign to life-threatening causes. *AJR Am J Roentgenol*. 2007;**188(6)**:1604-13

3 Bhatia NL, Steidley DE, Scott RL, Silva AC, Arabia FA, Mookadam F. Pneumatosis intestinalis associated with orthotopic heart transplantation in adults. *J Card Fail*, 2009;**15(6)**: S51-S52.

4 Galm O, Fabry U, Adam G, Osieka R. Pneumatosis intestinalis following cytotoxic or immunosuppressive treatment. *Digestion*, 2001;**64(2)**:128-32.

5 Chandola R, Laing B, Lien D, Mullen J. pneumatosis intestinalis and its association with lung transplant: Alberta Experience. *Exp Clin Transplant*. 2018;**16(1)**:75-80.

BIRTH RATE MAY INCREASE NINE MONTHS AFTER NATIONAL FOOTBALL SUCCESS

Editor,

We noted an increase in referrals to prenatal genetic clinics

Table 1:

FIFA World Cup and UEFA Euros start and finish dates with corresponding expected due date (E.D.D), 2006-2017.

	Tournament start	Tournament finish	E.D.D start	E.D.D finish
FIFA World Cup	12/06/2014	13/07/2014	05/03/2015	05/04/2015
	11/06/2010	11/07/2010	04/03/2011	03/04/2011
	09/06/2006	09/07/2006	02/03/2007	01/04/2007
UEFA Euros	10/06/2016	10/07/2016	03/03/2017	02/04/2017
	08/06/2012	01/07/2012	01/03/2013	24/03/2013
	07/06/2008	19/07/2008	28/02/2009	11/04/2009

after large sporting events such as the UEFA European Championship (Euros) and World Cups. Few reliable studies are reported, although birth spikes nine months after events are described in South Africa after they hosted the 2010 FIFA World Cup[1], the USA Super Bowl championship[2] and following a last-minute goal by Barcelona in the 2009 UEFA final[3].

We examined live birth rates nine months after the six UEFA Euros and FIFA World Cups, between 2006-2017[4]. The expected due date (E.D.D) of births, conceived during the period, was calculated as 38 weeks following the beginning and end of the tournaments, assuming births at ~40 weeks gestation. The tournaments occurred in June - July, so the E.D.D range corresponds to the following March (Table 1). We compared live births in March, as a proportion of total births for the corresponding year, with the average birth rate in the contiguous February and April, using chi-squared analysis.

RESULTS

Birth rates for the following March ranged from 1,780 to 2,113 (7.3% to 9.2% as a proportion of total births for each corresponding year). Average birth rates for February and April combined, ranged from 1,930 to 1,873 (7.2% to 8.1%) (Table 2).

We observed no significant difference in the proportion of live birth rates between 2007 – 2015, however, a statistically significant increase in births was noted in March 2017, nine months after the 2016 UEFA Euros Championship, compared with the contiguous February and April (2% (0.516 to 3.549), p 0.008) (Table 2). 2016 was the first occasion when the Northern Ireland (NI) football team qualified to compete in the UEFA Euros tournament and the team achieved relative success, reaching the second stage.

We postulate that the increase in birth rate nine months after NI's first appearance in the UEFA Euros may be the result

Table 2:

Comparison of proportionate births in March and February/April, corresponding to the E.D.D for conceptions occurring during World Cup and UEFA Euros tournaments (2007-2017).

Year	March births[a] % (n)	Average February/ April births[b] % (n)	Difference in births (%) March v. February/April	p. value[c]	95% Confidence Intervals[c]
2017^	9.2 (2,113)	7.2 (1,658)	2	**0.008**	**0.5136 - 3.5493**
2015*	8.1 (1,966)	7.7 (1,873)	0.4	0.593	1.0399 - 1.9231
2013^	7.3 (1,780)	8.1 (1,930)	0.8	0.298	0.7353 - 2.2324
2011*	8.6 (2,181)	7.3 (1,856)	1.3	0.072	0.1136 - 2.7810
2009^	8.4 (2,086)	8.1 (4,023)	0.3	0.685	1.1229 - 1.8014
2007*	7.9 (1935)	7.7 (3,765)	0.2	0.789	1.2340 to 1.7202

a. March births (%) calculated as a proportion of total births for the corresponding year.
b. Average of February and April births, calculated as a proportion of total births for the corresponding year.
c. P.values and 95% Confidence intervals calculated using chi-squared test.
^ Year corresponding to a conception during a UEFA European Championship.
* Year corresponding to a conception during a FIFA World Cup Championship.

of a potent combination of national excitement, enthusiastic fervour, celebration and inebriation.

Although there are few existing studies looking at the relationship between sporting events and birth rates, our findings are consistent with the South African World Cup, the USA super Bowl and Barcelona UEFA reports[1-3]. Mechanisms by which large sporting events influence reproductive behaviour are complex. Increased alcohol consumption, disinhibited behaviour and a sense of well-being as a result of national pride and excitement, may play a role. The association between the March 2017 birth rate in Northern Ireland and the timing of the 2016 UEFA Euros tournament does not prove causation and there may be other factors such as seasonal light and temperature variations and no significant rise in birth rate was noted following the other five football tournaments that we examined.

Future research may look at other sporting events (e.g. Olympics, Rugby World Cup). Any impact on reproductive behaviour may depend on which national team is competing and the degree of their success within the tournament. Following the relative success of England in the 2018 World Cup, we may see a spike in "World Cup babies" in March 2019.

Dr. Caoimhe S. McKenna[1] , Clinical Genetics Registrar & MD Student, UCL Great Ormond Street Institute of Child Health: Caoimhez.mckenna@belfasttrust.hscni.net. Dr. Anna Znaczko[1], Clinical Genetics Registrar: Anna.znaczko@belfasttrust.hscni.net. Prof. Patrick J. Morrison[1], Consultant Clinical Geneticist & Honorary Professor of Human Genetics: Patrick.morrison@belfasttrust.hscni.net

[1]Northern Ireland Regional Genetics Service, Belfast City Hospital, Belfast BT9 7AB. UK

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare

REFERENCES

1. Masukume, G., Grech, V. The sex ratio at birth in South Africa increased 9 months after the 2010 FIFA World Cup. *Early Hum Dev*, 2015;**91(12)**: 807-9.

1. Grech, V., Zammit, D. Influence of the Super Bowl on the United States birth sex ratio. *Early Hum Dev*. 2018; 19 Jan. (in press) S0378-3782(17)30656-4. doi: 10.1016/j.earlhumdev.2018.01.009. [Epub ahead of print]

2. Montesinos, J., Cortes, J., Arnau, A., Sanchez, J. A., Elmore, M., Macia, N., Bosch, J. Barcelona baby boom: does sporting success affect birth rate? *Brit Med J*. 2013;**347**: f7387. Available from https://www.bmj.com/content/bmj/347/bmj.f7387.full.pdf [Last accessed November 2018].

3. Northern Ireland Statistics and Research Agency (NISRA). The number of live births to Northern Ireland residents, registered each month, 2006 to 2018. Belfast: NISRA; 2018. Available from: https://www.nisra.gov.uk/publications/monthly-births [Last accessed November 2018].

ASSESSMENT OF HYPONATRAEMIA IN ACUTE MEDICAL PATIENTS

Editor,

Hyponatraemia is defined by a sodium level of less than 135mmol/L and is the commonest electrolyte abnormality, occurring in 15-20% of hospital patients [1]. It has also been identified as an independent predictor of mortality and is associated with severe complications such as cerebral oedema [2,3]. Despite this, the management of hyponatraemic patients has been poor [1,4].

The aim of our study was to evaluate the assessment of hyponatraemia in newly admitted hospital patients.

METHODS

Our study was a retrospective data collection analysis. Using data provided by the Biochemical laboratory at a South London hospital, we analysed patients that were admitted to their Acute Medical Unit with sodium levels below 133mmol/L (the trust's definition), across July and August 2017. Patients were excluded if their hyponatraemia developed after their Post-take ward round or if it was in the context of a hyperglycaemia (>20mmol). We separated patients by severity of their hyponatraemia – mild 130-133, moderate 120-130 and severe <120 - then further analysed data within these groups. Our analysis focused on the period between the patient's admission clerking notes and their post-take ward round notes – however we did look further in their notes to look at whether they had been admitted to ITU in that respective admission.

RESULTS

Our study revealed that 101 patients were admitted to AMU with hyponatraemia during the July-August 2017 period. 53/101 (52%) patients had their glucose checked. 2/53 were revealed to have a glucose level of above 20mmol/L and therefore had pseudohyponatraemia. We have excluded these two patients from further analysis. For the new patient group of 99 patients: 36 had mild hyponatraemia (130-133mmol/L), 51 had moderate hyponatraemia (120-130mmol/L) and 12 had severe hyponatraemia (<120mmol/L)

Reassuringly, all patients with severe hyponatraemia had this documented in their notes (12/12 100%), followed by the moderate category with 34/51 (67%), and the mild with 10/36 (28%). However, there was no such relationship between severity and volume assessment. Only 34% of patients had a volume assessment in the context of their low sodium (mild 28%, moderate 31%, and severe 67%).

Urinary sodium was poorly requested in the mild and moderate categories (0% and 7.8% respectively). Although, in severe hyponatraemia 75% of patients had a urinary sodium test requested. For good practice, it is recommended to check glucose levels AND request a urinary sodium in all patients presenting with hyponatraemia. This occurred in 7% of patients (including 2 excluded earlier). The majority of these patients (4/7) had severe hyponatraemia.

4/99 patients had their care escalated to the intensive care unit eventually at some point during their admission. However none of these patients were admitted with severe hyponatraemia.

CONCLUSION

Overall: *1*. The recognition and investigation of hyponatraemia in acute patients is poor; although there is some improvement with increasing severity of hyponatraemia. *2*. Investigations for hyponatraemia – blood glucose, urinary sodium and volume status assessment – aren't performed in all patients. *3*. The majority of hyponatraemic patients do not become critically ill requiring ITU admission.

Raafae Rana, Amrita Saravanan, Hisham Nizar

Acute Medical Unit, Croydon University Hospital, London.

REFERENCES

1. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Hyponatraemia Guideline Development Group, *et al*. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol*. 2014;170(3):G1-G47.
2. Sajadieh A, Binici Z, Mouridsen MR, Nielsen OW, Hansen JF, Haugaard SB. Mild hyponatremia carries a poor prognosis in community subjects. *Am J Med*. 2009;122(7):679-86.
3. Sterns RH. Disorders of plasma sodium - causes, consequences, and correction. *N Engl J Med*. 2015;372(1):55-65.
4. Fogarty J, Loughrey C. Hyponatraemia in hospitalised adults: a guide for the junior doctor. *Ulster Med J*. 2017;86(2):84-9.

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So You Want To Be A Clinical Research Fellow

Charlotte Addy[1], Judy Bradley[1], Lorcan McGarvey[1], J Stuart Elborn[2] , Damian Downey[1]

1 Centre for Experimental Medicine, Queen's University Belfast 2 Imperial College and Royal Brompton Hospital, London

Correspondence to: Dr Charlotte Addy

Email: c.addy@qub.ac.uk

Key words: Clinical Research Fellow; Academic training; Fellowships; Clinical Trials; Out Of Programme Research

INTRODUCTION

Clinicians with expertise in clinical research are essential to delivering high quality care, developing innovation and inspiring future researchers.[1] Clinical research skills are an essential part of postgraduate training, with all trainees required to complete an "academic checklist" during speciality training.[2] Specific academic training pathways are available,[3] but for those wanting to develop an interest in research without committing to a formal academic pathway, a period "out of programme" (OOP) as a Clinical Research Fellow can be undertaken.[4] Trainees can chose to do this at any stage in their career but this most commonly occurs during speciality training.[5,6]

WHAT IS A CLINICAL RESEARCH FELLOW?

A Clinical Research Fellow is a doctor employed in a research role[4] often leading to a higher degree e.g. MD/PhD. Research is usually carried out over 2-3 years.[4] Shorter term posts designed to assist in delivering larger studies are also available.[6] The diversity of roles undertaken by Clinical Research Fellows is vast with a variable balance between original research and delivering other studies.[6] Roles can encompass any part of clinical research from addressing basic science questions in the laboratory to clinical trials.

Conducting research requires new skills to complement those developed in clinical training.[5,6] There are a growing number of structured "training fellowships" which include specific training in research skills, alongside conducting original research.[6] These are supported by national funding bodies such as the National Institute of Health Research (NIHR)[6], Wellcome Trust[7] or Cancer Research UK[8] and by local Clinical Research Networks including the Northern Ireland Clinical Research Network (NICRN).[9]

Clinical Trial Fellowships

Specific training, legislative and governance requirements are required for any researcher or "Trialist" conducting clinical trials.[10] Clinical Trial Networks provide leadership, funding, education and support for trials and the teams delivering them. In the UK the largest group supporting fellowships in clinical trials is the NIHR, with competition for NIHR funding and fellowships consistently high.[6] As the need for researchers with specific "Trialist" skills increases structured fellowships in clinical trials are also increasing.[6-9]

The first NICRN[9] Fellowship "The James Fellowship in Clinical Trials" started in 2015. This was specifically designed to provide training and experience in delivering clinical trials combined with completion of the fellow's own trial as part of a PhD programme at Queen's University Belfast. This fellow participated in numerous trials, successfully delivered an original research study, published articles and presented work at international conferences. The success of this fellowship has allowed other NICRN fellowships to be created using a similar model.

Routes into fellowships

Routes into Clinical Research Fellow posts vary depending on the fellowship, associated higher degree and funding source. Posts are advertised in medical journals, online and increasingly on social media. Fellowships provided by large research bodies including the NIHR[6], Wellcome Trust [7] and Health and Social Care (HSC) Research and Development[11] have a competitive application and interview process. Applications require a project proposal supported by a senior researcher.[6-8] Making contact early is essential as this process may take over a year. Evidence of commitment to research including an intercalated degree, conference presentations and publications increase the chances of a successful application.

Whilst this sounds daunting the most important thing to remember is that nothing makes researchers happier than discussing their work. Senior researchers welcome interest from juniors who want to consider undertaking research and are happy to provide guidance on where to start. Many research projects have started off with a simple conversation.

BENEFITS OF BEING A CLINICAL RESEARCH FELLOW

The best aspects of being a Clinical Research Fellow are the varied opportunities on offer and the chance to develop research skills which can be taken into a future academic or clinical career. Fellowships offer the opportunity to develop research skills in a structured manner within a supportive environment.[6] Fellowships are flexible allowing better work/life balance and flexibility around outside commitments. These posts allow you to work within enthusiastic multi-disciplinary research teams and to learn from both your supervisors and the wider research team. Such posts offer the opportunity to develop your own research program and network of contacts by attending local, national and international meetings and conferences.[6-9,11] The investment of research bodies into fellowships provides additional support to encourage presentation and publication of your own research.[6-9,11]

CHALLENGES

However, undertaking a Clinical Research Fellow can be challenging. Once a post is identified time "Out Of Programme for Research" (OOPR) must be planned well in advance.[4] With planned changes to postgraduate training this may become easier in the future.[5,6] Clinical Research Fellow posts are often fully funded with a salary but checking whether this covers University fees, study budgets and other potential expenses is vital. Fellows usually have no on call commitments, which inevitably impacts on the salary paid.

Once in post, balancing competing commitments between your own research, training and clinical commitments requires organisation and efficient time management. Logistical challenges can be encountered in ensuring appropriate access to IT systems in both the university and Trust; as well as appropriate contracts and indemnity cover for all work you may be required to do.

WHAT CAN I DO AFTER A FELLOWSHIP?

After finishing a Clinical Research Fellow post trainees can return to clinical training [1,3] or if inspired to pursue a research career consider an academic training pathway.[1,5,6] Reviews of postgraduate and academic training highlighted the need for increased flexibility[3,5,6] leading to academic pathways becoming available at all stages of training.[4,5,6] An Academic Clinical Fellowship (ACF) or lectureship (ACL) combining clinical training with an ongoing research role can be applied for during core/speciality training.[4,5,6] Later in your career skills developed as a Clinical Research Fellow may allow negotiation of research time within a Consultant job plan or open up the possibility of a clinical academic post with time split between the NHS and a University.[6] National research bodies including the NIHR[6] and Academy of Medical Sciences[12] are increasingly supporting structured fellowships for post-doctoral researchers wanting to pursue an academic career. The drive to promote flexibility within academic training is likely to further increase the academic career options available.[5,6]

HOW DO I FIND OUT MORE?

There is a wealth of information on Clinical Research Fellow posts available on the NIHR website[6] and information on OOPR can be found the Royal College websites.[4,13] It is easiest to start by talking to other local trainees who have undertaken a Clinical Research Fellow post or look out for research showcase events aimed at trainees in your local area. In NI there is an annual Trainees research day with representatives from across the spectrum of clinical research supported by the Ulster Medical Society. Meet the expert events, conferences and guest lectures are also all useful places to make contact with research teams.

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REFERENCES

1. Irwin GW, Spence AR, McAuley DF, Kennedy RD, Gardiner KR, Elborn JS. Academic medicine–revolution, evolution or extinction? *Ulster Med J*. 2014;**83(3)**:141-5
2. Joint Royal College of Physicians Training Board Academic [JRCPTB]. Essential Academic competencies to be achieved by CCT by all clinical trainees. Checklist for all trainees [Internet]. JRCPTB; 2018. Available from: https://www.jrcptb.org.uk/documents/eportfolio-academic-checklist-all-trainees [Last accessed September 2018].
3. Report of the Academic Careers Sub-Committee of Modernising Medical Careers and the UK Clinical Research Collaboration. Medically- and dentally-qualified academic staff: recommendations for training the researchers and educators of the future. 2018. [Internet]. Available from: http://www.ukcrc.org/wp-content/uploads/2014/03/Medically_and_Dentally-qualified_Academic_Staff_Report.pdf. [Last accessed September 2018].
4. Conference of Postgraduate Medical Deans of the United Kingdom. [COPmED]. The Gold Guide. A Reference Guide for Postgraduate Specialty Training in the UK. 7th ed. January 2018. Version: GG7 31st January 2018. [Internet]. Available from: https://www.copmed.org.uk/images/docs/gold_guide_7th_edition/The_Gold_Guide_7th_Edition_January__2018.pdf. [Last accessed September 2018].
5. Greenaway D. Shape of Training. Securing the future of excellent patient care. Final report of the independent review Oct 2013. [Internet]. Available from: https://www.shapeoftraining.co.uk/static/documents/content/Shape_of_training_FINAL_Report.pdf_53977887.pdf [Last accessed September 2018].
6. National Institute for Health Research. NIHR trainees Co-ordinating centre. Ten years on: adapting and evolving to new challenges in developing tomorrow's health research leaders. July 2017. [Internet]. Available from: https://www.nihr.ac.uk/our-faculty/documents/TCC-NIHR-Strategic-Review-of-Training-2017.pdf [Last accessed September 2018].
7. Wellcome Trust. PhD Training Fellowships for Clinicians. 2018 [Internet]. Available from: https://wellcome.ac.uk/funding/clinical-phd-programmes [Last accessed September 2018].
8. Cancer Research UK. Opportunities for PhD students and postdoc researchers. 2018. [Internet] Available from: http://www.cancerresearchuk.org/funding-for-researchers/opportunities-for-phd-students-and-postdoc-researchers [Last accessed September 2018].
9. Northern Ireland Clinical Research Network. [NICRN]. 2017. [Internet]. Available from: http://www.nicrn.hscni.net/ [Last accessed September 2018].
10. Peace KE, Chen DG. Clinical trial methodology. Chapman & Hall/CRC Biostatistics Series CRC Press; 2010.
11. HSC Public Health Agency. HSC Research and Development Division Northern Ireland. Doctoral Fellowship Award Scheme. 2019. [Internet]. Available from: http://www.research.hscni.net/health-social-care-rd-doctoral-fellowship-award-scheme [Last accessed September 2018].
12. Postdoctoral Researchers: What's available for me? Academy of Medical Sciences; 2018. [Internet]. Available from: https://acmedsci.ac.uk/grants-and-schemes/whats-available-to-me/postdoctoral-clinical-researchers [Last accessed September 2018].
13. Joint Royal College of Physicians Training Board Academic [JRCPTB]. Training & certification. Out of programme. [Internet]. Available from: https://www.jrcptb.org.uk/training-certification/out-programme [Last accessed September 2018].

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Abstracts

21st Meeting of the Irish Society of Human Genetics

Friday 21st September 2018 Croke Park, Dublin

ORAL PRESENTATIONS:

OP01. GENES INFLUENCED BY MEF2C CONTRIBUTE TO VARIANCE IN COGNITIVE ABILITY IN THE GENERAL POPULATION.

Donna Cosgrove[1], L Whitton[1], G Donohoe[1], DW Morris[1]

[1]The Cognitive Genetics & Cognitive Therapy Group, The School of Psychology and Discipline of Biochemistry, The Centre for Neuroimaging & Cognitive Genomics, National University of Ireland Galway, Galway.

Myocyte enhancer factor 2 C (MEF2C) is a transcription factor that plays a central role regulating cell differentiation, proliferation, survival and apoptosis. MEF2C has been implicated in each of the most recent GWAS of cognitive ability (CA) and educational attainment (EA). Animal studies have indicated that knockout of Mef2c interferes with healthy development of brain regions associated with cognitive function, e.g. hippocampal dentate gyrus, neocortex. Furthermore, mutation/deletion of MEF2C can cause severe intellectual and developmental disability. We therefore hypothesised that genes regulated by MEF2C would be associated with cognitive function.

We created a set of differentially expressed genes (DEGs) based on an RNA-seq study that captured the transcriptional changes in mouse adult brain that result from early embryonic deletion of Mef2c in cortical and hippocampal excitatory neurons. This mouse DEG list was converted to human orthologues (n=1052) and tested for enrichment of genes associated with 1) CA, and 2) EA, using MAGMA and recent GWAS summary statistics for each phenotype. We also performed hypergeometric tests to investigate if the DEGs were enriched for current primary intellectual disability (ID), autism, and loss-of-function (LoF) intolerant (i.e. highly constrained) genes. We then used Ingenuity Pathway Analysis (IPA) to explore functional pathways implicated by the MEF2C DEGs.

The DEGs were significantly enriched for CA (p=1.08e-07) and EA (p=9.88e-09) genes; along with ID (p=0.008), autism (p=0.001) and LoF intolerant (p=5.55e-21) genes. The top functions IPA predicted to be decreased from these DEGs are 'development of neurons' (p=5.41e-38, z-score=-2.0) and 'formation of cellular protrusions' (p=1.02e-28, z-score=-2.1).

These findings indicate that genes influenced by MEF2C are highly constrained and contribute to cognitive function and neurodevelopmental disorders with severe cognitive deficits.

OP02. NOVEL DNA METHYLATION LANDSCAPE OF METASTATIC COLORECTAL CANCER REVEALS SIGNIFICANT EPIGENETIC REGULATION OF DISEASE-ASSOCIATED ENHANCER REGIONS

Sudipto Das[*1], B Moran[*1], D Smeets[2], A Kel[9],S George[10], T Van Brussel[2], G Peutman[2], R Klinger[1, 8], B Fender[3], K Connor[1,8], M Ebert[5], T Gaiser[5], JHM Prehn[4], O Bacon[4,6], E Kay[6], B Hennessy[6], V Murphy[7], A Byrne[4], W.M Gallagher[8,3], D Lambrechts[2], D O'Connor[4].

[1]Department of Molecular and Cellular Therapeutics, RCSI, Dublin.[2]Department of Translational Genetics, VIB, K.U. Leuven, Belgium.[3]OncoMark Ltd, Nova UCD, Ireland.[4]Department of Physiology, RCSI, Dublin.[5]University of Heidelberg, Mannheim, Germany.[6]Beaumont Hospital, Dublin.[7]Irish Clinical Oncology Research Group, Dublin.[8]Cancer Biology and Therapeutics Lab, Conway Institute, University College Dublin. [9]GenExplain GmbH, Germany.[10]Georgia Institute of Technology, Georgia, Atlanta, USA.

Nearly 50% of all colorectal cancer patients progress to develop metastatic lesions (mCRC) and despite ongoing efforts the survival rates for these patients remains significantly low (<20%). This to a great extent can be attributed towards a substantial lack of understanding of the genomic and epigenomic architecture of the mCRC tumours, which would ultimately allow us to identify novel diagnostic and/or therapeutic targets. In order to map the DNA methylation alterations in mCRC, we applied targeted sequence capture sequencing approach encompassing variable enhancer loci, p53 binding sites and all known CpG islands to FFPE-derived DNA from 58 mCRC tumours and 10 matched normal. Differential methylation analysis for the first time revealed a 377-loci based tumour specific methylation signature consisting of >90% CRC-specific enhancer regions, which was subsequently integrated with RNAseq derived gene expression in order to identify gene-enhancer pairs. Applying motif and transcription factor identification algorithms to the methylation signature, showed intricate networks of disease-associated transcription factors whose binding sites are significantly impacted as a result of the altered methylation within these enhancer regions. Utilization of deep machine learning approaches to the methylation data, demonstrates specific methylation patterns that allow stratification of patients independent of their clinical features. Finally, we show that two methylation derived patient clusters overlap significantly with expression derived consensus molecular subtype (CMS) -2 (WNT-p53 cluster) and CMS-4 (EMT-like). This study for the first time presents a critical insight into an enhancer driven epigenomic landscapes, which potentially regulates disease-associated phenotype within mCRC.

OP03. DNA METHYLATION AND INFLAMMATION MARKER PROFILES ASSOCIATED WITH A HISTORY OF DEPRESSION.

Therese M Murphy[1], B Crawford[1], Z Craig[2], G Mansell[1], I White[1], A Smith[1], S Spaull[2], J Imm[1], E Hannon[1], A Wood[1], H Yaghootkar[1], Y Ji[1], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium[1], N Mullins[3], C M. Lewis[3,4], J Mill[1].

[1]University of Exeter Medical School, University of Exeter.[2]NIHR Exeter Clinical Research Facility, University of Exeter Medical School.[3]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's

College London.[4]Division of Genetics and Molecular Medicine, King's College London.

Depression is a common and disabling disorder, representing a major social and economic health issue. Moreover, depression is associated with the progression of diseases with an inflammatory aetiology including many inflammatory-related disorders. At the molecular level, the mechanisms by which depression might promote the onset of these diseases and associated immune-dysfunction are not well understood. In this study we assessed genome-wide patterns of DNA methylation in whole blood-derived DNA obtained from individuals with a self-reported history of depression (n=100) and individuals without a history of depression (n=100) using the Illumina 450K microarray. Our analysis identified 6 significant (Sidak corrected $P < 0.05$) depression-associated differentially methylated regions (DMRs); the top-ranked DMR was located in exon 1 of the LTB4R2 gene (Sidak corrected $P = 1.27$ x 10-14). Polygenic risk scores (PRS) for depression were generated and known biological markers of inflammation, telomere length (TL) and IL-6, were measured in DNA and serum samples respectively. Next, we employed a systems-level approach to identify networks of co-methylated loci associated with a history of depression, in addition to depression PRS, TL and IL-6 levels. Our analysis identified one depression-associated co-methylation module ($P = 0.04$). Interestingly, the depression-associated module was highly enriched for pathways related to immune function and was also associated with TL and IL-6 cytokine levels. In summary, our genome-wide DNA methylation analysis of individuals with and without a self-reported history of depression identified several candidate DMRs of potential relevance to the pathogenesis of depression and its associated immune-dysfunction phenotype.

OP04. AAV-MEDIATED GENE REPLACEMENT IN A PATIENT-DERIVED FIBROBLAST MODEL OF RETINITIS PIGMENTOSA

Ciara Shortall[1], A Palfi[1], N Chadderton[1], PF Kenna[1,2], M Carrigan[1], S Boomkamp[3], S Shen[3], AJ Hardcastle[4], GJ Farrar[1]

[1]Institute of Genetics, University of Dublin, Trinity College, Dublin 2.[2]Research Foundation, Royal Victoria Eye and Ear Hospital, Adelaide Road, Dublin 2. [3]Regenerative Medicine Institute, School of Medicine, National University of Ireland Galway. [4]UCL Institute of Ophthalmology, 11-43 Bath Street, London.

Mutations in *RP2* are responsible for approximately 15% of X-linked Retinitis Pigmentosa cases. RP2 is ubiquitously expressed and involved in ciliary trafficking of lipid-modified proteins. A patient harbouring the most common nonsense *RP2* mutation, R120X, was identified through the Target 5000 programme. This enabled the generation of a patient-derived primary fibroblast disease model. The aims of this study were (i) to identify a vector capable of effectively transducing primary fibroblasts, (ii) to rescue RP2 expression in the R120X cell model and (iii) to explore potential assays for evaluating rescue of RP2 function in these cells.

Transduction efficiencies were determined by treating normal fibroblasts with a CAG.EGFP construct packaged in AAV2/2, 2/5 and 2/8 capsids. The results were 55.5% ± 2.5, 17.5% ± 15.4 and 2.2% ± 1.0, respectively. The expression level of RP2 mRNA in untreated R120X fibroblasts was 7.5 fold ± 3.2 lower than that of wild type fibroblasts, while RP2 protein was absent in R120X cells. Transduction of mutant cells with AAV2/2.CAG.RP2 resulted in overexpression of RP2 protein by 1.19 fold ± 0.67. The R120X cell line was evaluated for phenotypes associated with absence of RP2, including Golgi fragmentation and mislocalisation of an intraflagellar trafficking protein, IFT20.The areas of both GM130 and IFT20 were significantly larger in mutant fibroblasts compared to control cells. Treatment with AAV2/2.CAG.RP2 was beneficial in reversing Golgi fragmentation, as the Golgi area in transduced R120X fibroblasts was reduced by 1.5 fold ± 0.5 when compared to untreated cells ($p < 0.0001$).

OP05. GWAS-PATHWAY ANALYSIS AND FUNCTIONAL VALIDATION IDENTIFIES NOVEL GENES INVOLVED IN PANCREATIC CANCER.

Naomi Walsh[1], S Nelson[1], H Zhang[2] and R Stolzenberg-Solomon[2]

[1]National Institute for Cellular Biotechnology, Dublin City University. [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

Background: Genome-wide association studies (GWAS) identify associations of individual SNPs with cancer risk but usually only explain a fraction of the inherited variability. Pathway analysis of genetic variants is a powerful tool to identify networks of susceptibility genes.

Methods: we conducted a large agnostic pathway-based meta-analysis of GWAS data using the summary-based adaptive rank truncated product (sARTP) method to identify gene sets and pathways associated with pancreatic ductal adenocarcinoma (PDAC) in 9,040 cases and 12,496 controls. We performed expression quantitative trait loci (eQTL) analysis and functional annotation of the top SNPs in genes contributing to the top associated pathways and gene sets.

Results: We identified 14 pathways and gene sets associated with PDAC at FDR < 0.05. After Bonferroni correction (*P*-value ≤ $1.3x10^{-5}$), the strongest associations were detected in five pathways and gene sets, including maturity onset diabetes of the young (MODY), regulation of beta cell development, role of epidermal growth factor (*EGF*) receptor transactivation by G-protein-coupled receptors in cardiac hypertrophy pathways, and the Nikolsky breast cancer chr17q11-q21 amplicon and Pujana *ATM* Pearson correlation coefficient (PCC) network gene sets. We identified and validated rs876493 and three correlating SNPs (*PGAP3)* and rs3124737 (*CASP7)* from the Pujana *ATM* PCC gene set as eQTLs in two normal derived pancreas tissue datasets.

Conclusion: Our agnostic pathway and gene set analysis integrated with functional annotation, eQTL analysis and experimental validation provides insight into genes and pathways that may be biologically relevant for risk of PDAC, including those not previously identified.

OP06. DETECTING FINE SCALE POPULATION STRUCTURE, MIGRATION AND RECENT POPULATION EXPANSION IN THE NETHERLANDS.

Ross Patrick Byrne[1], W van Rheenen[2], LH van den Berg[2], JH Veldink[2], RL McLaughlin.[1]

[1]Smurfit Institute of Genetics, Trinity College Dublin. [2]Department of Neurology, Brain Centre Rudolf Magnus, University Medical Centre Utrecht.

We carried out a detailed genetic study of the population structure, local migration rates and population changes across in the Netherlands using cutting edge methods. Our dataset couples genome wide SNP data and geographic information (N=1422), which together allow us to investigate the interplay between genetics and local geography. To interrogate fine scale population structure we applied the haplotype-based method Chromo Painter/ fineSTRUCTURE, which partitions data based on patterns of haplotype sharing. FineSTRUCTURE identified 16 genetic clusters which correlate closely with regional geography. At the finest level, this clustering has the resolution to distinguish subtly different eastern and western genetic groups within the North-Brabant province. At the coarsest level, clustering delineates a clear north/

south split in the Netherlands, reflecting deeper differences. We investigated whether our clustering reflects barriers to gene flow using the "Estimating Effective Migration Surfaces" (EEMS) method, and observed a strong migrational cold spot splitting the country, broadly overlapping the course of the Rhine. We also estimated recent changes in the effective population size (Ne) using the IBDNe method, observing super-exponential population growth across the past 50 generations. This expansion rapidly increases in rate from ~1650 CE onwards, potentially driven by the Dutch Golden age of the 17th Century. Notably our Ne estimates are systematically lower in northern populations than southern suggesting lower diversity in the north, which is consistent with reported ROH and IBD analysis. Combined our results paint a picture of the dynamic population genetics of the Netherlands that are strongly linked to geography.

OP07. A GENOMIC COMPENDIUM OF AN ISLAND: DOCUMENTING CONTINUITY AND CHANGE ACROSS IRISH HUMAN PREHISTORY.

Lara Cassidy[1], D Bradley[1].

[1]Smurfit Institute of Genetics, Trinity College Dublin

We present here a demographic scaffold for Irish prehistory based on the palaeogenomic analysis of 93 ancient individuals from all major periods of the island's human occupation, sequenced to a median of 1X coverage. ADMIXTURE and principal component analysis identify three ancestrally distinct Irish populations, whose inhabitation of the island corresponds closely to the Mesolithic, Neolithic and Chalcolithic/Early Bronze Age eras. Large scale migrations into the island are implied during the transitionary periods carrying with them ancestry ultimately derived from Anatolia and later the Russian steppe. Patterns of haplotypic-sharing and Y chromosome analysis demonstrate strong continuity between the Early Bronze Age and modern Irish populations, suggesting no major population replacement has occurred on the island since this point in time. We further dissect the genetic affinities of each Irish population with reference to wider palaeogenomic datasets, using both allele and haplotype-sharing methods, the latter made possible through genotype imputation.

OP08. TOWARDS ESTIMATING THE INCIDENCE OF RARE DISEASES IN A PAEDIATRIC POPULATION, BORN IN IRELAND IN THE YEAR 2000.

Emer Gunne[2], A Ward[1], E Treacy[3], D Lambert[3], SA Lynch[1, 2, 3]

[1]Dept. of Genetics, Our Lady's Children's Hospital Crumlin. [2]Temple Street Children's University Hospital. [3]National Rare Disease Office, Mater Hospital.

Background: Rare diseases (RDs) affect at a minimum 5 per 10,000 people. Although individually rare and under-recognised in healthcare systems, collectively RDs are common with up to 8,000 diseases now described. The National Plan for RDs (2014), recommended the need for epidemiological studies, highlighting the requirement for RD coding to identify RD patients and thereby improve both cost efficiencies and care of patients with RDs.

Objectives: To derive an estimate of the number of childhood onset RDs through analysis of records held at TSCUH & OLCHC.

Methods: Reports of patients born in the year 2000 were extracted from: the National Paediatric Mortality Registry office; clinical, cytogenetics and molecular genetics databases, and the Hospital In-Patient Enquiry system (HIPE) TSCUH/OLCHC. RD cases were identified using electronic/manual results and assigned orpha-codes.

Results: 54, 7893 livebirths, census 2000. National Paediatric Mortality Register, 73 deaths of children born in year 2000 of these 60 had a RD (82%). Clinical, cytogenetic and molecular genetics from TSCUH/OLCHC identified 603, 121 and 77 cases of RD respectively. HIPE TSCUH/OLCHC searches to-date have identified 202 and 242 cases of RD respectively.

Conclusions: RD epidemiological data is difficult to acquire in the current structure of the Irish health service, requiring multiple sources and an inordinate amount of time accessing manual records. This study to-date has identified over 1,000 RD patients presenting by age 17 to OLCHC/TSCUH giving a minimum incidence of 2% for paediatric RDs. In the coming year records from TSCUH specialties will be accessed for inclusion in the study.

OP09. NEWBORN SCREENING FOR CYSTIC FIBROSIS: A 5 YEAR REVIEW

Marija Kostocenko[1], N Lang[2], T Clark[3], A Ward[3], DE Barton[3] SA Lynch[3,4,5].

[1]School of Medicine, Royal College of Surgeons in Ireland. [2]School of Medicine, NUI Galway. [3]Department of Clinical Genetics, Our Lady's Children's Hospital Crumlin. [4]Temple Street Children's University Hospital, Dublin. [5]University College Dublin.

Background & Aims: Newborn screening for Cystic Fibrosis (CF) commenced in the Republic of Ireland in July 2011. The aim of this study was to do a comprehensive review of the first five years, focusing on those who had CFTR genetic testing following an elevated IRT.

Methods: This study included all neonates screened from July 2011 to June 2016. Data was expanded by cross-referencing patient charts, clinical and lab databases with the Non-NBS database to track down cascade tested relatives.

Results: In this period a total of 342,424 infants were screened. 141 CF and 19 CF-SPID cases were identified in addition to 238 healthy carriers. 2 babies died from unrelated illnesses, before their Sweat Test. A total of 300/400 (75%) couples with a CF/CF-SPID/Carrier child were seen by a Genetic Counsellor. Phe508del was the most common mutation (79.9%) followed by Gly551Asp (8.7%). Consequently, 185/238 Carrier parents (78%) underwent genetic testing, identifying 1 carrier couple. 101/160 (63%) CF/CF-SPID parents were tested. 255 additional relatives came forward for cascade testing - 184 from 68/162 CF affected/CF-SPID/RIP families (42%), resulting in 3 new CF cases, 3 new CF-SPID cases and 64 additional carriers. Two cases were siblings born prior to NBS. One case was missed though NBS. 71 relatives from 33/238 Carrier families (14%) came forward for cascade testing, identifying a further 18 carriers.

Conclusion: Through early detection of CFTR mutations, NBS provides the opportunity of early intervention and complication prevention as well as improvements in prenatal diagnoses and availability of cascade testing.

OP10. UNCERTAINTY IN INHERITED CARDIAC PATHOLOGIES

Terri McVeigh[1], , LJ Kelly[2], E Whitmore[3], T Clark[1], B Mullaney[1], DE Barton[1], A Ward[1], SA Lynch[3,4]

[1]Our Lady's Children's Hospital Crumlin, Dublin 12. [2]School of Medicine, Royal College of Surgeons in Ireland. [3]The Children's University Hospital, Temple St, Dublin 1. [4]University College Dublin.

Background: Multi-gene testing is useful in genetically heterogeneous conditions, including inherited cardiac pathologies. Extended panels increased diagnostic yield of variants where pathogenicity is certain (class 5), likely (class 4) and uncertain (class 3). Concerns exist regarding management of class 3 and 4 variants in conditions of oligogenic inheritance or variable expressivity.

Aim:

1. To review diagnostic yield of genetic tests performed in families with inherited cardiac pathologies

2. To assess management of different classes of variants by clinicians internationally.

Methods: A retrospective cohort analysis was undertaken. Patients in whom "cardiac" genetic tests were requested between 2015 and 2017 were identified from a prospectively maintained departmental patient database. Data regarding indication for testing, diagnostic yield, and classification of variants were retrieved by manual chart review. An electronic survey regarding clinical management of variants (www.surveymonkey.com/r/cardiacvariants) was distributed to colleagues internationally via professional bodies and direct email.

Results: 636 tests (630 patients) were performed between 2015 and 2017 in our centre (183 diagnostic; 453 predictive). At least one variant was identified in 71(39%) patients (28(15%) class 5; 9(5%) class 4; 38(21%) class 3. 135 respondents (23 countries) completed the survey. Considering class 4 variants, 110(81%) counselled patients about the possibility of variant reclassification. In the case of a negative predictive test, 17(13%) were fully reassuring that the patient would not develop the familial phenotype.

Conclusion: Considerable variability in management of class 3 and 4 variants exists. Decision-making relies on interpretation of the phenotype, family history and genotype. Close multi-disciplinary working between cardiology and clinical/molecular genetics teams is critical.

OP11. UPDATE ON GENETIC DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLAEMIA IN THE REPUBLIC OF IRELAND.

Sarah Savage[1], A Rakovac-Tisdall[1], , E Rasheed[1], B Mac Namara[1], E Keogh[1], P O'Connor[2], M Durkan[3], V Maher[3], D Griffin[3], B MacAdam[3], C Vaughan[3], M Ryan[3], S Heggarty[4], P Hart[4], VEF Crowley[1]

[1]Biochemical Genetics Laboratory, Biochemistry Department, St James's Hospital, Dublin 8. [2]Dept of Pharmacology& Therapeutics, TCD Health Sciences Building, St James's Hiatal, Dublin 8. [3]Irish Lipid Network. [4]Northern Ireland Regional Genetics Unit, Belfast City Hospital.

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder due primarily to mutations in *LDLR, APOB* and *PCSK9*, which causes marked increases in LDL cholesterol levels and predisposes to premature CVD. Given a prevalence of 1:250, there are approximately 23,000 FH sufferers in the Republic of Ireland, most of whom are as yet undiagnosed. The most cost-effective strategy for identifying FH is genetic cascade screening in kindreds with an identified proband. We report interim outcomes of a FH genetic diagnostic service configured around an initial screen of 40 known FH variants followed by either a confirmatory analysis or a full variant scan using PCR and direct nucleotide sequencing, in positive and negative screens respectively.

To date our service has genetically diagnosed 69 patients with FH, including 50 index cases and 19 positive cascade screens. In total, 30 disease-associated variants in *LDLR* and *APOB* have been identified including four due to copy number variation using MLPA. Based on phenotypic classification by Dutch Lipid Clinic Network scoring 75% of those designated "Definite/Probable FH" were genetically confirmed compared with <10% of "Possible FH". Regarding the 40 variant screen, 83 subjects with Definite/Probable FH were analysed with 22% reported positive, while all 16 Possible FH patients were screen negative. Mutation positive patients had significantly higher mean serum LDL Chol (7.7 ±1.7mmol/L) relative to patients designated Possible FH (5.6 ± 0.7mmol/L).

Overall, progress has been made in developing an FH genetic diagnostic service. Cost and clinical-effectiveness of this service will depend on the appropriate classification of Definite/Probable FH.

OP12. VALIDATION OF A BRCA GENE PANEL FOR GERMLINE AND TUMOUR MUTATION ANALYSIS.

Brendan Mullaney, [1] S McQuaid[1], C O'Brien[2], T McDevitt1, K Brosnan[2], DE Barton.[1]

[1]Dept. Clinical Genetics, Our Lady's Children's Hospital, Crumlin. [2]Cancer Molecular Diagnostics, St James's Hospital, Dublin 8.

Hereditary Breast & Ovarian Cancer syndrome (HBOC) is caused by mutations in BRCA1/2 genes and is associated with a high life time risk of breast cancer and ovarian cancer. Ovarian tumours with inherited (germline) *or* acquired (somatic) BRCA1/2 mutations respond to drugs that inhibit poly ADP-ribose polymerase (PARPi). Currently, mutation screening for HBOC patients are 'sent away' to the UK, with a predictive (pre-symptomatic) service for known familial mutations offered at DCG. At this time, there is no service for tumour BRCA testing for potential PARPi treatment. Supported by the National Cancer Control Programme, DCG & CMD have collaborated to assess next generation sequencing BRCA gene panels & platforms to establish a pathway for germline & tumour mutation analysis and validate an optimal clinical testing method for diagnostic and therapeutic use.

The ThermoFisher Oncomine panel with the Ion Torrent PGM/S5 was used to target and sequence 64 unique germline samples with a wide range of known BRCA mutations. These were analysed using JSI SeqNext software and others. After optimisation, 99.84% (624/625) variants were detected at some level. However, there were 117 false positive calls, all in homopolymer regions. Distinguishing false positives from some true positives with a low variant fraction was challenging. Subsequently, the Nimagen EasySeq kit (employing single molecule Molecular Inversion Probes, smMIPs) with the Illumina MiSeq was used for 32 samples. There was a 100% variant call rate (376/376) with no false positive calls. Initial tumour results are also very convincing. Now proceeding to a full clinical validation.

OP13. ANALYSIS OF THE PATHOGENICITY OF A MISSENSE VARIANT C.137G>T P.(SER46ILE) WITHIN A DIAGNOSTIC LABORATORY.

Peter Logan[1], C Byrne[1], J Scott[2], S Heggarty[1], T Dabir[2].

[1]Regional Genetic laboratories, Belfast City Hospital. [2]Department of Clinical Genetics, Belfast City Hospital.

Establishing the pathogenicity of missense variants detected in Lynch syndrome / Hereditary Non Polyposis Colorectal Cancer (HNPCC) families is a challenge for diagnostic laboratories. Here we consider two families from Northern Ireland who meet Amsterdam II Criteria for HNPCC, in whom the presence of a *PMS2* gene missense variant c.137G>T p.(Ser46Ile) rs121434629 has been shown. This variant occurs within a conserved ADP/ATP binding region of the PMS2 protein. Disruption of this domain is predicted to result in reduced mismatch repair efficiency and has previously been reported in the literature as a recurrent and founder variant in the *PMS2* gene. However, no co-segregation data has been published for this variant.

Adoption of the ACMG Standards and guidelines (Richards *et al* Genetics in Medicine 2015) along with the release of ACGS best practice guidelines for the interpretation of sequence variants has initiated a review of the classification of variants detected within the region against these standards.

Bioinformatic analysis and evidence available in the published press, had led to a classification of likely pathogenic for this variant. However, addition of the co-segregation evidence provided by local families, at the strong level, enables the variant to be re-classified as pathogenic.

In conclusion, we have shown co-segregation of the *PMS2* c.137G>T p.(Ser46Ile) variant with Lynch syndrome associated phenotype to a Path P1 strong level of significance through family studies.

POSTER PRESENTATIONS

P01. DNA METHYLATION OF HYPERTENSION-RELATED GENES IS INFLUENCED BY THE *MTHFR* 677TT GENOTYPE AND RIBOFLAVIN SUPPLEMENTATION

Sophia.D. Amenyah[1, 2], A. McMahon[2], M Ward[2], J. Deane[1], H McNulty[2], C.F. Hughes[2], J.J. Strain[2], G. Horigan[2], J. Purvis[3], C.P. Walsh[1], D.J. Lees-Murdock[1].

[1]Genomic Medicine Research Group. [2]Nutrition Innovation Centre for Food and Health (NICHE), Ulster University, Coleraine. [3]Department of Cardiology, Altnagelvin Area Hospital.

The C677T polymorphism in the folate metabolising enzyme methylenetetrahydrofolate reductase (MTHFR) is associated with hypertension. Riboflavin is a cofactor for MTHFR in one-carbon metabolism, for generating methyl groups important in DNA methylation. Supplementation with riboflavin has been shown to lower blood pressure in *MTHFR* 677TT genotype individuals. The mechanism regulating this gene-nutrient interaction is currently unknown but may involve aberrant DNA methylation also implicated in hypertension. This study examined DNA methylation of hypertension-related genes in adults stratified by *MTHFR* genotype and the effect of riboflavin supplementation on methylation of these genes in the *MTHFR* 677TT genotype group.

We measured DNA methylation using pyrosequencing in a set of candidate genes associated with hypertension including angiotensin II receptor type 1 (*AGTR1*), G nucleotide binding-protein subunit alpha 12 (*GNA12*), insulin-like growth factor 2 (*IGF2*) and nitric oxide synthase 3 (*NOS3*). Stored leukocyte samples from participants with the *MTHFR* C677T genotype who had participated in targeted RCTs (1.6mg/d for 16wks) at Ulster University were accessed for this analysis (n=120). Baseline methylation differed between *MTHFR* C677T genotype groups at *NOS3* (p=0.026) and *AGTR1* (p=0.045). Riboflavin supplementation in the *MTHFR* 677TT genotype group resulted in altered average methylation at *IGF2* (p=0.025) and CpG site specific alterations at the *AGTR1* and *GNA12* loci.

This study demonstrates an interaction between DNA methylation of hypertension-related genes and riboflavin supplementation in adults with the *MTHFR* 677TT genotype. Further work using a genome-wide approach is required to better understand the role of riboflavin in altering DNA methylation in these genetically at-risk individuals.

P02. THE ASSOCIATION BETWEEN Y CHROMOSOME SNPS AND CHRONIC KIDNEY DISEASE.

Kerry Anderson[1], M Cañadas-Garre[1], AP Maxwell[1,2], AJ McKnight[1].

[1]Centre for Public Health, Queen's University Belfast. [2]Regional Nephrology Unit, Belfast City Hospital.

Chronic kidney disease (CKD) is considered a major public health problem, affecting approximately 10% of the global population. While a comprehensive review of known CKD biomarkers yielded many results, it also highlighted a lack of research in chromosome Y. Single nucleotide polymorphisms (SNPs) on chromosome Y have previously been associated with a 50% increase in risk of developing coronary artery disease, a condition with close links to CKD. Therefore, Y chromosome SNPs may also impart increased risk of developing CKD. Individuals from the Genetics of Nephropathy: an International Effort (GENIE) consortium (n=791) and the Northern Ireland Cohort for the Longitudinal Study of Aging (NICOLA; n=1241) were genotyped using the Illumina HumanOmni1-Quad array and the Illumina CoreExome-24 array, respectively, to determine if any association exists between Y chromosome SNPs and CKD, or estimated glomerular filtration rate (eGFR), a measure of kidney function. However, poor coverage of chromosome Y resulted in only 3 SNPs in the GENIE cohort and 421 SNPs in the NICOLA cohort passing quality control. Association analysis of both datasets did not reveal any significant associations. Due to limitations of this study, further analysis is required to determine whether SNPs on chromosome Y are associated with CKD and/or eGFR. An array with greater Y chromosome coverage will be selected and be used to re-genotype these individuals, and individuals from additional cohorts, allowing greater SNP coverage and direct comparison of SNPs between these cohorts. Increased SNP coverage and increased participant numbers will allow meta-analysis to be performed with sufficient power.

P03. INVESTIGATING THE LINK BETWEEN HYPOXIA AND MIR-21 IN PROSTATE CANCER.

Zoe Angel[1], CP. Walsh[1], DJ. McKenna.[1]

[1]Genomic Medicine Research Group, Biomedical Sciences Research Institute, Ulster University, Coleraine, BT52 1SA

Background: Tumour hypoxia is a major driver of prostate cancer progression and metastasis. miR-21 is a microRNA which has been previously linked to hypoxia, but this relationship remains poorly characterised in a prostate cancer setting. Therefore, in this study, we investigate the link between hypoxia and miR-21 in prostate cancer cells.

Methods: We have used 2D and 3D cell prostate cell models of hypoxia to investigate the functionality of miR-21. Expression levels of miR-21 have been measured by qPCR and functional bioassays used to examine its effect on prostate cell behaviour. Target genes have been identified and bioinformatic analysis has been employed to investigate a clinical significance for miR-21 in prostate cancer.

Results: miR-21 is induced by hypoxia in prostate cancer cell-lines. Over-expression of miR-21 impacts upon target genes which in turn affects cell behaviour. Data-mining of online repositories of clinical data and bioinformatic analysis of miR-21 cellular networks reveal that miR-21 exerts a wide influence on several important cell processes, the dysregulation of which can lead to development of prostate cancer.

Conclusions: We propose that miR-21 could be an important microRNA in the pathogenesis of prostate cancer and has potential as a biomarker in this disease.

P04. THE GENETIC HISTORY OF THE MALTESE ARCHIPELAGO DURING THE NEOLITHIC PERIOD.

Bruno Ariano[1], V Mattiangeli[1], LM Cassidy[1], TR McLaughlin[2], RK Power[5], JT Stock[3], B Mercieca-Spiteri[4], S Stoddart[3], C Malone[2], DG Bradley.[1]

[1]Smurfit Dept. of Genetics, Trinity College Dublin. [2]Queens University Belfast.[3]Cambridge University.[4]Superintendence of Cultural Heritage, Malta. [5]Macquarie University, Australia

The Neolithic period begins in Europe around 8500 years before present (BP) and is characterized by the adoption of farming and domestication of various types of animal. In our project we focus on the structure of the Maltese population during the latter part of the Neolithic period. Nine individuals, from 4900 to 4350 years BP,

collected from the Xaghra Circle site in the island of Gozo, were sampled. DNA was extracted from both teeth and the inner part of petrous bones giving an average endogenous DNA respectively of: 1.7% for 4 teeth and of 21% for 5 petrous bones. We then used a median of 363,579 SNPs from the Human Origin dataset to compare our samples with 37 ancient individuals from Neolithic and Bronze Age period and 604 present-day European individuals already published. PCA analysis shows, for the 5 high coverage samples, places the Maltese individuals with the early European farmers (EEF) from Germany and Hungary. Further analysis with D-statistics depict that the Maltese population do not resemble any hunter-gatherer population from Caucasus or Eastern Europe, while they show a higher affinity with Western European hunter gather individuals (WHG).

P05. GENE EXPRESSION ANALYSIS FOLLOWING PROSTAGLANDIN TREATMENT *IN VITRO*.

Sarah D Atkinson[1], N Campbell[1], L Windrum[1], P Hassett[2], AJ Bjourson[1].

[1]Northern Ireland Centre for Stratified Medicine, Ulster University. [2]Ophthalmology, Altnagelvin Area Hospital, Western Health and Social Care Trust.

According to the WHO, glaucoma is the second leading cause of blindness in the world and is the leading cause of irreversible blindness. The total number of suspected cases of glaucoma is estimated to be over 60 million worldwide, increasing to 79.6 million by 2020.

Commonly, glaucoma is treated using eye drops containing prostaglandin analogs, including latanoprost and bimatoprost. However, these treatments come with ocular adverse reactions including ocular surface irritation, acute iritis, conjunctival hyperemia, thickening and elongation of eyelashes, induced iris darkening as well as periocular skin pigmentation. Patient compliance has been shown to be affected by these side-affects including non-compliance for cosmetic reasons with thickening and lengthened eyelashes and the occurrence of pigmentation. This study aimed to identify whether there are differences in gene expression between those prostaglandin treatments containing preservatives and those without preservatives.

Primary human trabecular meshwork cells were stained with phalloidin to determine morphology. The cells were treated with prostaglandins either with or without preservatives, gene expression analysis was performed by PCR to determine differences between preservative containing and preservative free treatments.

Differences in gene expression were shown at different time-points after treatment. Differences were also shown between treatments which were preservative free and those treatments which contained preservative.

With the significant differences in gene expression levels between prostaglandins containing preservatives and those without preservatives, it indicates that prostaglandins without preservatives are likely to produce less side effects in glaucoma patients.

P06. THE POPULATION GENETICS OF PREHISTORIC PORTUGAL.

Emily Breslin[1], LM Cassidy[1], R Martiniano[2], V Mattiangeli[1], AM Silva[3], DG Bradley[1]

[1]Smurfit Institute of Genetics, Trinity College Dublin, [2]Department of Genetics, University of Cambridge, Downing Street, Cambridge. [3]Laboratory of Prehistory, Research Center for Anthropology and Health, Department of Life Science, University of Coimbra.

For the majority of its history the field of ancient population genetics was restricted to non-human samples due to the difficulties with modern contamination and the nature of ancient DNA (aDNA) sequences: short, highly degraded, chemically modified and present in low concentrations with high concentrations of microbial contamination. The development of efficient extraction techniques, the discovery that the petrous part of the temporal bone is a rich reservoir for aDNA and the development of high-throughput next-generation sequencing (NGS), have resulted in the rapid expansion of the field, with sequences from over 1000 ancient individuals published to date.

Portugal occupies a unique position in Europe; facing both the Atlantic and the Mediterranean it was connected to two major maritime trade and migration routes, as well as experiencing influx from central mainland Europe throughout its prehistory. Many open questions remain about population changes in the Iberian Peninsula at major transition periods in European prehistory, such as the transition to the Bronze Age involving migrations from the Pontic Steppe, the source for the R1b Y-chromosome haplotype now dominant in European populations.

In this study we present high quality whole genome sequences (0.05-2.9X, 13 samples at ~1X) from 25 ancient Portuguese individuals, covering a period of over 3000 years, to examine the demographic and selection processes acting on prehistoric Portuguese populations. We use principal component analysis (PCA), outgroup f_3 statistics, Patterson's *D*-statistic and ADMIXTURE analysis to investigate questions such as hunter-gatherer admixture in the Neolithic and Steppe introgression in the Bronze Age.

P07. A PHARMACOGENOMIC ASSESSMENT OF ADVERSE DRUG REACTIONS TO THE ANTI-EPILEPTIC DRUG LEVETIRACETAM.

Ciaran Campbell[1,2], M McCormack[1], C Stapleton[1], the EpiPGX Consortium, CP Doherty[2,3], N Delanty[2,4], GL Cavalleri.[1,2]

[1]Molecular and cellular therapeutics, RCSI, Dublin. [2]FutureNeuro Research Centre, RCSI. [3]Department of Neurology, St James' Hospital, Dublin. [4]Department of Neurology, Beaumont Hospital, Dublin.

Background: Epilepsy is a neurological condition affecting an estimated 50 million people worldwide and roughly 40,000 people in Ireland. Levetiracetam (LEV) is an effective anti-epileptic drug, but 10-20% of patients exposed to LEV report behavioural side-effects and up to 1% of those treated experience acute psychosis. We set out to determine contribution of common genetic variation to these adverse drug responses (ADRs).

Methods: Individuals from the EpiPGX study cohort were screened for European ancestry and matched to predefined phenotypic criteria. Controls were exposed to LEV, but without any adverse reactions.

GWAS were carried out on patients who experienced behavioural disorders (n=149), acute psychosis (n=19), or any affective symptoms in response to LEV treatment (n=90).

After identification of a genome-wide significant hit in the affective disorder analysis, a further GWAS was performed in a replication cohort (n=68).

Following this, polygenic risk scores (PRS) for all cases and controls were calculated using the results from the Psychiatric Genomics Consortium's GWASes of Schizophrenia (SCZ) and Bipolar Disorder (BIP).

Results: A genome-wide significant result was found in SNP rs7500119 in the CALB2 gene. Upon replication the SNP lost genome-wide significance but maintained nominal significance. PRS analysis for both SCZ and BIP were predictive of LEV-induced psychosis.

Discussion: The univariate analysis did not identify a genome-wide significant signal for neurological ADRs to LEV that survived replication in an independent cohort. Further work with larger sample sizes may identify such variants.

Increased PRS for SCZ and BIP are associated with LEV-induced psychosis, this analysis will also benefit from a larger sample

P08. A SIMULATION STUDY ON THE ORIGIN OF NATURAL SELECTION IN AN ADMIXED POPULATION.

Niall Cooke[1], D. G. Bradley[2], S. Nakagome[1]

[1]School of Medicine, Trinity College Dublin. [2]Smurfit Institute of Genetics, Trinity College Dublin.

The impact of natural selection on beneficial alleles can be observed in modern human genetic variation; however deciphering the origins of these alleles is complicated by the vast complexity of human history, in which many population splits and admixture events have occurred. Here we describe a new statistical framework of Approximate Bayesian Computation (ABC) that can detect which ancestral group an allele undergoing selection first appeared. We assume a specific model in which a source population splits into two groups that later undergo admixture to form the lineage leading to the contemporary population and simulate the origin of beneficial alleles at different stages of the population's history. Using genetic variation observed at the allele at the present time, as well as the knowledge we have of the timing of demographic changes and admixture events, we test if our approach can accurately predict the time the allele arose, and in which ancestral population it first emerged in. In this presentation, we will show preliminary results from our simulation study and discuss a potential application of the method for whole-genome data from an admixed human population.

P09. CAN THE RELATIONSHIP BETWEEN SNP-GENETIC PROFILES AND ADVERSE DRUG METABOLITE CONCENTRATIONS HELP US PREDICT DRUG TREATMENTS THAT WOULD WORK BEST FOR PATIENTS WITH RHEUMATOID ARTHRITIS?

Potential personalised treatment modality stratification in Rheumatoid Arthritis by assessment of genetic profiling of SNPs and evaluation of drug metabolites against DMARDs.

Leon.G. D'Cruz[1], K. McEleney[1], K.B.C. Tan[1], D. Cobice, S. Dobbins[2], A Tahanver[1], C. McLaughlin[1], C.Conway[3], D.Small[4], P. Connolly[4], P. Gardiner[4], D. Gibson[1].

[1]Dept. of Stratified Medicine, Ulster University, CTRIC building, Altnagelvin hospital campus, Londonderry.[2]Core Technology Unit, Mass Spectrometry Centre, Ulster University, Cromore Road, Coleraine. [3]Genomics Core Centre, Ulster University, Cromore Road, Coleraine.[4]Rheumatology Department, Altnagelvin Hospital, Western Health & Social Care Trust, Glenshane Rd, Londonderry.

There are over 12000 people in Northern Ireland living with rheumatoid arthritis (RA); a painful, systemic autoimmune disease, causing swelling, stiffness, loss-of-function in joints, disability and significantly lowering ones quality of life.

Various medication options are available; low-dose (10 to 25 mg/wk.) methotrexate (MTX), a small-molecule disease-modifying anti-rheumatic drug (DMARD), is a first-line therapy, due to its affordability, cost-effectiveness and efficacy. Other DMARDs used in RA are sulfasalazine, chloroquine, hydroxychloroquine, azathioprine, and leflunomide. However, there is significant person-to-person variability in treatment responses with nearly 50% of patients indicating poor or no-response to any of these medications.

Serum drug metabolite concentration of 100 RA patients treated with DMARDs were determined using tandem mass-spectrometry. Allelic discrimination analysis using Taqman probes was performed on the following SNPs; rs246240 (ABCC1), rs1476413 (MTHFR), rs2231142 (ABCG2), rs3740065 (ABCC2), rs4149081 (SLCO1B1), rs4846051 (MTHFR), rs10280623 (ABCB1), rs16853826 (ATIC), rs17421511 (MTHFR) and rs717620 (ABCC2). Demographic analysis, clinical parameters and disease scores (e.g. DAS28) were also recorded.

These SNPs are located within the genes involved in the metabolism of DMARDS and anecdotal evidence has been reported in the literature of their participation in modulating normal metabolism and function of DMARDs.

Correlation statistics was used to determine if the genetic profiles associate with the emergence of drug metabolites responsible for poor or non-response to DMARDs.

Our findings suggest that genetic-profiling studies may help predict future treatment responses of patients to certain DMARDs. A stratified medicine strategy can help prioritise treatments to those patients most likely to respond while avoiding ineffective treatments.

Abbreviations: single nucleotide polymorphisms (SNP); rheumatoid arthritis (RA), disease-modifying anti-rheumatic drug (DMARD), methotrexate (MTX)

P10. SDCCAG8 IS A SCHIZOPHRENIA RISK GENE THAT IS REQUIRED FOR EFFICIENT PRIMARY CILIOGENESIS.

Mairead Flynn[1, 3], L Whitton[1], M Gill[2], A Corvin[2], G Donohoe[1], D Morris[1], CG. Morrison[3].

[1]Cognitive Genetics and Cognitive Therapy Group, Neuroimaging and Cognitive Genomics (NICOG) Centre, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway.[2] Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine and Discipline of Psychiatry, Trinity College Dublin.[3]Centre for Chromosome Biology, Discipline of Biochemistry, National University of Ireland Galway.

Rare mutations in genes that encode centrosomal or ciliary proteins cause disorders that present with severe cognitive deficits and variable neuropsychiatric phenotypes. We set out to explore the involvement of centrosomal/ciliary genes in schizophrenia, a neuropsychiatric disorder that affects 1% of adults and is a major global health issue. Our analysis of publicly-available genome-wide association study (GWAS) data revealed that seven schizophrenia risk genes encode proteins with centrosomal functions. Of these, SDCCAG8 is also associated with educational attainment.

To analyse the molecular function of SDCCAG8, we used genome editing to ablate it in SHSY5Y neuronal and hTERT-RPE1 retinal epithelial cells. Loss of SDCCAG8 impairs cells' ability to make primary cilia and the signalling capacity of residual cilia, although centrosome structure appears normal by immunofluorescence microscopy. Recent RNA-Seq analysis on RPE1 SDCCAG8 deficient cells compared to wildtype cells revealed a large number of differentially expressed genes (DEGs; n=2,045) in the absence of SDCCAG8. Pathway analysis of DEGs revealed that there is enrichment in axonal guidance signalling ($p=2.51^{-15}$). There were also significant enrichments for several pathways that are involved in the production and turnover of extracellular matrix (ECM). Previously, many components of the ECM have been shown to be perturbed in patients with schizophrenia.

Using MAGMA gene-set analysis, we found that set of DEGs were enriched for genes associated with schizophrenia (p=0.03) and cognitive ability (p=0.03). This study shows that a combination of gene editing and genomic analyses can help uncover the processes that implicate centrosome/ciliary genes in neurodevelopmental

phenotypes.

P11. GENETIC ANCESTRY AND POPULATION STRUCTURE OF SCOTLAND AND ITS SURROUNDING ISLES

Edmund Gilbert[1], S O'Reilly[2], M Merrigan[2], D McGettingan[2], V Vitart[3], PK Joshi[4], DW Clark[4], H Campbell[4], C Hayward[3], S Ring[5], J Golding[6], N Timpson[7], P Navarro[3], S M Kerr[3], C Amador[3], A Campbell[8], CS Haley[3,9], DJ Porteous[8], GL Cavalleri[1,10*], JF Wilson[3,4*].

[1]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin.[2]Genealogical Society of Ireland, Dún Laoghaire, Dublin.[3]MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh. [4]Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh.[5]Bristol Bioresource Laboratories, Population Health Sciences, Bristol Medical School, University of Bristol.[6]Centre for Child and Adolescent Health, Bristol Medical School, University of Bristol.[7]Avon Longitudinal Study of Parents and Children, MRC Integrative Epidemiology Unit, University of Bristol, Bristol UK. [8]Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh.[9]The Roslin Institute and Royal School of Veterinary Sciences, University of Edinburgh, Edinburgh.[10]FutureNeuro Research Centre, Royal College of Surgeons in Ireland, Dublin.

Scotland and Ireland are separated in places by less than 20 kilometres of sea. They share the Gaelic language and similar frequencies of particular alleles and phenotypes, hinting at shared ancestry. The population structure within England and Ireland have recently been described. However, the extent of structure within the majority of Scotland, its surrounding islands, and their links to Ireland are currently unknown. We present an analysis of the British Isles and Ireland using a combined and comprehensive sample (n=2,556) of all major regions – expanding coverage in mainland Scotland (n=567), the Hebrides (n=57), the Isle of Man (n=40), Orkney (n=111) and Shetland (n=172). By analysing individuals with extended ancestry from specific regions, we demonstrate extensive structure in all regions of the British Isles and Ireland, as well as some of the finest scale structure observed worldwide within Orkney. We resolve the shared genetic history between Ireland and Mainland Scotland, confirm the strongest differentiation of Orkney and Shetland from other populations, show the major differentiation in Mainland Scotland is between the south-west and the north-east, and reveal the distinctiveness of the Hebrides and the Isle of Man. We additionally show decreasing cline of Norwegian ancestries across northern Britain, following the spread of the Norse Vikings. Our work represents a comprehensive description of genetic structure in the British Isles and Ireland and greatly expands the knowledge of genetic stratification within the north of the British Isles, informing on the study of rare genetic variants and genetic trait associations in these populations.

P12. THE EFFECTS OF GENETIC VARIATION ON THE COGNITIVE PHENOTYPES OF INTELLIGENCE AND WORKING MEMORY AND EPISODIC MEMORY IN SCHIZOPHRENIA.

Áine McNicholas[1], D Cosgrove[1], DO Mothersill[1], L Holleran[1], J Holland[1], M Dauvermann[1], M Gill[2], A Corvin[2], DW Morris[1], G Donohoe[1]

[1]Dept. of Psychology, National University of Ireland Galway, [2]Neuropsychiatric Genetics Research Group, Department of Psychiatry, Institute of Molecular Medicine, Trinity College Dublin.

The Savage et al. (in press) GWAS meta-analysis of intelligence of healthy controls supports increasing findings on variability in intelligence and evidence of overlap with schizophrenia. Utilising convenience sample of pre-existing Irish dataset of broad psychosis cases (916 cases and 330 controls), wherein the controls participated in the Savage et al. (in press) meta-analysis, the present study functioned as secondary analysis of said meta-analysis findings regarding the broad psychosis cases. With the five most significant single nucleotide polymorphisms (SNPs) as identified by Savage et al. (in press) and patient diagnosis as independent variables, this statistical regression analysis focused on the extent to which these genetic variances were of importance in a clinical population by examining the effects in schizophrenia of previously identified genetic variation associated with intelligence (IQ) in healthy controls. Further objective was to extend the Savage et al. (in press) findings to investigate the effects in schizophrenia of genetic variation on memory (working memory and episodic memory). As hypothesized the present study observed nominal trend association for SNP rs2726491 with decreased errors in performance IQ, and a nominally significant association with decreased errors in working memory for rs2726491 across both healthy and clinical population samples. These nominal associations would be suggestive of stronger effects in psychosis, however, the present study was underpowered to observe an association at the corrected level. Nevertheless, future research building on these suggestive findings could further our understanding of the biological psychopathology of schizophrenia, and crucially bring about improved cognitive function in schizophrenia patients.

P13. MULTIWAY ADMIXTURE INFERENCE FROM GENOTYPE DATA

Michael Salter-Townshend[1], SR Myers[2].

[1]School of Mathematics and Statistics, University College Dublin.[2]Dept. Of Statistics, University of Oxford.

We present a model, algorithm, and results for multiway admixture events. This is where two or more genetically differentiated groups come together. Data from such events can inform us of the demographic history of a species, carry signatures of natural selection, and may increase the power of genome wide association studies. Our model is based on Li and Stephens style haplotype copying and delivers accurate local ancestry estimation along the genome for each admixed individual. Unlike existing methods that return local ancestry, we do not assume knowledge of the relationship between sub-groups of donor reference haplotypes and the unseen mixing ancestral populations. Instead, our approach infers these in terms of conditional copying probabilities. We also infer admixing proportions, timings, and recombination rates. Furthermore, we can estimate drift between modern reference populations and the unseen mixing groups using a version of Fst that is computed on putative partial genomes derived by assignment of chromosome segments to ancestral backgrounds.

We demonstrate compelling results using the Human Genome Diversity Panel, including replication of some known admixture events, and we detail novel findings such as a recent 4-way admixture in San-Khomani individuals.

Keywords: Population Genetics, admixture, demography, local ancestry estimation.

P14. DONOR-RECIPIENT SHARED GENETIC ANCESTRY DOES NOT PREDICT RENAL TRANSPLANT OUTCOME IN A EUROPEAN POPULATION OF UNRELATED DECEASED DONOR TRANSPLANTS.

Caragh P. Stapleton[1], On behalf of the UK and Ireland Renal Transplant Consortium[2], PJ. Conlon[3] and GL. Cavalleri[1]

[1]Department of Molecular and Cellular Therapeutics, Royal College of Surgeons, Dublin, Ireland. [2]As part of the Wellcome Trust

Case Control Consortium.[3]Department of Nephrology, Beaumont Hospital, Dublin, Ireland

Sibling transplant pairs have better transplant outcomes than unrelated donor-recipient (DR) pairs suggesting shared genetic ancestry between donors and recipients has potential for predicting transplant outcome. We set out to evaluate methods to detect and quantify shared ancestry using GWAS data, to see which could best predict renal-transplant outcome.

We tested three different methods for estimating shared genetic ancestry on deceased donor DR pairs of European ancestry. Method 1 calculated identity by descent (IBD) which was then used to estimate the degree of relationship. Method 2 calculated genetic distance using identity by state which examines the number of shared alleles across the genome. Method 3 created a mosaic of an individual's genome from the haplotypes of the other individuals in the dataset. The similarity of mosaic genomes in a given DR pair was used as a measure of shared ancestry. These measures were then tested against estimated glomerular filtration rate (eGFR) at 1 year (DR pairs, n=1,450) and 5 years (DR pairs, n=1,309) post-kidney transplant, change in eGFR between 1 and 5 years (Δ eGFR; DR pairs, n=982) and time to graft failure (DR pairs, n = 1,806).

We did not find significant correlations between any of the measures of shared ancestry in the European ancestry deceased-donor DR pairs and graft function. The genetic relationship between the vast majority of our donor-recipient pairs was distant, and not detectable via IBD. The effect size of shared ancestry at the genomic level on eGFR is limited, and not detectable in our analysis.

P15. STRATIFICATION OF TYPE-2 DIABETES COMORBIDITIES USING GENOTYPIC ARRAY AND MACHINE LEARNING

Angelina T Villikudathil[1], D McGuigan[1], A English[1], C Kelly[1], P McClean[1], T Bjourson,[1] P Shukla[1].

[1]Northern Ireland Centre for Stratified Medicine (NICSM), Biomedical Sciences Research Institute, University of Ulster, C-TRIC Building, Altnagelvin Area Hospital, Glenshane Road, Londonderry.

Background: The treatment of comorbidities remains costly and represents a major priority in Evidence Based Medicine (EBM). Determining genetically the molecular-subclasses of pro-inflammatory comorbid conditions is important to stratify patients that may more effectively respond to specific treatment interventions. The objective of this study is to develop a Machine Learning (ML) based classifier to stratify patients with Type-2-Diabetes and different comorbidities.

Methods: A preliminary dataset of samples from 254 people with Type-2-Diabetes recruited at NICSM were genotyped with an Affymetrix UKBioBank Axiom Array. SNP results for 80 patient samples of class DCM1 (i.e. Type-2 Diabetes associated with comorbidities of circulatory system) and 90 patient samples of class DCM2 (i.e. Type-2-Diabetes associated with comorbidities of digestive system) were filtered through feature selection using ANOVA, Chi-square and Fast Correlation Based Filter. The top-10 SNPs along with information from Electronic Care Records (ECR), were selected for building 5 ML binary classifiers, using Support Vector Machine, Random Forest, Artificial Neural Network, Decision Tree and Naive Bayes algorithms, and their performances were tested with a 10-fold cross validation.

Results: Of the 5 classifiers, the Naive Bayes algorithm outperformed all others with an Area under the Curve score of 0.681, overall Classification Accuracy of 65.68% and Mathews Correlation Coefficient of 0.316.

Conclusion: Further improvement in the performance of our ML classifier is currently in-progress. With the inclusion of further data from ECR, as well as data from public repositories, we hope to build a better classifier.

P16. INVESTIGATING THE IMPACT OF AGEING AND FOLATE METABOLISM IN DRIVING MITOCHONDRIAL HETEROPLASMY AND NUCLEAR DNA METHYLATION.

Darren J Walsh[1], A Parle-McDermott[2]

[1]School of Biotechnology, Dublin City University.[2]Wellcome Trust, National Institutes of Health.

This project aims to investigate the relationship between folate status and the accumulation of mutations within the human mitochondrial genome. Folate is an essential B vitamin that is required for DNA synthesis, methylation reactions and is a major contributor to NADPH production through the folate one-carbon metabolism (FOCM) pathway. As a diet with a suboptimal level of folate can impact on DNA precursor availability, there is a strong biological plausibility that this will cause an increased occurrence of mutations within a cell's genome due to errors in DNA replication. Mitochondrial dysfunction has been linked to many age-related conditions such as cardiac myopathies, neurological disorders and muscular wastage. The accumulation of mutations within the mitochondria over one's lifetime may increase the level of mitochondrial dysfunction thus increasing the likelihood of developing such diseases. This project will look at the potential relationship between folate-status and the frequency of mutations occurring within the mitochondrial genome using a combination of both cell line and animal models plus a human cohort with known folate status and age ranges.

P17. COMMON VARIANTS ASSOCIATED WITH COGNITION ARE ENRICHED IN HIGHLY CONSTRAINED GENES AND IN GENOMIC REGIONS UNDER BACKGROUND SELECTION.

Laura Whitton[1], A Pardinas [2], G Donohoe[1], J Walters [2], D Morris[1]

[1]Cognitive Genetics and Cognitive Therapy Group, Neuroimaging and Cognitive Genomics (NICOG) Centre, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway. [2]MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff.

Common variants associated with schizophrenia are enriched among highly constrained (HC) genes. As schizophrenia and cognition are genetically correlated, we hypothesized that genes associated with cognitive function are enriched for HC genes. Using MAGMA to perform gene set analysis of the largest available GWAS datasets, we found that HC genes (n=3,230 (loss-of-function intolerant)) are strongly enriched for genes associated with educational attainment(EA; p=1.27E-09) and cognitive ability(CA; p=5.64E-09) in comparison to genes under lesser or weak constraint (p>0.05 for both EA and CA). This signal remained significant following conditional analysis to co-vary for 'brain-expressed' (n=14,243) and 'brain-specific' (n=1,424) gene-sets. In schizophrenia, evidence shows that common variants are likely to persist in the population due to background selection (BGS) mechanisms. BGS refers to the phenomenon by which selection against deleterious variants reduces genetic diversity, impairing the overall efficiency of selection and allowing alleles with small effects to rise in frequency by drift. We ran a stratified linkage disequilibrium score regression (LDSR) analysis to test for heritability enrichment in EA and CA for SNPs within genomic regions that are under various types of selection. The heritability of EA and CA is enriched for SNPs in regions under background selection(p=0.028 for EA and p=0.002 for CA) and depleted for SNPs in regions under positive selection. Recent studies

suggest that natural selection is acting against phenotypes such as EA or CA. This study suggests a mechanism by which variants contributing to these phenotypes are not removed by negative selection and are maintained in the population.

P18. EXPLORATION OF AN AAV-MEDIATED TULP1 REPLACEMENT GENE THERAPY IN A MURINE MODEL.

Adlet Yesmambetov[1], A Palfi[1], N Chadderton[1], P Kenna[1], GJ Farrar[1]

[1]School of Genetics and Microbiology, Trinity College Dublin,

Mutations in the photoreceptor-specific tubby-like protein 1 (TULP1) are associated with recessive retinitis pigmentosa 14 and Leber congenital amaurosis 15; severe, early-onset forms of retinal degeneration. We have explored an adeno-associated virus (AAV)-mediated gene replacement therapy in a murine model carrying a targeted disruption of the *Tulp1* gene (*Tulp1* -/- mice). The human *TULP1* cDNA driven by the chicken beta-actin promoter (CBA) promoter was generated in an AAV serotype 5 (AAV-CBAP-TULP1). 1x10e[11] vg of AAV-CBAP-TULP1 (+1:600 of an AAV-EGFP vector for tracing) was delivered to TULP1$^{-/-}$ mice at postnatal day 2 via sub retinal injection. Immunoblotting and qPCR demonstrated that the replacement TULP1 protein had the correct molecular weight and that the level of expression of protein achieved was ~55 % (n=8; p<0.05) of endogenous Tulp1 in wildtype mice (n=8). Immunohistochemical analysis detected TULP1 in the inner segments and synaptic region in treated Tulp-/- mice similar to endogenous Tulp1 in wildtype mice (n=8). The effect of AAV-CBAP-TULP1 delivery was assessed by histological analysis and TUNEL assay. Preliminary data indicated a modest increase the outer nucler layer thickness compared to AAV-EGFP treated controls; 34.07 µm ± 4.97 SEM and 24.07 µm ± 6.8 SEM respectively (n=8; p<0.05) and TUNEL assays showed a significant reduction in apoptotic cells (n=8; p<0.001). However, no differences were observed using functional assays such as the ERG and OKR. Despite the conserved C-terminal region (~200 bp) of human and mouse Tulp1 proteins, a significant divergence at the N-terminus may possibly contribute to the low efficacy of *TULP1* replacement in Tulp-/- mice and warrants further investigation.

P19. EVALUATION OF DIFFERENTIALLY EXPRESSED URINARY EXOSOMAL MICRORNAS IN TYPE 2 DIABETIC KIDNEY DISEASE

Jinnan Zang[1], DA Simpson[2], AP Maxwell[1], GJ McKay[1]

[1]Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom.[2]Centre for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom.

Background: Diabetic kidney disease (DKD) is the most frequent cause of end stage renal disease. There is a need for improved biomarkers for the early detection of DKD. MicroRNAs (miRNAs) are short, non-coding regulatory RNA molecules commonly found in urinary exosomes that may be differentially expressed during renal dysfunction. Therefore, we profiled urinary exosomal miRNA expression in type 2 DKD (T2DKD).

Methods: Qiagen Human Urine Exosome Focus miRNA Panel was used to profile 87 miRNAs in a discovery cohort of 14 T2DKD and 15 age and gender matched type 2 diabetic patients with normal renal function (T2NC). Differentially expressed miRNAs were validated in a second cohort of 22 T2DKD, 18 non-diabetic patients with poor renal function (CKD), and 22 T2NC.

Results: Three urinary miRNAs (miR-21-5p, let-7e-5p and miR-23b-3p) were significantly upregulated (P<0.05) and two (miR-30b-5p and miR-125b-5p) were significantly downregulated (P<0.05) in T2DKD compared to T2NC. In a logistic regression analysis adjusted for age, gender and mean arterial blood pressure, only miR-21-5p remained significantly associated with T2DKD (odds ratio=3.28, confidence intervals: 1.14–9.43; P=0.03). Independent validation in the replication cohort confirmed up-regulation of miR-21-5p expression in T2DKD (2.13-fold, p<0.01) and also in CKD (1.73-fold, p<0.05). In contrast, miR-30b-5p was downregulated in T2DKD (1.22-fold, p<0.01) and in CKD patients (1.52-fold, p<0.005).

Conclusion: Our data identified differential expression of miR-21-5p and miR-30b-5p in individuals with poor renal function, although further clarification to determine if these are associated with general mechanisms of renal dysfunction is required.

P20. WERNER SYNDROME - A UNIFYING HYPOTHESIS FOR NAFLD, INSULIN RESISTANCE AND MULTIPLE ENDOCRINOPATHY.

Vivion Crowley[1], E Walsh[1], S Abdelfadil[1], S Savage[1], B MacNamara[1], S McKiernan[2], A Pazsderska[3], R Murphy[4], K McCarroll[5]

[1]Biochemistry Department, St James's Hospital, Dublin 8.[2]Hepatology Centre, St James's Hospital.[3]Dept of Endocrinology and Diabetes, St James's Hospital, Dublin 8. [4]Cardiology Department, St James's Hospital.[5]Bone Health Clinic, MISA, St James's Hospital.

Werner syndrome (WS) is a rare genetic disorder due to mutations in the WRN or LMNA genes, with an estimated global incidence of 1 in 1,000,000 - 10,000,000. It is a segmental progeroid disorder characterised by an array of clinical features consistent with accelerated aging. We report the case of a 28 year old female patient, the offspring of a consanguineous union, who was referred to our metabolic clinic for review. She reported a history of vocal cord paralysis aged 19 years and subcapsular cataracts aged 24 years. Moreover, she had been diagnosed with primary hypothyroidism, primary hyperparathyroidism and subfertility despite normal menstruation. Further diagnoses included NAFLD with mild fibrosis. On examination, she had skin atrophy, hyperkeratosis, a loud S2, scalp alopecia, axillary acanthosis nigricans, and marked visceral adiposity with lipodsytrophic upper and lower limbs. Echocardiography confirmed trace regurgitation in aortic, mitral and tricuspid valves and DEXA confirmed osteoporosis. HOMA score was > 11 confirming severe insulin resistance and AMH levels were low. Phenotypically the patient had a diagnosis of definite WS but genetic confirmation was sought. Analysis of *LMNA* did not identify pathogenic variants. An RT-PCR method with direct sequencing was developed in-house to examine the extensive coding region of *WRN*. This revealed a homozygous genotype for the nonsense variant g.129, 248C>T, c.3961C>T, p.Arg132Ter. To our knowledge this is the first reported case of WS in the Republic of Ireland. In cases with multiple early-onset morbidities a genetic basis should be considered, particularly if there is a risk of consanguinity.

P21. POSSIBLE CANDIDATE INHERITABLE MARKERS BY NEXT GENERATION SEQUENCING INDICATING PREDISPOSING LONGITUDINAL RISK TO LUNG CANCERS WITH ATYPICAL PRESENTATION OF LUNG CAVITATION FROM FUNGAL LUNG DISEASE IN A KENT FAMILY OF IRISH DESCENT.

Leon G. D'Cruz[1,2,3,5], SA Husain [2], Z Yousef [3], S Edkins [4], K Ashelford [4] , FA Lai [5,6]

[1]Dept. of Stratified Medicine, Ulster University, CTRIC building, Altnagelvin hospital campus, Londonderry. [2]Dept. of Respiratory Medicine, Maidstone Hospital, Kent. [3]Dept of Cardiovascular Surgery, Cardiff University Hospital. [4]Wales Gene Park, Institute of Medical Genetics, Cardiff University. [5]Dept. of Biosciences, Sir Martin Evans Building, Museum Avenue, Cardiff University.[6]School of Medicine, Qatar University, Qatar.

Hyperlucent zones within areas of pulmonary consolidations may represent cavitatory lung lesions on CT imaging, from multi-factorial causes such as TB, pulmonary infarction, pyogenic lung abscess, pneumocystis pneumonia, Klebsiella pneumonia and less frequently due to necrotic processes from fungi.

We were presented with this clinical conundrum in a patient against a background of refractory asthma, chronic cough, worsening dyspnoea, poor spirometry results and becoming progressively unwell. Due to a strong history of cancer in the family, EBUS-TBNA was carried out to obtain lung-biopsy samples. Laboratory histological analysis and ROSE revealed hyphae and fungal spores within the tissue samples biopsied, no malignant cells were recovered from the lymph node biopsy samples in all stations. We initiated anti-fungal treatment; itraconazole, 200mg once daily for 2 days after which the patient began to show signs of improvement.

Seven family members with prior history of fungal-lung disease had developed lung-cancer later in life, and anecdotal prior research had shown that a premature stop-codon mutation at the tyrosine-238 residue of the dectin-1 gene in a Dutch family had predisposed patients to risks of contracting fungal-lung disease and subsequently developing lung-cancers in the long-term.

We carried out Sanger-sequencing of all the exons of the dectin-1 gene as well as whole-exome sequencing on the HiSeq (Illumina) platform to identify candidate markers that may explain the heritability in this Kent family of Irish descent. We highlight the results of this study in this presentation.

Abbreviations: endo-bronchial ultra-sound transbroncial-needle-aspiration; EBUS-TBNA, Rapid-OnSite-Examination; ROSE, tuberculosis; TB

P22. BREAST CANCER IN IRISH PATIENTS WITH LYNCH SYNDROME

Marie Duff[1], N Cody[1], C Clabby[1], S O'Reilly[2], TP McVeigh[1], AJ Green[1]

[1]Our Lady's Children's Hospital, Crumlin, Dublin 12. [2]Cork University Hospital, Cork.

Lynch syndrome (LS) (previously Hereditary Non-Polyposis Colorectal Cancer syndrome) is a cancer predisposition syndrome conferring variable risks of endometrial, colorectal, upper gastro-intestinal, urinary and biliary tract cancers. Lynch syndrome is a dominantly inherited trait, caused by pathogenic germline variants in one of the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, or *PMS2;* and more rarely by deletions in *EPCAM* causing hypermethylation of the *MSH2*promoter.

A recent report suggested that germline variants in MSH6 or PMS2 are associated with an increased incidence of breast cancer. Other data with respect to this association is conflicting, and prospective studies have not shown evidence for this association.

Here, we report a case of a 37-year old female patient with multi-focal breast cancer demonstrating defective MMR, associated with a germline variant in *MSH2*.

This prompted us to undertake a respective cohort study to assess the prevalence of breast cancer in patients with Lynch syndrome managed in our centre. We report on 60 consecutive patients (including the case described here above) tested and found to carry germline pathogenic/likely pathogenic variants in MMR genes were identified from a prospectively maintained departmental database. Pedigrees from these patients were analysed, and number of breast cancers in probands and first and second degree relatives were recorded. Age at diagnosis, phenotypic data and genotype were noted.

P23. CAG INTERMEDIATE-REPEATS EXPANSION IN *ATXN2* ASSOCIATED WITH INCREASE OF RISK IN ALS

Jennifer Hengeveld[1], MA Doherty[1], L Dupuis[2], A Vajda[3], M Heverin[3], D Bradley[1], O Hardiman[3], RL McLaughlin[1].

[1]Smurfit Institute of Genetics, Trinity College Dublin. [2]Department of Biology, University of West Florida. [3]Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College Dublin.

Amyotrophic lateral sclerosis (ALS), usually23 known as a motor neuron disease, is a fatal neurodegenerative disorder which causes death of neurons controlling voluntary muscles. ALS has no cure, and its underlying cause is mostly unknown, although a strong genetic component is known to play a role. The gene *ATXN2* normally has a repeat structure of around 22-23 triplets encoding for glutamine (CAG) within the reading frame of the gene encoding the ataxin two protein. Studies have shown that harbouring more than 40 repeats causes spinocerebellar ataxia type 2 (SCA2). Recently, it was discovered that intermediate-length repeat expansions (27-33 repeats) in *ATXN2* are significantly associated with the risk of ALS. The aim of this study is to genotype the *ATXN2* gene in a cohort of controls and patients from the Irish ALS bank in order to assess the association between this genotype and ALS. The most common alleles in this cohort were 22, 23, and 27 repeats, at frequencies (cases and control combined) of 87.0%, 8.3% and 1.9%. Trinucleotide repeat counts ≥27, ≥29 and ≥30 for the larger allele were significantly associated with ALS ($p < 3.6\times10^{-3}$, corresponding to $\alpha = 0.05$) and the odds ratio for ALS in the established ALS risk range was 1.90 (95% CI 1.03-3.51). This study further exemplifies the correlation between this gene and ALS in the Irish population, contributing to the research of causative genes for this devastating disease. Currently, our research is assessing the length of repeat expansions in other ataxia-associated genes, including *ATXN1*.

P24. HOW MANY AT-RISK RELATIVES AVAIL OF HUNTINGTON'S DISEASE TESTING?

Niamh Lang[1], TP McVeigh[2], JJ O'Byrne[2], RM Kelly[2], SA Lynch[2]

[1]School of Medicine, NUI Galway. [2]Department of Clinical Genetics, Our Lady's Children's Hospital Crumlin.

Introduction: Huntington's disease (HD) is a progressive, incurable, autosomal dominant, neurodegenerative disease. Genetic testing for HD has been available in the Department of Clinical Genetics since 1995. This clinic employs the gold-standard multistep approach to genetic testing, involving pre-test counselling, two blood draws and psychiatric review, allowing patients time to consider the consequences of testing and to withdraw at any time.

Aims: To establish the uptake of predictive testing among first-degree relatives of patients diagnosed with HD.

Methods: Families with at least one relative referred for genetic counselling between 2014 and 2016 were identified from a prospectively maintained departmental database. Familial pedigrees were analysed to identify at-risk relatives. Data was collected by retrospective chart review regarding number of first-degree relatives of the family proband attending clinical genetics for predictive testing, number who completed testing, diagnostic yield and patient demographics.

Results: 241 asymptomatic adult first-degree relatives of the proband in 35 families were identified. 125 of these were children of the proband and 106 were siblings. 41 (17.4%) self-referred for predictive testing and 26 (10.8%) completed testing (9 positive; 17 negative). The median age for those seeking genetic testing was 36y (23-69). Patients completing testing were younger than those

withdrawing from process (median 35 (23-55)-vs-40 (33-69y)).

Conclusion: Uptake of genetic testing among relatives of patients affected by HD is currently low, in-keeping with rates reported in international literature. However, this may change in time with increasing advent of therapy. Decision-making in an incurable disorder is complex and may explain this low figure.

P25. DOWN'S SYNDROME, OBSERVING THE SHIFT IN ACADEMIC FOCUS.

Caoimhe McKenna[1], P Morrison[1], M Lakhanpaul[2]

[1]Dept. of Genetics, Northern Ireland Regional Genetics Service. [2]GOSH Institute of Child Health, University College London.

Introduction: Over recent decades the life expectancy of those with Down Syndrome (DS) has increased dramatically. Much of this improvement can been attributed to early intervention, and the research which supports these interventions. Despite medical advancements, individuals with DS still have a greater mortality and morbidity compared with individuals from the general population and those with other forms of intellectual disability. Demonstrably there is a need for ongoing research to improve the quality and duration of life for those with DS. In modern academia there have been significant developments in the prenatal diagnosis of DS (e.g. Non-Invasive Prenatal Testing). Some of these developments have been met with controversy from members the DS community.

Methods: A structured PubMed search was performed utilising comprehensive terms to identify publications focusing on DS, childhood and the prenatal period. This was compared to the total number of publications available on PubMed per year (1990-2017).

Results: Since 1990, there are has been a general increase in the number of publications focusing on DS. However, the proportion of publications focusing on DS, compared to total PubMed publications, has decreased. Among those publications focusing on DS there has been a decline in the proportion of studies focusing on childhood and a proportionate increase in those focusing on the prenatal period.

Conclusion: The results of this preliminary review of the literature suggest a general decline in the proportion of academic publications focusing on DS and a shift in focus away from childhood and towards prenatal studies

P26. PHENOTYPIC DELINEATION OF A 12Q21 DELETION SYNDROME

Caoimhe McKenna[1], N Saxena[2], TA Dabir[1], J Jones[1], G Smith[1], PJ Morrison[1,3]

[1]Dept. of Genetics, Belfast City Hospital. [2]Department of Paediatrics, Ulster Hospital Dundonald. [3]Queens University Belfast, Belfast.

Introduction: Interstitial deletions of 12q are rare with around 6 cases including 12q21 deletions described in the literature. We identified a male infant with 12q21.1-q21.33 deletion with phenotypic features including wide sandal gap and longitudinal plantar creases, short upturned nose, low set ears, feeding difficulties and delayed development.

Methods: Array-CGH using the Agilent (ISCA*v2) 8x60K oligo array (genome assembly Build GRCh37)was undertaken on a chorionic villus sample at 13 weeks gestation due to raised nuchal translucency, and confirmed on venous blood after birth. A comparison of a-CGH microarray profiles was undertaken on the existing described cases.

Results: Array-CGH confirmed a ~16Mb deletion containing nine OMIMMorbid genes ALX1 (OMIM *601527), BBS10 (OMIM *610148), CEP290 (OMIM *610142), DUSP6 (OMIM *602748), KITLG (OMIM *184745), MYF6 (OMIM *159991), OTOGL (OMIM *614925), PTPRQ (OMIM *603317) and TMTC3 (OMIM *617218). Using overlapping features of different 12q21 cases allowed microarray profiles to confirm a common deletion region including a non-morbid gene LIN7A. Its role encodes a scaffold protein within the CASK pathway which is important in synaptic function and is a possible responsible gene for the intellectual disability and cortical development present in all described cases. Parental a-CGH was normal confirming our case is de-novo.

Conclusion: We delineate a 12q21 deletion syndrome with characteristic phenotypic features. LIN7A is a consistent deleted gene in this region and may be responsible for the intellectual disability due to cortical maldevelopment in this syndrome.

P27. DO NOT MISS TRISOMY 18 IN BILATERAL RADIAL RAY ANOMALIES

Caoimhe McKenna[1], A Znaczko[1], D Hurrell[2], T Dabir[1]

[1]Dept. of Genetics, Northern Ireland Regional Genetics Service. [2]Paediatric Pathology Department, Belfast City Hospital

Trisomy 18 (T18) is a relatively common chromosomal disorder with a prenatal prevalence of ~1/2,500. Features associated with T18 include congenital heart defects (CHD), microcephaly, over-riding fingers and rocker bottom feet. Radial ray anomalies (RRA) occur in ~ 1/10,000 pregnancies. RRA are associated with prenatal teratogen exposure, abnormal glycaemic control in pregnant women and syndromic disorders. To date there are few reported cases of T18 and bilateral RRA in the literature.

We describe two cases of T18 with bilateral RRA:

Case A: Male infant who passed shortly after delivery at 31 weeks gestation to 37 year old mother with a history of Crohn's disease. PM identified CHD, significant growth restriction, overlapping fingers, bilateral talipes equinovarus and bi-lateral absent radii and thumbs.

Case B: Male infant born at 16+4 weeks gestation to a 44 year old mother. PM examination identified significant growth restriction, an omphalocele, absent left radius, dysplastic right radius and absent thumbs, among other anomalies.

For Case A and B karyotype and FISH analysis performed at post mortem confirmed T18. In both cases the diagnosis of T18 was not made antenatally.

Here we discuss the importance of antenatal assessment which combines the use of ultrasound, clinical, genetic, cytogenetic and molecular testing in order to obtain the correct diagnosis from a wide spectrum of differentials. Foetal karyotype analysis should be considered in cases of RRA, especially if other malformations are detected. Cases with bilateral lesions have a significantly higher association with aneuploidy, in particular T18.

P28. TRIAGE IN A CLINICAL GENETICS SETTING - INVESTIGATING CONSISTENCY WITHIN AND BETWEEN UNITS.

Terri McVeigh[1], D Donnelly[2], M Al Shehhii[1], E. A. Jones[3], A Murray[4], S Wedderburn[5], M Porteous[6], SA Lynch[1,7,8]

[1]Our Lady's Children's Hospital Crumlin, Dublin.[2]Belfast Health and Social Care Trust, Belfast. [3]Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, Manchester. [4]Institute of Medical Genetics, University Hospital of Wales, Cardiff. [5]NHS Greater Glasgow and Clyde, Glasgow. [6]SE Scotland Genetic Service, Edinburgh. [7]Temple Street Children's University Hospital, Dublin. [8]University College Dublin.

Background: Clinical Genetics services provide a diagnostic, counselling and genetic testing service for children and adults

affected by, or at risk of, a genetic condition, most of which are rare, or genetically heterogeneous. Appropriate triage of referrals is crucial to ensure the most urgent referrals are seen as quickly as possible, without negatively impacting the waiting times of less urgent cases.

Aim: To examine triage practice in 6 Clinical Genetic centres across the UK and Ireland.

Method: Thirteen simulated referrals were drafted based on common referrals to Clinical Genetics. Copies of each referral were forwarded to each centre, where 10 nominated clinicians were asked to triage each referral. Triaged referrals were returned to the coordinating author for analysis. An electronic questionnaire was contemporaneously completed by clinical leads in each unit to gather local demographic details and local operating procedures relevant to triage.

Results: Widespread inconsistencies were noted both within and between units, with respect to acceptance of referrals to services, prioritisation, and designated clinic type. Referral rates, staffing levels, and waiting lists varied widely between units.

Conclusion: Inconsistencies observed between units are likely influenced by a number of factors including; staffing levels, referral rates, and average family size. Inconsistency within units likely reflects the complex nature of many Clinical Genetic referrals and triage guidelines should help improve decision making in this setting.

P29. LOSS-OF-FUNCTION AND MISSENSE VARIANTS IDENTIFIED IN A WEST OF IRELAND BREAST CANCER POPULATION

Úna M McVeigh[1], TP McVeigh[2], N Miller[3], DW Morris[3], MJ Kerin[1]

[1]Discipline of Surgery, Lambe Institute for Translational Research, NUI Galway. [2]Department of Clinical Genetics, Our Lady's Children's Hospital Crumlin, Dublin. [3]Discipline of Biochemistry, NUI Galway.

Ireland's breast cancer(BC) incidence is 122.6/100,000. 3% of BCs are attributed to variants in *BRCA1*/*BRCA2*. Knowledge of pathogenic variants drastically changes the risk management of patients. Variants in other genes(*CHEK2*, *ATM*) confer moderate-risk; up to 50% of inherited BC risk is unexplained. Analysing multiple genes in a cost-effective manner is possible through next-generation sequencing(NGS).

We aimed to identify variants contributing to Irish BC susceptibility using NGS.

A custom gene-panel was designed; genes were primarily selected from clinical panels (BC, BC and ovarian cancer, broad cancer) and candidate genes identified through GWAS. Captured libraries from 90 BCs and 77 controls were sequenced using Illumina's NextSeq. Variant calling was performed following GATK best practices. Following variant annotation (VEP, ANNOVAR, SnpEff), loss-of-function(LOF) and missense variants were analysed. Missense deleteriousness prediction scores were obtained from five sources. Clinvar reports were considered. Frequencies were obtained from ExAC/gnomAD.

LOF variants were identified in BCs/controls in known BC risk genes *BRCA1, ATM, CHEK2,* and M*SH6*(candidate risk gene). A splice-region LOF variant in *PBRM1* was identified (4 BCs:1 control). 22 novel LOF variants were identified.

Deleteriousness prediction tools unanimously scored 40 missense variants "damaging"; three in *BRCA1, BRCA2, ATM* had opposing Clinvar reports. Rare missense variants were identified in *FANCD2, SFN, ARID1B*. Novel missense variants were identified in genes appearing on clinical panels(*XPC, FANCA)* and reported in GWAS(*PTGS2, NOTH2, CYP1B1)*.

These results demonstrate the challenges of accurately predicting variant pathogenicity, and highlights the need for caution when considering the use of broad panel testing on an unselected population.

P30. A SEARCH FOR RARE VARIANTS IN A FAMILY-BASED STUDY OF ASD

Fiana Ní Ghrálaigh[1], E Kenny[1], L Gallagher[1], LM Lopez[1]

[1]Department of Psychiatry, Trinity College Dublin.

Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with a population frequency of ~1 in 88, frequently co-occurring with other psychiatric disorders. While it is accepted that ASD is a highly heritable disorder (h^2>0.8), much of the effect of genetic variation on autism remains unclear. A major search is currently underway to seek out the variation underpinning this disorder.

Methods and Results: A family was enrolled comprised of unaffected parents and 4 ASD-affected offspring. DNA was extracted from saliva samples using Perkin Elmer Prepito D cyto kit. All six samples were sequenced using SOPHiA GENETICS Whole Exome Panel covering 26,000 genes, run on HiSeq 4000 (2x250). QC was performed as standard. Data analysis was carried out using SOPHiA DDM. The identification and annotation of variants implicated in ASD will be reported.

Discussion: This study will contribute to the autism genomics field with the most up to date technology in a clinically relevant family based study. The genes identified will add to those already associated with ASD, giving a deeper understanding of the genomics of the disorder. In turn, this genomic understanding will bring a clearer picture of the mechanism of disease, both on an individual level and on a global level. This gives the opportunity to develop personalised therapies and management strategies, improving patient outcomes. Genomics is certain to play a crucial role in the diagnosis and intervention of ASD in the future.

P31. MITOCHONDRIAL DISEASE IN IRELAND – CHARACTERISATION OF PATIENTS ATTENDING THE NATIONAL CENTRE FOR METABOLIC DISEASE/ADULT METABOLIC SERVICE

James J O'Byrne[1], N Byrne[1]*, D Tapiea[1]*, Z Abidin[1], GM Pastores[1], EP Treacy[1].

[1]National Centre for Inherited Metabolic Disorders Adult Unit, Mater Hospital, Dublin.

Background: Little is known of the true epidemiological burden or character of mitochondrial disease in Ireland. Yet such information is important for provision/planning of evidence-based health policies/ future services.

Aim of study: 1) to characterise the cohort of patients with mitochondrial disease attending the National Centre for Inherited Metabolic Disease(NCIMD)/Adult Metabolic Service in reference to phenotype (clinical and biochemical), genotype, treatments/ management and outcomes.

Methods: A retrospective study was conducted on all patients attending the NCIMD/Adult Metabolic Service with a diagnosis of mitochondrial disease.

Results: Fifty five patients (33/55 (60%) male and 22/55 (40%) female) have a mitochondrial disease diagnosis. Pathogenic variants were identified in 39/55 (71%), testing pending in 5/55 (9%) and no pathogenic variants were identified in 11/55 (20%).

31/55 (57%) patients have MELAS; 2/55 (4%) have Kearns-Sayre syndrome and 1/55 (2%) have leber hereditary optic neuropathy or pyruvate dehydrogenase deficiency (PDD) deficiency or neuropathy, ataxia and retinitis pigmentosa. 19/55 patients (34%) have another mitochondrial disorder with only 9/19 (47%) having a confirmed genetic diagnosis.

Conclusions: MELAS, due to m.3243A>G, is the most common mitochondrial disorder which is in keeping with international studies.

30% of patients have a mitochondrial diagnosis due an abnormal biochemistry. Mitochondrial disease criteria (Wolf NI *et al*., 2002) will be applied to identify those for further genetic testing.

Low numbers of patients suggest there is a large cohort of mitochondrial patients not yet captured by this clinic.

The study will be expanded to calculate the prevalence of adult mitochondrial disease in the Irish population.

P32. ATYPICAL CASES OF SILVER RUSSELL SYNDROME AND ITS MOLECULAR CHANGES.

Erina Sasaki[1], T McVeigh[1], B O'Hici[1], S O'Connell[2], SA Lynch[1]

[1]Department of Genetics, Our Lady's Children's Hospital, Crumlin.[2]Department of Diabetes and Endocrine, Our Lady's Children's Hospital, Crumlin.

Abnormal methylation affecting allele-specific expression of the H19, IGF2, KCNQ1 and CDKN1C genes at the 11p15.5 locus are variably associated with congenital disorders of growth including Beckwith Weidemann syndrome (BWS), Silver Russell syndrome (SRS), and isolated lateralizing overgrowth. Methylation defects causing isolated hemi-hypertrophy commonly overlap with those causing BWS.

At the 11p15.5 locus, hypomethylation of the H19 DMR (differentially methylated region) (IC1) on the paternal allele, or hypermethylation of the KCNQ1OT1: TSS – DMR (IC2) on the maternal allele are mechanisms underlying SRS.

We present atypical cases related to SRS methylation abnormalities at the 11p15.5 locus.

Patient 1 is a 2y-old girl with leg-length discrepancy, and asymmetric facies. Relatively small at birth (5lb 4oz), post-natal growth velocity was normal. Patient 2 is a 16y-old boy measuring over 6ft with isolated hemi-hypertrophy. In both cases, hypomethylation at H19 was reported. Patient 3 is a 2y-old boy with history of IUGR, speech delay and short stature. Investigations identified a maternally inherited duplication of KCNQ1OT1: TSS – DMR. His mother inherited the same duplication from her mother, and was mildly affected, with final adult height of 4' 11", without growth hormone treatment, and no issues with development or feeding.

The Netchine-Harbison Clinical Scoring system outlines diagnostic criteria for SRS, including pre- and post-natal growth restriction, feeding issues, and characteristic facies. None of these cases would fulfil these criteria and yet have molecular defects consistent with SRS. A low threshold for investigation of methylation abnormalities should be adopted in cases of short stature or isolated hemi-hypertrophy.

P33. AN UNUSUAL CASE OF SHOX

Erina Sasaki[1], D Betts[1], L McArdle[1], A Hegarty[1], SA Lynch[1]

[1]Department of Clinical Genetics, Our Lady's Children's Hospital, Crumlin.

SHOX deficiency is characterised by a clinical spectrum from idiopathic short stature to Leri Weill dyschondroestosis with triad of disproportionate short stature, Madelung deformity and mesomelia. Heterozygous mutations or deletions of the SHOX gene located in terminal Pseudo-Autosomal pairing region (PAR1) of either Yp11.2 or Xp22.33, cause this condition in both sexes. This disorder behaves as an autosomal dominant disorder, (rather than X linked) due to its location within the pseudo-autosomal region.

Case: The proband was seen by clinical geneticist due to a co-incidental paternally inherited chromosome deletion in her son. The proband was noted to be short (143cm, 7cm below 3rd centile) and has shortened and bowed forearms. Analysis by aCGH showed an atypical Xp chromosome deletion of 881kb that included the SHOX gene. (Typical deletion involving SHOX is about 1.5Mb). In addition, she had gain of Yq11.221-q12 chromosomal material, which was inserted onto the distal region of Xp.

She and her elder sister attended paediatric endocrinologist 25 years ago for their short stature. Her sister responded to growth hormone therapy, pre-treatment height (10cm below the 3rd centile) improved to above 3rd centile, height 10cm > than the proband who was not treated. Their parents heights were both <3rd centile. Her father is short (152cm <<3rd centile) and has bowed forearms.

Both sisters are fertile, proband has one child and her sister 5 children despite the presence of significant amount of Yq chromosomal material.

This case illustrates that fertility can be preserved despite the presence of a large amount of Yq chromosomal material.

P34. MALAN SYNDROME: SHOULD THE PHENOTYPE OF THIS OVERGROWTH SYNDROME INCLUDE AORTIC ROOT DILATATION?

Erina Sasaki[1], H Gill[1], O Flanagan[2], C McMahon[3], L Bradley[1]

[1]Department of Clinical Genetics, Our Lady's Children's Hospital Crumlin. Dublin. [2]Paediatric Department, Galway University Hospitals. [3]Cardiology Department, Our Lady's Children's Hospital Crumlin.

Malan syndrome, also known as Sotos 2 syndrome as it clinically resembles Sotos syndrome, is a recently described overgrowth syndrome.

It is associated with deletions or mutations affecting the N terminal DNA binding site and dimerization domain (exons 2 and 3) in the Nuclear Factor I type X encoding gene (NFIX) on chromosome 19p13. Other mutations within the donor splice site of exon 6 of NFIX are known to cause the distinct clinical entity Marshall Smith syndrome.

Typical clinical features are tall stature, macrocephaly, craniofacial features such as narrow and long face with high forehead, developmental delay, intellectual disability and behavioural abnormalities such as autistic traits and anxiety. Musculoskeletal abnormalities such as advanced bone age and scoliosis are also well described.

Here we report a case of Malan syndrome with typical and atypical features, thus expanding the known phenotype, who was originally treated and referred as clinically suspected Marfan's syndrome. She presented to the Department of Clinical Genetics at 13 years of age having been referred by her General Paediatrician. She was tall and slim, macrocephaly, with mild intellectual disability who showed a mildly dilated aortic root for which she was prescribed a beta-blocker. Subsequent to genetic and biochemical investigation, a pathogenic mutation was identified in the NFIX gene.

This case emphasises the need to consider NFIX gene analysis in FBN1 negative Marfanoid appearing patients presenting with an atypical history and features such as intellectual disability, joints contractures, and dilated aortic root. Moreover, screening

Malan syndrome patients for aortic root dilatation may help further understanding of the possible involvement in vasculature development of the NFIX gene function.

P35. RETROSPECTIVE ANALYSIS OF BRCA 1 AND 2 SCREEN OUTCOMES FOR HIGH GRADE SEROUS OVARIAN CARCINOMAS THROUGH THE NORTHERN IRELAND REGIONAL GENETIC SERVICE APRIL 2016 – APRIL 2018.

Janice Scott[1,2], R Martin[1,2], P Logan[1,2], T Dabir[1,2].

[1]Dept. of Clinical Genetics, Belfast City Hospital.[2]Genetic laboratory services, Belfast City Hospital.

Guidelines published by the Institute of cancer research (2013) and NICE (2017) recommend testing all women diagnosed with high grade serous ovarian carcinoma (HGSOC) for germline pathogenic variants in the BRCA1 and BRCA2 genes. It is predicted that using these guidelines that 10% of cases in this cohort harbour a pathogenic variant. We have carried out a retrospective study on 2years of data (April 2016-March 2018) from genetic screening of BRCA1 and BRCA2 genes on HGSOC patients. The aim of this audit was to establish the number and incidence of germline BRCA1 and BRCA2 pathogenic variants identified within this cohort in Northern Ireland and to explore the contributing factors to these results.

During this period, 155 women with ovarian cancer were screened for germline mutations in the BRCA1 and BRCA2 genes by fluorescent sequence analysis of the coding sequence and associated splice sites and screening for whole exon deletion/duplication variants. The clinical details and family history of these patients were reviewed in light of existing screening guidelines and amendments to local testing protocols considered.

P36. IRISH ASSOCIATION OF GENETIC COUNSELLORS (IAGC) – SETTING UP A PROFESSIONAL BODY AND WORKING TOWARDS REGULATION.

Alana Ward[1], T Clark[1], C Giffney[2], D Lambert[3], C Peyton[4], J Turner[3], N White[4], E Whitmore[5].

[1]Dept. of Clinical Genetics, Our Lady's Children's Hospital Crumlin, Dublin. [2]Cancer Genetics Service, Mater Misericordiae University Hospital, Dublin 7. [3]National Rare Diseases Office, Mater Misericordiae Hospital, Dublin 7. [4]Cancer Genetics Service, St James' Hospital, Dublin 8. [5]Clinical Genetics, Temple Street Children's University Hospital, Dublin 1.

The rapidly emerging field of Genomics promises improved diagnosis and personalised medicine at the front line of patient care. Genetic counsellors (GCs) bring essential skills and knowledge for delivering genomic information to patients and in education of healthcare professionals. In the Republic of Ireland there are 13 Genetic Counsellors (GC) working across different hospital sites with a variety of clinical roles. The majority have attained professional registration through the UK Genetic Counselling Registration Board (GCRB) or the European Board of Medical Genetics (EBMG) and/or an MSc in Genetic Counselling. The number of GCs falls significantly below recommendations for the Irish population as compared to other European countries.

We are in the process of setting up a professional body called the Irish Association of Genetic Counsellors (IAGC) to represent the profession in Ireland. To achieve this two working groups have been established:

Professional body: this working group has developed a constitution detailing membership, council roles and setting out the aims for the organisation - advocating for the profession, development of CPD opportunities and education of allied health professionals.

Regulation: Given the significant implications associated with mishandling of genomic information this working group will aim to achieve consideration for the statutory regulation of the Genetic Counselling profession. Initial steps include direct approach to CORU - Ireland's health and social care professional regulator. Our goal is to promote high standards of professional conduct, education, training and competency in the Genetic Counselling profession.

P37. MANAGING THE EXPECTATIONS: RETROSPECTIVE ANALYSIS OF GERMLINE MLH1 MUTATION DETECTION RATE FOR ISOLATED LOSS OF MLH1 PROTEIN EXPRESSION ON TUMOUR TISSUE

Anna Znaczko[1], P Logan[1], T Dabir[1]

[1]Dept. of Genetics, Northern Ireland Regional Genetics Service

Immunohistochemistry (IHC) performed on tumour tissue to detect loss of mis-match repair (MMR) protein expression is used to screen individuals at risk of Lynch Syndrome (HNPCC). Germline mutation analysis for HNPCC is guided by loss of expression of MMR proteins on IHC and it has been local practice to arrange MLH1 mutation analysis for isolated loss of MLH1/PMS2 protein expression for all cases without testing the tumour tissue for BRAF or promoter hypermethylation as recommended by NICE guidelines due to lack of access to BRAF/promoter hypermethylation testing locally. Presence of BRAF and/or presence of methylation of MLH1 promoter region suggest sporadic cancer and therefore molecular testing for HNPCC is not indicated in these cases. It is likely that sporadic bowel cancer is being tested for HNPCC based on IHC results alone as per existing practice. This audit would help us to quantify the issue and will help us in creating a testing pathway incorporating BRAF/ promoter hypermethylation testing for better diagnostic yield. This would avoid unnecessary genetic testing and would be a cost saving measure for the service helping us to utilize our resources efficiently

P38. NAIL-PATELLA SYNDROME PRESENTING WITH PURE RENAL PHENOTYPE: CASE REPORT OF A FAMILY WITH AUTOSOMAL DOMINANT *LMX1B*-ASSOCIATED NEPHROPATHY.

Anna Znaczko[1], T Dabir[1], P Morrison[1]

[1]Dept. of Genetics, Northern Ireland Regional Genetics Service

Mutations in the *LMX1B* gene cause nail-patella syndrome, a rare autosomal dominant disorder which is characterized by abnormalities of the nails, knees, elbows, and pelvis. The features of nail-patella syndrome vary in severity between affected individuals, even among members of the same family. Other areas of the body that can be affected in this condition are eyes (glaucoma) and kidneys where progressive disease can cause renal failure.

The *LMX1B* gene provides instructions for producing a protein that binds to specific regions of DNA and regulates the activity of other genes. On the basis of this role, the *LMX1B* protein is called a transcription factor. The *LMX1B* protein appears to be particularly important during early embryonic development of the limbs, kidneys, and eyes. Mutations in the *LMX1B* gene lead to the production of an abnormally short, nonfunctional protein or affect the protein's ability to bind to DNA. It is unclear how mutations in the *LMX1B* gene lead to the signs and symptoms of nail-patella syndrome.

We describe a family with significant history of kidney failure and no systemic manifestations of nail-patella syndrome

Molecular studies identified a pathogenic variant in one allele of *LMX1B* c.737G>A missense p.Arg246Gln predicted to result in an arginine to glutamine substitution at amino acid position 246. This variant has been described previously in multiple unrelated families who presented with autosomal dominant nephropathy without nail

and patellar abnormalities, which suggest this variant mutation is phenotype specific.

This case reports adds to a growing evidence of *LMX1B*-associated nephropathy without nail and skeletal manifestations seen in classical nail-patella syndrome.

P39. RETROSPECTIVE ANALYSIS OF BRCA 1 AND 2 SCREEN OUTCOMES FOR TRIPLE NEGATIVE BREAST CANCERS THROUGH THE NORTHERN IRELAND REGIONAL GENETIC SERVICE APRIL 2016 – APRIL 2018.

Anna Znaczko[1], R Martin[1], P Logan[1], T Dabir[1]

[1]Dept. of Genetics, Northern Ireland Regional Genetics Service

ICR guidelines recommended testing all women diagnosed with triple negative breast cancer (i.e. negative for the oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)) under 50 years old should be offered genetic testing for BRCA 1 and 2 pathogenic mutations. It was predicted that testing in this population should identify pathogenic mutations in around 10% of this cohort. This retrospective study will analyse 2 years (April 2016 – March 2018) of BRCA 1 and 2 testing in women diagnosed with triple negative breast cancer under 50 years of age. The main aim would be to find out if BRCA 1 and 2 mutations are accurately represented for our population and to explore the contributing factors to these results. For example, establish true pathology of the triple negative referrals tested and the strength of the family history of cancer in these cases. The hope is to identify whether tighter departmental guidelines for testing and developing a testing criteria proforma for mainstreaming could be beneficial for better mutation pick up rate.

P40. NEXT GENERATION SEQUENCING TO CHARACTERIZE THE GENETICS OF POLYCYSTIC KIDNEY DISEASE

Katherine A Benson[1], C Kennedy[2], S Murray2, C Stapleton[1], GL Cavalleri[1], P Conlon[2]

[1]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin. [2]Department of Nephrology, Beaumont Hospital, Dublin.

Background: Polycystic kidney disease, the most common inherited renal disease, is characterized by renal cysts and progressive reduction in kidney function. Although it is well established that autosomal dominant (ADPKD) is primarily caused by mutations in *PKD1* and *PKD2*, sequencing of *PKD1* is difficult due to multiple pseudogenes. Further, there is considerable unexplained variance in the age-of-onset of PKD even within families.

Aims: Firstly, to apply NGS technologies for the molecular diagnosis of ADPKD. Secondly, to identify, using genomic and clinical data, large PKD 'super-families' to facilitate investigation of genetic modifiers of age-of-onset.

Methods**:** NGS sequencing was performed using a custom Roche NimbleGen SeqCap targeted panel on the Illumina platform. Bioinformatics was performed using a custom, in-house pipeline based on GATK best practices. Copy number variants were identified from NGS data. Whole exome sequencing was performed on selected families using Roche NimbleGen library preparation. Pathogenicity was assigned to variants using ACMG pathogenicity guidelines.

Results**:** 73 ADPKD patients were sequenced and a molecular diagnosis was obtained in 63% (41/73) indicating that NGS technologies were successful for variant identification in difficult to sequence *PKD1* regions. We identified five pairs of individuals recorded as unrelated who shared rare *PKD1* variants and have inflated genomic relatedness (IBD) scores.

Conclusions: NGS with specific capture methods is suitable for the sequencing of renal disease genes including *PKD1*. We identified one large ADPKD pedigree chart using genomic data for the generation of Irish ADPKD 'super-families'. Sequencing of additional ADPKD patients (underway) will facilitate expansion of 'super-families' concept.

P41. FUNCTIONAL GENOMIC SCREENING IDENTIFIES USP11 AS A NOVEL REGULATOR OF ERA TRANSCRIPTION IN BREAST CANCER

Lisa Dwane[1], S Das[1], B Moran[2], A E. O'Connor[2], L Mulrane[2], A M. Dirac[3], B Mooney[1], K Jirstrom[4], J P. Crown[5], R Bernards[3], W M. Gallagher[2], T Ní Chonghaile[6] and D P. O'Connor[1]

[1]Molecular and Cellular Therapeutics, Royal College of Surgeons Ireland, 123 St. Stephen's Green, Dublin 2, Ireland. [2]Cancer Biology and Therapeutics Laboratory, UCD School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Ireland. [3]Division of Molecular Carcinogenesis, Netherlands Cancer Institute, Amsterdam, the Netherlands. [4]Department of Laboratory Medicine, Malmö University Hospital, Lund University, Malmö, Sweden. [5]St Vincent's University Hospital, Elm Park, Dublin 4, Ireland. [6]Physiology and Medical Physics, Royal College of Surgeons Ireland, 123 St. Stephen's Green, Dublin 2, Ireland.

Approximately 80% of breast cancers overexpress the estrogen receptor α (ERα) and depend on this key transcriptional regulator for growth. The discovery of novel mechanisms controlling ERα function represents major advances in our understanding of breast cancer progression and potentially offers new therapeutic opportunities. Here, we investigated the role of deubiquitinating enzymes (DUBs), which remove ubiquitin moieties from proteins, in regulating ERα in breast cancer.

We performed an RNAi loss-of-function screen using a library of shRNA vectors targeting all 108 known or putative human DUB genes. Suppression of a number of DUBs repressed or enhanced the activity of an estrogen-response-element (ERE) luciferase reporter. Interestingly, suppression of the BRCA2-associated DUB, USP11, was found to downregulate ERα transcriptional activity.

Subsequent validation using two individual siRNAs targeted to USP11 revealed a reduction in expression of endogenous ERα target genes in ZR-75-1 cells, as quantified using qRT-PCR. Estradiol (E2) stimulation enhanced USP11 expression in the cell nucleus, while proteomic analysis by mass spectrometry revealed a significant change to the proteome in USP11 knockdown cells in the presence of E2 only. Furthermore, USP11 expression was found to be upregulated in LCC1 breast cancer cells when compared to other cell lines. RNA-seq in LCC1 USP11 knockdown revealed a downregulation of several putative ERα target genes and many cell cycle-associated genes.

To support the prognostic relevance of USP11, immunohistochemical staining of a breast cancer tissue microarray (103 ERα+ patients) was performed. Kaplan-Meier analysis of this cohort revealed a significant association between high USP11 expression and poor overall (p=0.030) and breast cancer-specific survival (p=0.041).

These results suggest a role for USP11 in ERα transcriptional activity and identify USP11 as a potential therapeutic target in ERα+ breast cancer.

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Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. United Kingdom.
Contact details: T/ F: (+44) 028 9097 5780 E: umj@qub.ac.uk W: www.ums.ac.uk

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