ISSN 0041-6193

THE ULSTER MEDICAL JOURNAL

Volume 88 (2) May 2019

The Ulster Medical Journal

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

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

Statement: The Ulster Medical Journal is an international general medical journal with contributions on all areas of medical and surgical specialties relevant to a general medical readership. It retains a focus on material relevant to the health of the Northern Ireland population.

Disclaimer: The Ulster Medical Journal is owned and published by The Ulster Medical Society, itself founded in 1862 by the amalgamation of the Belfast Medical Society (founded 1806) and the Belfast Clinical and Pathological Society (founded 1853). The owner grants editorial freedom to the Editor of the Ulster Medical Journal. The Ulster Medical Journal follows guidelines on editorial independence produced by the World Association of Medical Editors, and the code of good practice of the Committee On Publication Ethics.

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

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

Ulster Med J 2019;**88(2):**81-82

Guest Editorial

A Rend in the Fabric of Medicine

Michael Trimble

In February the Royal College of Physicians of London (RCP) fulfilled its commitment to resurvey its members regarding the question of assisted dying. In some ways it was a strange time to be raising the issue as, since the last survey in 2014, there have been a number of unsuccessful attempts to challenge the current legal position either through parliament or the courts and the issue seems settled for the time being. However, assisted dying is an emotive issue about which individuals have strongly held views. That some remain keen for change was demonstrated by *Health Care Professionals for Assisted Dying's* campaign which was timed to coincide with the RCP's survey. The result of the survey was split: 43.4% of respondents thought the RCP should be opposed to a change in the law on assisted dying, 31.6% want the RCP to support a change and 25% thought the RCP should be neutral. Following the poll, the Council of the RCP decided almost unanimously to move to a position of neutrality. Whilst the College may be keen to stress that neutral means neutral, proponents of assisted dying are already presenting the results in terms of the College having withdrawn opposition to the legalisation of assisted dying.

There are many, including within the profession, who view assisted dying as a good and compassionate thing. Professor Ray Tallis expresses his incredulity "That anyone could oppose such a humane ambition as decriminalization of assisted dying." My own view is that it would be a grave mistake for the profession to start down this road. What may be framed as a matter for personal choice, in fact, has massive implications for both the profession and society.

If a patient's right to die with a doctor's assistance was to be recognized in the United Kingdom, what might the implications be? It is often forgotten that for every right there is a corresponding duty: If someone has a right to die with medical assistance at a time of their choosing then someone else must have a duty to fulfil that right. Perhaps this accounts for the fact that on the whole the profession has been much less enthusiastic about assisted dying than the public. If assisted dying becomes legal, then it becomes an expected part of the health service. Who would be responsible? Analysis of the 2014 RCP survey shows that Palliative Care physicians have the least enthusiasm for assisted-dying, with 85% of respondents being opposed. Perhaps it will fall, as with so many other tasks, to the general physicians. What about conscientious objection? It can be seen already in the aftermath of the Republic of Ireland's referendum on provision of abortion services that there is debate as to the scope of individual conscience in regard to a state-funded service. What about the trainees? If physicians are expected to provide this service, then they will need appropriate training. Will this become part of the Internal Medicine curriculum? How will competency be assessed? How many deaths will it take? It has been said that to go against the public wish for assisted-dying is an example of medical paternalism. However, at the same time we are urged to tell our patients to stop smoking, lose weight and drink less. How is one paternalism and the other allowing patient choice?

There is also scope for confusion in the terminology used in the RCP survey. Rather than *physician assisted suicide,* the RCP has favoured the term *assisted dying* which they define as

> The supply by a doctor of a lethal dose of drugs to a patient who is terminally ill, who meets certain criteria and who requests those drugs in order that they may be used by the person to end their own life.

In fact, there is no standard or legal definition of assisted dying and this is not the only possible use of the term. In the book *Debating Euthanasia*, Law Professor Emily Jackson states that she will "use the term assisted dying to refer to both euthanasia and assisted suicide." And indeed the distinction is not clear cut. Even using the RCP definition, if the patient cannot physically take the medication it is tacitly implied that it would need to be administered. Physician assisted-dying blurs into euthanasia, but that is not the question which was asked in the survey.

I understand that those who advocate assisted dying are motivated by compassion. It is hard to watch someone suffer, standing by wishing you could do something. But we need to be aware of the broader consequences. Once the line is crossed, it becomes harder to draw the boundaries for acceptable ethical practice. There are wider issues around the question of when a life could legitimately be ended. Physicians act for the good of their patients and if death becomes seen as a 'good' then how can it be withheld from anyone who seeks it? Whilst Dignity in Dying maintain their campaign is for limited provision of assisted dying to adults with a terminal illness and a life expectancy of 6 months, others, for example Humanists UK, would be less restrictive. For Ludwig Minelli, human rights lawyer and founder of Dignitas, the Swiss euthanasia clinic, "It's a right, a human right, without condition except capacity of discernment."

Concern regarding the blurring of the boundaries of acceptable practice is more than idle speculation. A recent

journal article describes worrying trends in the experience of doctors in the Netherlands. This included the increasing number of requests from patients for assisted dying for non-medical reasons and difficulties with the physician's role in the midst of pressure from patients or families to provide the service. Of concern was the move of the clinician from caregiver to 'mere provider' of the service; the moral discomfort of physicians assisting death in patients whose pain is 'mostly existential'; and compromise in the criteria used to assess patients for the suitability for assisted dying. We would do well to heed this experience and watch carefully regarding future trends. The situation in Belgium is more extreme, as euthanasia is extended to children, the mentally ill, and, in some cases, those who have not requested it.

In medicine, when discussing ethical issues, we may refer to the principle of 'sanctity of life'. Legal scholar John Keown prefers the term *inviolable*. Whether one believes that human life has been set apart as special by God or marked out as such by society, we recognise that it is inviolable: Taking a human life is wrong. In my opposition to assisted dying I will doubtless be accused of employing a 'slippery slope' style argument, however I would prefer the analogy of making a rend or tear in the fabric of medical practice. With a slippery slope you at least may have an idea where you will end up but a tear can progress along unanticipated lines – and is always damaging.

Dr Michael Trimble

Clinical Lecturer Honorary Consultant in Medicine.

RCP Council Member

Centre for Medical Education, Queen's University, Belfast, Mulhouse Building, 1st Floor, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BJ

E-mail: m.trimble@qub.ac.uk

The opinions expressed in this article are those of the author and do not reflect UMS or UMJ policies nor RCP Council policy.

REFERENCES

1. Press release, Royal College of Physicians, London 21.3.2019 https://www.rcplondon.ac.uk/news/no-majority-view-assisted-dying-moves-rcp-position-neutral [accessed 29.3.2019]
2. Dignity in Dying Press release ROYAL COLLEGE OF PHYSICIANS WILL DROP ITS LONGSTANDING OPPOSITION TO ASSISTED DYING https://www.dignityindying.org.uk/news/royal-college-physicians-drop-longstanding-opposition-assisted-dying-neutral/ [accessed 1.4.2019]
3. Karen Porter and Katherine G Warburton. Physicians' views on current legislation around euthanasia and assisted suicide: Results of surveys commissioned by the Royal College of Physicians. *Future Healthcare Journal* 2018;**5**:30-4
4. https://www.rte.ie/news/2018/1013/1002952-abortion-conscience/ [accessed 13.3.2019]
5. Emily Jackson and John Keown. 2012 *Debating Euthanasia* Hart Publishing; UK. P 2
6. Quoted in Assisted suicide 'a marvellous possibility' says Dignitas founder Ludwig Minelli The Daily Telegraph 2 Apr 2009
7. M C Snijdewind, D G van Tol, B D Onwuteaka-Philipsen, D L Willems Developments in the practice of physician-assisted dying: perceptions of physicians who had experience with complex cases *Journal of Medical Ethics* 2018;**44(5)**:292-296
8. T Quill. Dutch practice of euthanasia and assisted suicide: a glimpse at the edges of the practice *Journal of Medical Ethics* 2018;**44(5)**:297-298
9. Belgium authorised euthanasia of a terminally ill nine and 11-year-old in youngest cases worldwide Daily Telegraph 7 August 2018 https://www.telegraph.co.uk/news/2018/08/07/belgium-authorised-euthanasia-terminally-nine-11-year-old-youngest/ [accessed 14th March 2019]
10. Dierickx et al. Euthanasia for people with psychiatric disorders or dementia in Belgium: analysis of officially reported cases *BMC Psychiatry* (2017) **17**:203
11. Outrage as dementia patient who never asked to die is euthanized at request of family in Belgium Daily Mail 6 February 2018 https://www.dailymail.co.uk/news/article-5399059/Death-dementia-patient-stirs-Belgium-euthanasia-fears.html
12. John Keown. *The Ethics and Law of Medicine*, 2012, Oxford University Press, Oxford p 3ff

Ulster Med J 2019;**88(2):**83-84

Presidential Address

What Is a Physician?

Presidential Address to the Ulster Medical Society. 4th October 2018

Dr Peter Watson

On social occasions I am sometimes asked what I do for a living. When I say I am a doctor I am often asked "what type of doctor?", and when I say I am a physician, I am often then faced with the next question "What is a physician?" I have been a consultant physician for 27 years and for most of that time I have not had to think too hard about what a physician does-it seemed obvious, at least to me. As a student and later as a junior doctor the main activities in the general hospital divided into "Medicine" and "Surgery" The main thing that differentiated them was that operative procedures were performed in Surgery and not in Medicine but today even that differentiation is blurred with interventional cardiology, interventional radiology and endoscopic operative procedures performed in gastroenterology.

As a Senior Lecturer in Medicine and Academic Head of Clinical Medicine I am responsible for devising the curriculum in Medicine and delivering it to undergraduate students. I and my colleagues in the Centre of Medical Education at Queen's became aware that our students were confused and unhappy about the nature of "General Medicine" This is illustrated by the results of a recent focus group of third year students, asked to comment on their experience on attachment to General Medicine (Fig 1).

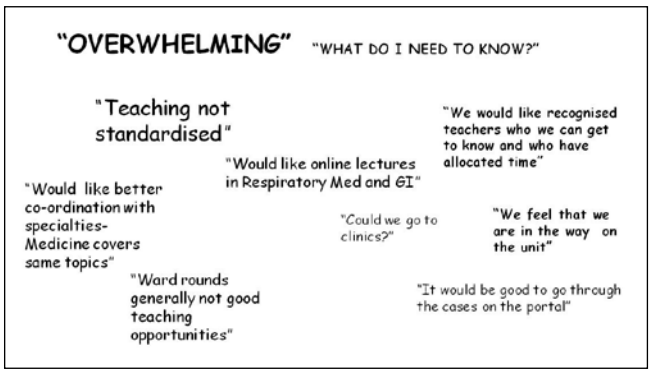


Fig 1 Comments of 3rd year students about their attachment in General Medicine The frequency of comments is indicated by the size of wording

The attachments in General Medicine and General Surgery have been enshrined in the curriculum well before when I was a student right up to the present day, but medical practice and medical education have changed considerably. In Table 1, I have outlined what I consider to be the service-related and student-related factors that have led to student dissatisfaction: mainly the disappearance of "general medicine" as an entity from most hospitals with fragmentation into a large number of specialties in relation to service and from a student perspective the increasing difficulty of enjoying a prolonged apprenticeship due to the increasingly large number of students and limited time allocation.

What are the difficulties?

Service related
- Less "General medicine", Medicine is more fragmented with specialist units.
- More complex-multiple co-morbidities
- Patients acutely ill in hospital, fewer relatively well enough for teaching
- Pressure of work for staff, loss of culture of teaching
- "Shift working", loss of the "firm"

Students
- Uncertain about what General Medicine is, as opposed to Specialties
- Variability of experience determined by attachment
- Time limited
- Expectation of didactic teaching - transition to self-learning and less structured programme difficult. In 2nd year clinical skills teaching provided appropriate cases on the day, in 3rd year and final year more opportunistic.
- They don't feel that they rightly belong in a unit, and are therefore inclined to be less involved.

Table 1 Suggested factors leading to student difficulties with general medicine attachment

There has always been emphasis on student self-directed learning, especially for senior students, but when the subject is large and diffuse and getting ever more complex it can appear overwhelming. Because of the lack of general medical units, it has been necessary to allocate students to specialist units such as Gastroenterology and Respiratory Medicine. Inevitably this leads to quite different student experience and a sense of a lack of standardisation and hence inequality.

Getting back to the polite enquiry at a party "What is a physician?" I usually manage to say something about being a medical detective-it is my job to try to make an accurate diagnosis of what is causing a patient to be unwell and then organise an effective treatment plan. On one occasion, a young man recognised my description as relating to the fictional character Gregory House in the TV series House. Although House is a wonderfully gifted diagnostician he is rude and egotistical, which works well for a TV series but is not really a suitable role model for a physician. I would much rather prefer to compare myself to the greatest detective of them all-Mr Sherlock Holmes. His creator, Sir Arthur Conan Doyle (1859 - 1930), trained as a doctor in Edinburgh where he later worked for a time, and based Sherlock Holmes on Sir Joseph Bell, with whom he worked. Bell was an eminent surgeon, and surgeon to Queen Victoria when she went to Scotland. Bell liked to emphasise the importance of close observation

Correspondence to Prof. Peter Watson

E-mail: peterrg.watson@belfasttrust.hscni.net

in making a diagnosis. To illustrate this he would often pick a stranger, and by observing him, deduce his occupation and recent activities. Because of these skills he was considered to be a pioneer in forensic science at a time when science was not yet widely used in criminal investigation. Such skills and systematic collection of evidence feature in the Sherlock Holmes stories. When his narrator Dr Watson is astonished at how he arrived at a certain conclusion, Holmes frequently refers to "the method". The parallels with medical practice are clearly evident. As well as close observation, deduction is evidence based. Holmes has an encyclopaedic knowledge of criminal activity based on newspaper reports, equivalent to our medical journals. He recognises recurrent common patterns. He has a minute knowledge that is helpful to him, such as the different composition of paper depending on its origin, the idiosyncrasies of hand writing and how type writer characters wear with use. He has done his own research, such as the changes with time of blood stains, and published his findings. These are all reminiscent of a top physician.

When my colleagues and I started to think about how we should deal with the disenchantment of our medical students for general medicine we came across a definition by the Joint Royal Colleges of Physicians Training Board which they have used in developing their new curriculum for internal medicine

"*The practice of Internal Medicine encompasses the knowledge and skills to manage patients presenting with a wide range of medical symptoms and conditions. It involves particular emphasis on diagnostic reasoning, managing uncertainty, dealing with co-morbidities, and recognising when speciality opinion or care is required."*

If we accept that Physicians practice Medicine then this definition takes us close to answering the question "What is a physician?" In essence it embodies a certain philosophy and outlines a particular approach or "Method". The analogy with being a detective is central but also includes the important familiar aspects of managing uncertainty, dealing with co-morbidities and recognising your own limitations and the need for specialist input.

On this basis the JRCPTB have developed a curriculum encompassing generic skills and systematic clinical skills related to symptoms rather than systems, which has tended to be the approach in the past. It is timely and looks useful (1).

At Queen's we have put the diagnostic process at the heart of the curriculum in Medicine (Fig2).

It will be familiar to all doctors whatever their specialty and in an effort to give students a common experience, we are introducing a standard set of virtual cases as case-based-discussions, that all students will do on attachment, facilitated by a teacher. In this way the course will be standardised, at least in part, and makes it easier for students to be aware of what they should know for assessment and easier for teachers to know what they should teach.

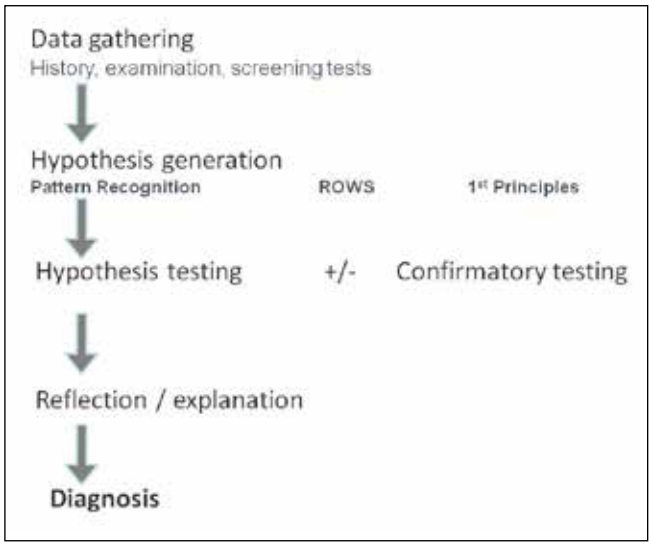


Fig 2. The diagnostic method. ROWS = Rule Out Worst-Case Scenario By kind permission of Dr Michael Trimble QUB

The skills of a physician are core skills and useful for all clinicians but in terms of a role with the title "physician", Accident and Emergency physicians and acute physicians at the front door of the hospital perhaps come closest. Interestingly because of the rush to form lots of specialties it has become necessary to invent a new grade of health worker: Physician Assistants in the USA or Physician Associates in the UK. They do some of the things that physicians used to do, in particular co-ordinating care for patients with multiple co-morbidities, which of course these days is most patients.

There is another group of doctors who can lay claim to being true physicians, the definition adopted above is virtually an exact fit for their job description: these are our primary care physicians. Everything in the definition is their "bread and butter", so perhaps it is they who have inherited the true mantle of being physicians. Also bearing in mind that physicians are key educators, primary care physicians deal with a wide range of undifferentiated cases and are in a particularly good position to apply and teach the diagnostic method. In almost all UK medical schools students are now rightly spending more and more time in primary care to benefit from such experience.

In summary the role of the hospital doctor practicing medicine (a physician) has rapidly evolved into various specialties but the core skills of diagnostic reasoning and professionalism are a necessary and integral part of every doctor's skill set. We are medical detectives and problem solvers. During my Presidential year I have arranged a series of talks that will explore aspects of these skills and deepen our understanding. It is these core skills that we need to highlight and pass on to our students when we practice and teach Medicine.

REFERENCES

1. New Internal Medicine Curriculum, Joint Royal Colleges of Physicians Training Board 2019. http://www.jrcptb.org.uk/imt Last accessed March 2019.

Book Case

The Editor reviews 6 favourites from his bookshelf.

FIRST MAN. THE LIFE OF NEIL A ARMSTRONG.

James R Hansen. Simon & Schuster UK. ISBN-13: 978-1471177873. Paperback. RRP £8.99

I must admit that I haven't seen the recent movie but I found the book quite worthwhile. Neil grows up as a small-town boy but is interested in flight and space so joins the US Navy as an aviator where he benefits from generous military scholarship schemes to take a Master's in Engineering. The book documents his combat history flying some early jet fighters in the Korean war.

After this, he becomes a test pilot, eventually flying the Mach 6 sub-orbital X15 rocket plane in the 1960s. Unlike many of his peers, Neil is noted for his calm stance and ability to give proper feedback about problems to the engineers on the ground. He joins NASA and after flying in the Gemini program joins the roster of astronauts waiting for a chance to fly Apollo to the Moon. Fellow pilots die all the time in this book – whether its combat, the tragedy of the Apollo 1 capsule fire or just random accidents as the astronauts must fly small jet trainers to keep up their flight logs. I guess Formula 1 in the 1960s probably had a similar mortality rate.

The book really comes into its own during the Apollo 11 mission. I wont spoil things but suffice to say that Neil's relationship with the somewhat prickly Buzz Aldrin comes to the fore and eventually it's NASA that decides Neil must be first out of the hatch to step onto the Moon.

The aftermath of the historic flight is that Neil never gets to fly in space again but for the rest of his life becomes an ambassador for the event. Plagued by reporters, he learns that the best way to ensure accurate coverage is to give press conferences rather than one-on-one interviews. Buzz suffers problems with depression and alcohol abuse and it becomes clear that NASA made the right long term choice.

ENDURANCE.

Scott Kelly. Doubleday. ISBN-13: 978-0857524751. Paperback. RRP £8.99

From 1969 to 2017. Most people will have heard of Tim Peake and Chris Hadfield as International Space Station astronauts, but I wonder if you have come across Scott Kelly. Like Neil Armstrong, Scott was a naval aviator and test pilot before joining NASA. He commanded Space Shuttle missions before being tasked with a very unusual mission – spending a year on the ISS whilst his twin brother Mark – also an astronaut - didn't! Essentially Scott has committed himself to a life-long twin study experiment on the effects of one year's exposure to radiation at Low Earth Orbit levels. Just like Neil Armstrong, his mission will have lifelong consequences.

The book details modern US astronaut training – the need to learn Russian and practice on the Soyuz simulators before launching from Baikonur, Kazakhstan. One can read how much the US is dependent on Russia for launches in the post Shuttle era – 2019 should see the first US commercial crew launches for Space X and Boeing.

On board, Scott paints an excellent picture of the day to day running of the ISS. His particular bugbear is the CO_2 scrubber which removes a potentially fatal buildup of CO_2 in the atmosphere. The technology is old and the system (and spare) require a lot of maintenance. Scott dreads having a full crew of 6 on board as the extra CO_2 load puts the system under strain and he suffers headaches as the CO_2 level rises. One wonders how such a system would cope on a long Mars mission!

Overall a very enjoyable and technical account of modern-day astronaut training and living on the edge of space.

PSYCHO VERTICAL.

Andy Kirkpatrick. Arrow. ISBN-13: 978-0099519522. Paperback RRP £10.99.

This is the story of specialist vertical rock climber Andy Kirkpatrick. Dyslexic and with a borderline attention deficit disorder, he struggled at school but always enjoyed art and the occasional climb with his father on local hills. Bored during quiet spells working in a local climbing equipment shop, he started to read the glossy and glamourous climbing magazines and started to dream of ascending some of the world's most forbidding vertical walls.

His first few trips involved scrounging some kit and driving to the Alps with whatever mate was available for a week or so and climbing the first slope to hand. His naivety led him to take on ascents way above his league – sometimes he failed but more often he succeeded and started to make a reputation solo-climbing some of the most difficult routes. The sheer strength of will to spend a week or ten days solo climbing a vertical face is impressive – sleeping in a narrow hammock (Portaledge) on the face, hundreds on feet above the ground secured by just 2 or 3 ropes anchored in turn to a steel wedge inserted into a crack in the rock isn't something I would take on. A 13-day solo ascent of the Reticent Wall on El Capitan in California is detailed.

Two things related to his disabilities help him – firstly, he can visualise the 3-D route of a climb up a face much better than his peers. Secondly, he develops an almost obsessive knowledge of the "kit" involved in rock climbing – hexes, nuts, knife-blades, cams and copperheads.

With success comes sponsorship and the opportunity to write for the very magazines he used to read in the shop. His attempts at writing are initially mocked by his English teacher wife but he perseveres and finds his own style. The desire to climb more brings him into conflict with his wife and young family who worry about his safety. A very enjoyable and well-written book packed with technical info about rock climbing and kit. His struggles with fitness (he can't see the point of training!) and leaving his young family make this a very human and rewarding read.

THE SPARROWHAWK.

Ian Newton. Poyser. ISBN-13: 978-1408138342. OOP – Paperback around £3.00

I was brought up as a city boy but moving to the North West in 1995 has introduced me to many new interests and hobbies. My wife, Caroline, likes feeding finches and small birds and sometimes we would have 30 or 40 birds in the garden at one time. This also tends to attract local apex predators in from woodland about half a mile away – Sparrowhawks. Next door's ginger cat doesn't really count as an apex predator.

These birds are small – a large female is no bigger than a wood pigeon and the male is considerably smaller – during the breeding season, he hunts to bring food for the female who broods and rears the chicks.

I find them quite beautiful and they are extremely agile flyers. We would probably be visited by a Sparrowhawk at least once a day and I try to keep a camera handy to catch some images.

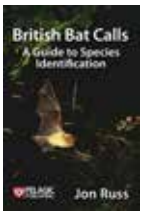
This book is a comprehensive and scientific reference source for all things related to the bird. Originally written in 1986, it was reproduced in 2010 and is regarded as a standard reference text.

The chapter about hunting techniques is quite relevant to my attempts at photography! Usually visits to the garden are *short stay perch hunting* where the Sparrowhawk races in to alight on a fence or tree, scattering and raising prey in the approach. The hawk pauses to scan the surrounding opportunities before moving on – maybe 10 seconds on the perch. *Still hunting* offers the best photo opportunities for me – the hawk keeps very still, hoping unwary prey will come close – I've observed and photographed a male sitting for more than 40 minutes near some bird feeders– just pretending not to be there.

High soaring and swooping – essentially dive bombing (!) is fantastic to watch but impossible to for me to photograph. A specialist book but a great insight into the life of this woodland bird who has become a suburban garden visitor.

Not there for the peanuts. A yearling female Sparrowhawk perched on a bird feeder in the Editor's garden

BRITISH BAT CALLS. A GUIDE TO SPECIES IDENTIFICATION.



Jon Russ. Pelagic Publishing. ISBN 978-1-907807-25-1. Paperback. RRP £31.99

Another garden visitor, this time at twilight from April through to about September. For some years, I had noticed these small and supremely agile flyers appearing each night at dusk just a few feet above my head. Sometimes there might be 6 or 7 in the garden weaving about catching insects and moths, then as the night darkened, they would seem to move further afield.

I didn't really think too much more about it until last year when I decided to buy a bat detector. This converts the high frequency ultrasound used by the bats down to something that is audible to humans – different modes of transformation are used, most simple bat detectors use Heterodyne or Frequency Division modes and produce clicking noises. The gold standard used by serious hobbyists is Time Expansion mode which produces rich, plaintive calls not unlike whale song.

I bought a BatBox Duet (both Heterodyne and FD) recorder and armed with this book, ventured into the garden with the detector set at 47 kHz, the frequency used for communication and hunting by the commonest UK bat, the Pipistrelle. Recordings can be saved and analysed later in software. Bats are really loud at ultrasonic frequencies! The detector could pick them up from several gardens away and I found it fascinating to hear their clicks suddenly go into a high cadence targeting mode as they detected a moth and swooped on their prey.

It appears that we have two common bat species resident in our garden, Common (max = 47kHz) and Soprano Pipistrelles (max = 55kHz).

If you enjoy watching bats then a detector and this book will add to your interest and knowledge.

COLLINS BTO GUIDE TO BRITISH BIRDS.

Paul Sterry and Paul Stancliffe. Collins. ISBN-13: 978-0007551521. Paperback. RRP £19.99

After attracting birds to your garden, you will no doubt wish to identify interesting and rare visitors. This handy A5 paperback manual is supported by the British Trust for Ornithology and conveniently groups birds together into broad families so this book is ideal when you know the object of your attention looks a bit like something else.

When I started, I thought most grey-brown birds were Sparrows but thanks to this guide, I've been able to spot Dunnocks, Lesser Redpolls and Reed Buntings in our garden where I previously thought they were slightly odd-looking Sparrows. What I thought was a very large Chaffinch was a Brambling – much rarer in Northern Ireland and a migrant winter visitor.

Each page contains a small distribution map in the UK so that you can see if a bird is common, rare or never seen in your area. A clock face type graphic gives monthly abundance for migratory birds or when the resident population is supplemented by migrants. Images of males and females aid identification and each bird has a write-up about appearance, voice, habits, abundance and any migratory activity.

Frequently grabbed from the bookshelf when something odd is spotted – highly recommended.

Looks like a Sparrow is actually a male Reed Bunting – Thank you Collins BTO guide!

Game Changers

IRREVERSIBLE ELECTROPORATION TREATMENT OF PANCREATIC ADENOCARCINOMA – A FIRST IN NORTHERN IRELAND

Miss R Wilson, Mr R S McCain, Mr G Kirk, Dr R Sathyanarayana, Dr R Lindsay

Department of Hepatobiliary Surgery and Interventional Radiology, Mater Hospital and Royal Victoria Hospital, Belfast

Pancreatic cancer has a rising incidence in the Western world and is the 5th most common cancer in the UK. Five-year survival rates are reported to be as low as 5%. Thirty percent of patients have unresectable disease due to the disease being locally advanced, and in this group median overall survival varies between 9 to 32 months. Irreversible electroporation (IRE) is a new technique with the potential to improve survival in these patients. This is a soft tissue ablation technique which involves the pulsation of electric currents through the tumour. It does this without significant heating of the targeted tissues and so limits damage to surrounding structured cells such as vessels and ducts. Studies have reported a median overall survival of up to 22-35 months following treatment of localised disease with IRE.

Intraoperative IRE debuted in Northern Ireland in November 2018 at the Mater Hospital, Belfast in a patient who had a locally advanced tumour and a previously failed pancreaticoduodenectomy. IRE probes were placed under ultrasound guidance by interventional radiologists following surgical exposure and the tumour was ablated. The patient made a full recovery and a follow-up CT scan showed a satisfactory ablation zone.

IRE provides another treatment modality for patients who previously would have only had the option of palliative chemotherapy. It is great to see this exciting new treatment is now a possibility for patients with inoperable pancreatic tumours in Northern Ireland.

1. Ansari D, Kristoffersson S, Andersson R, Bergenfeldt M. The role of irreversible electroporation (IRE) for locally advanced pancreatic cancer: a systematic review of safety and efficacy. *Scand J Gastroenterol*. 2017; **52(11)**: 1165-1171. Epub 2017 Jul 7.

2. Holland MM, Bhutiani N, Kruse EJ, Weiss MJ, Christein JD, White RR, et al. A prospective, multi-institution assessment of irreversible electroporation for treatment of locally advanced pancreatic adenocarcinoma: initial outcomes from the AHPBA pancreatic registry. HPB (Oxford). 2019 Feb 5. pii: S1365-182X(19)30005-X

THE NAIL-BED AS A WINDOW TO DISEASE: THE DEVELOPMENT OF A NURSE LED CAPILLAROSCOPY SERVICE.

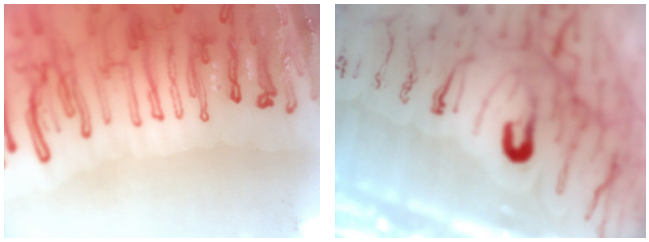
Dr A Elliott, Sister D Torrens, Dr A Pendleton

Department of Rheumatology, Royal Victoria Hospital, Belfast, BT12 6BA

Nail fold capillaroscopy is a non-invasive method of examining the nail-bed of patient's with raynaud's phenomenon (RP) to asses for any abnormalities. The first use of a microscope to visualise the capillary loops was when JC Klaus described his findings around 400 years ago[1]. In the 20th Century the technique has found favour again with physicians describing specific patterns that relate to connective tissue disease. Three to twenty percent of the population have RP[2] and 10% of these patients will have connective tissue disease. These abnormalities include findings of capillary dilatation, bleeding and reduced density. Nail fold capillaroscopy now forms part of the European and American criteria for systemic sclerosis and not only does it allow earlier diagnosis and treatment for those with scleroderma but it can also facilitate discharge of those patients with RP and normal capillaroscopy findings.

Within the Belfast Trust members of the rheumatology service have been able to learn the technique under the tutelage of Professor Cutolo in Italy, an expert in the technique. After a pilot scheme in 2018 a nurse led service has now been established within the Trust. The technique involves a microscope linked with a camera; cedar oil is placed on the nail bed to create a smooth surface. The 2nd-5th fingers are visualised on both hands. Normal capillaries are homogeneously sized, hairpin shaped and regularly arranged, running parallel to skin surface. There is usually between 6 and 14 capillaries per millimetre with 9 being average.

Up to 60% of the normal population have isolated morphological anomalies but key features that are pathological include giant capillaries (>100nmicrometres), extensive areas with loss of capillary density and recurrent haemorrhages and neoangiogenesis. These changes are specific for systemic sclerosis but non-specific abnormalities can also be seen in dermatomyositis, mixed connective tissue disease and SLE.



Images from Belfast Trust Capillaroscopy clinic (Patient permission granted) 200x Magnification:

Image Left - Normal Capillaroscopy with hairpin capillaries and normal density.

Image Right - Abnormal Image in Systemic Sclerosis with a Giant capillary and loss of Capillary density.

1. Chojnowski, Marek M et al. "Capillaroscopy - a role in modern rheumatology" *Reumatologia*. 2016; **54 (2)**: 67-72.

2. Goundry Beth et al. "Diagnosis and management of Raynaud's phenomenon" British Medical Journal. 2012; **344**: e289.

HYPERTENSION TARGETS - MOVING THE GOALPOSTS AGAIN!

Dr N Sharkey, Prof P Maxwell

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

Hypertension, defined as blood pressure ≥140/90 mmHg, is the leading risk factor for mortality and disability-adjusted life years.[1] To promote earlier intervention and reduce the risk of complications that occur at lower blood pressure levels recent US guidelines have reduced the threshold for diagnosis to ≥130/80 mmHg (Stage 1 Hypertension)[2]. Intervention includes lifestyle advice and risk modification. They advocate that only those with Stage 1 Hypertension with a previous cardiac event or a 10 year atherosclerotic cardiovascular risk of 10% or higher should be commenced on pharmacological treatment. In the UK, NICE https://www.nice.org.uk/guidance/indevelopment/gid-ng10054/documents are also advocating for similar changes to hypertension guidelines.

It is predicted that half the US population will have hypertension with the new guidelines (compared to one third at present). The largest increase in prevalence will be amongst younger adults (doubling in women <45 years old and tripling in men <45 years old).[3] There is no comparable UK data available yet.

Guideline authors stressed that increasing the prevalence of hypertension will heighten awareness, promote healthy lifestyles and reduce cardiovascular and renal risks. They argue that medication use will only rise modestly, but will be more focused and aggressive in those deemed to have established cardiovascular risk.

The defining blood pressure levels have been lowered but arguably the approach to hypertension is changing too. Reference is made to "resource constrained populations" and the need to consider socio-economic context when developing management strategies. In instances where more than one medication is required, preference should be given to combination formulations in order to promote patient adherence. Telehealth and mobile phone communication are cited as ways to promote health literacy.

Publication of the SPRINT study potentially favours more aggressive treatment aims for hypertension, although not without considerable risk of adverse events from medications.[4] There are also broader questions to ask. Are we too quick to deal with numbers instead of real people when it comes to treatment strategies and how can we improve the experience of living, not just by reducing mortality?

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*. 2012; **380(9859)**: 2224-60.

2. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2017; **13**: 24430.

3. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright Jr JT, et al. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Journal of the American College of Cardiology*. 2018; **71(2)**: 109-18.

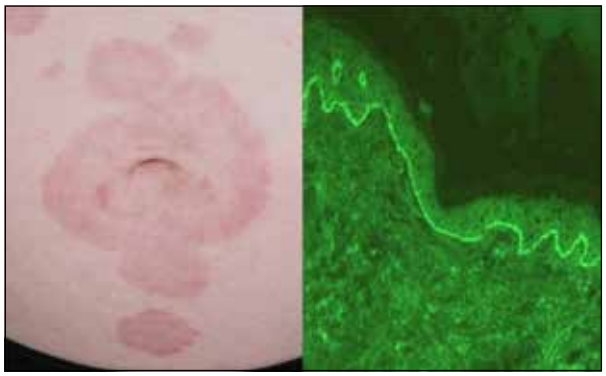
4. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clinical Trials*. 2014; **11(5)**: 532-46.

Ulster Med J 2019;**88(2):**89-90

Curiositas

UNDERGRADUATE QUIZ

This image shows the abdomen of a pregnant woman and a specialist dermato-pathological investigation.

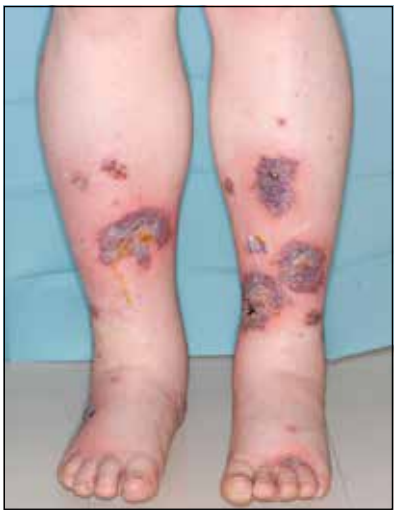


1. What is the diagnosis?
2. What investigations are necessary?
3. What is the management of this condition?

J. Moradzadeh (Medical student, Queen's University Belfast), W. Abdelrahman (Specialty registrar, Department of Dermatology, Belfast Health and Social Care Trust), D. O'Kane (Consultant Dermatologist, Department of Dermatology, Belfast Health and Social Care Trust).

POSTGRADUATE QUIZ

A patient presents with the following leg lesions:



1. What is the diagnosis and what are the causes?
2. What investigations are necessary?
3. What is the management of this condition?

R. Dawson (Core Trainee), W. Abdelrahman (Specialty Registrar), K. McKenna (Consultant) (Department of Dermatology, Belfast Health and Social Care Trust).

GENERAL PRACTICE QUIZ

Blood is taken from a patient at your surgery in the late afternoon. It is centrifuged at the practice and refrigerated overnight. You note the following appearance the next morning, and later that day, laboratory staff telephone to report that the serum sodium is low at 123 mmol/L (reference range 136-145 mmol/L).

1. What is unusual about the appearance of the sample?
2. What is the likely cause of the hyponatraemia?
3. What additional test could the laboratory staff perform on the sample that would offer reassurance in terms of the hyponatraemia?

P. Hamilton (Clinical Lecturer, Centre for Medical Education, Queen's University Belfast and Honorary Consultant in Chemical Pathology, Department of Clinical Biochemistry, Belfast Health and Social Care Trust).

AND FINALLY…

Image credit*: By Jason Hollinger, CC BY 2.0, https://commons.wikimedia.org/w/index.php?curid=9693284*

1. On which tree would this foliage and fruit be found?
2. What is its contribution to modern medicine?

P. Hamilton (Clinical Lecturer, Centre for Medical Education, Queen's University Belfast and Honorary Consultant in Chemical Pathology, Department of Clinical Biochemistry, Belfast Health and Social Care Trust).

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. The appearance of a pruritic, urticated rash during pregnancy that involves peri-umbilical skin is suggestive of pemphigoid gestationis. This is an autoimmune pregnancy-associated skin disease characterised by a vesiculo-bullous eruption typically involving the periumbilical area initially but becoming more widespread. It occasionally involves the palms and soles but typically spares the face and mucous membranes. It is most common during the second and third trimesters. In the majority of cases the condition will resolve spontaneously after delivery. 75% of patients who notice an improvement during the end of pregnancy will usually experience a post-partum flare. Another differential to consider is polymorphic eruption of pregnancy (also known as pruritic, urticarial, papules and plaques of pregnancy (PUPPP)); this however, typically involves striae and spares the peri-umbilical area. Complications are rare but include premature delivery and transient blistering of the newborn. There is also a high incidence of maternal Graves' disease.

2. Skin biopsy for histology and direct immunofluorescence are essential to confirm the diagnosis along with serum testing for indirect immunofluorescence. One biopsy is taken from lesional (involved) skin for histological evaluation and typically demonstrates sub-epidermal blisters with an eosinophil-predominant infiltrate. Another skin biopsy from peri-lesional (uninvolved) skin is analysed by direct immunofluorescence, which typically demonstrates a linear band of C3 deposition along the basement membrane zone. Around 25-50% of patients may also demonstrate IgG. Antibodies can also be detected in the patient's serum (indirect immunofluorescence). These histological and immunofluorescence findings mirror those seen in bullous pemphigoid.

3. Topical corticosteroids and antihistamines are first-line agents to treat pemphigoid gestationis. For recalcitrant disease, systemic corticosteroids or steroid-sparing agents such as azathioprine or ciclosporin may be required depending on whether the pregnancy is ongoing as this may limit use of certain agents due to their teratogenicity.

J. Moradzadeh (Medical student, Queen's University Belfast), W. Abdelrahman (Specialty registrar, Department of Dermatology, Belfast Health and Social Care Trust), D. O'Kane (Consultant Dermatologist, Department of Dermatology, Belfast Health and Social Care Trust).

POSTGRADUATE QUIZ

1. The appearance of blisters on a background of purpura is in keeping with bullous vasculitis. In over 50 % of cases the cause is unknown. Infection accounts for 20% of cases, and it is important to test for hepatitis in adults or Henoch-Schönlein Purpura in children. Medications may also cause bullous vasculitis, most commonly beta-lactam antibiotics, NSAIDs and sulphonamides. Connective tissue disorders can be associated with bullous vasculitis, particularly seropositive patients with longstanding nodular disease. 5% of cases are attributed to malignancy, usually of the lymphoproliferative type such as multiple myeloma, Hodgkins disease, mycosis fungoides and adult T cell lymphoma. Inflammatory bowel disease is also associated.

2. In any patient with cutaneous vasculitis it is important to rule out systemic involvement (p/c ANCA) as this determines whether management is targeted at skin disease only or whether further specialist input is required. Assessing urinalysis is paramount specifically looking for proteinuria and haematuria. If abnormal, this may indicate renal involvement. The presence of haematuria warrants the need for assessment of the presence of red cell casts. In most cases a diagnosis of vasculitis can be made on clinical grounds without the need for a biopsy. Doing a biopsy however, doesn't explain what caused the vasculitis. The classic histological features of vasculitis are a perivascular inflammatory infiltrate composed mainly of neutrophils, extravasated erythrocytes and fibrinoid necrosis of the vessels with fibrin extravasation. A variable number of eosinophils can be seen and if present in high number may suggest a drug related aetiology. Direct immunofluorescence may be requested to look for deposits of immunoglobulin in vessel walls, for example IgA in HSP and deposition of IgG and C3 component of complement in Lupus. It is not necessary, however, to demonstrate immune complexes in order to make a diagnosis of vasculitis.

3. The management of vasculitis depends on whether it is limited to skin only or whether there is systemic involvement. For localised disease, potent topical corticosteroid therapy can be used to ease symptoms of burning or itch. If there is extensive cutaneous involvement or no response to topical therapy, a reducing course of oral corticosteroid therapy may be considered. If patients on reducing oral steroids find that their disease recurs then steroid-sparing agents are considered such as dapsone, azathioprine, mycophenolate mofetil or methotrexate.

R. Dawson (Core Trainee), W. Abdelrahman (Specialty Registrar), K. McKenna (Consultant) (Department of Dermatology,, Belfast Health and Social Care Trust.

UNDERGRADUATE QUIZ

1. Three layers are visible in the sample. From top to bottom these are serum, separator gel layer (present in the tube) and blood clot. Instead of the usual pale yellow appearance, the serum of this patient's blood is turbid reflecting gross lipaemia.

2. In the presence of severe hypertriglycerideaemia, modern clinical chemistry analysers can report hyponatraemia even if the true serum concentration is normal. This is so-called 'pseudohyponatraemia.'

3. The finding of a normal serum osmolality would provide evidence that the hyponatraemia was artefactual.

P. Hamilton (Clinical Lecturer, Centre for Medical Education, Queen's University Belfast and Honorary Consultant in Chemical Pathology, Department of Clinical Biochemistry, Belfast Health and Social Care Trust).

AND FINALLY…

1. The photograph shows the Pacific Yew tree (*Taxus brevifola).*

2. Paclitaxel, a chemotherapy drug, was originally isolated from the bark of this tree. It has been used to treat a variety of types of cancer. Other drugs in the same class – 'taxanes' – are now synthesized synthetically.

P. Hamilton (Clinical Lecturer, Centre for Medical Education, Queen's University Belfast and Honorary Consultant in Chemical Pathology, Department of Clinical Biochemistry, Belfast Health and Social Care Trust).

Ulster Med J 2019;**88(2):**91-97

Grand Rounds

Radiation Oncology: A Clinical Update from The North West Cancer Centre.

Walls GM[1,2], Lyons C[1], Jellett LJ[1], Evans R[1], Bedair A[1], Brady D[1], McLaughlin LM[1], Reilly E[1], Reilly A[1], McAleer JJ[3,4], Stewart DP[1].

Accepted: 1st March 2019
Provenance: externally peer reviewed

HISTORY OF THE NORTH WEST CANCER CENTRE

Following an announcement in 2008 from Mr Michael McGimpsey, Minister for Health, Social Services and Public Safety, a business case was developed for a new Cancer Centre based at Altnagelvin Area Hospital. It was designed to provide radiotherapy and chemotherapy treatment for a population of around 500,000 in the North and West of Northern Ireland. The Irish government agreed to provide revenue and capital funding to facilitate the provision of radiotherapy-only services for the population of most of County Donegal. In May 2011, Mr Edwin Poots, then Minister for Health, Social Services and Public Safety, approved funding for the North-West Cancer Centre (NWCC), including this cross-border service. The plan represented a successful collaboration between the governments of Northern Ireland and the Republic of Ireland.

Fig 1. The North West Cancer Centre, Altnagelvin Area Hospital

The Centre is the second radiotherapy centre in Northern Ireland and is designed to address an anticipated increase in cancer incidence. It has also improved access to cancer treatment for a population which previously had to travel 2-4 hours for radiotherapy in Belfast, Galway or Dublin. The NWCC has three linear accelerators (Linacs) for delivering radiotherapy and space for a fourth. Curative and palliative treatments are offered and emergency treatment is available. From the outset, emerging technical radiotherapy planning techniques have been incorporated into the NWCC. It is one of the few UK centres to integrate MRI-based simulation, image artefact removal methods and iterative cone-beam CT scanning to visualize anatomy on the Linac. These techniques facilitate safer delivery of radiotherapy by reducing potential toxicity and maximising tumour control. Less common tumours are better managed centrally at the regional Cancer Centre at Belfast City Hospital - contribution of NWCC to managing these tumours will be modest.

Currently, curative-intent radiotherapy is available for patients with cancer of the breast, prostate, bladder, rectum, head/neck and haematological systems. Local patients treated in Belfast who have unscheduled admissions at NWCC receive integrated care, in part due to regional electronic Oncology records. Systemic therapies such as chemotherapy and immunotherapy are delivered in the same building and a new Macmillan Centre for holistic and supportive care has been located nearby. An active clinical trials portfolio is planned. Working together in multi-professional teams is facilitated by grouped office space for physicians from Clinical and Medical Oncology and Palliative Medicine, medical physics and radiographers, administrative and managerial staff. Over 200 staff are now employed at the Centre, and the building's architects won national and international prizes for its design (Figure 1). On 9th May 2017, the NWCC was officially opened by His Royal Highness, Prince Charles and Camilla, Duchess of Cornwall.

INTRODUCTION TO RADIOTHERAPY

Radiotherapy is the use of ionising radiation as treatment for benign and malignant disease. Approximately 40% of patients diagnosed with cancer will receive radiotherapy during the course of their illness.[1] Increasing cancer incidence, improved understanding of tumour biology and advances in engineering have led to improvement in radiotherapy treatment in recent decades. The complex therapies available have contributed to improved survival and quality of life and have enabled

[1]The North West Cancer Centre, Western Health & Social Care Trust
[2]Centre for Cancer Research & Cell Biology, Queen's University Belfast
[3]Cancer Centre Belfast City Hospital, Belfast Health & Social Care Trust

Correspondence to Dr Gerard Walls

E-mail: g.walls@qub.ac.uk

Clinical Oncologists to reduce early and late radiation side-effects. This article is intended to update clinical colleagues on the optimal radiotherapy management of some common cancers.

GENERAL RADIOTHERAPY PRINCIPLES

Mode of Action

"Ionising radiation" refers to moving particles which interact with atoms to cause liberation of electrons. In radiotherapy, the resulting chemical reactions induce lethal damage in cells by a variety of mechanisms (Table 1). The underlying principle is that cancer cells are less effective in repairing damage than normal cells and are therefore more susceptible to radiation. The dose of radiation required to kill all the tumour cells in a cancer would cause intolerable toxicity if given as a single treatment. This is mitigated by dividing the total dose into smaller (often daily) treatments (fractions), over a period of weeks. This causes cumulative damage to the tumour, whilst allowing the surrounding normal tissue time to repair. Several different types of ionising radiation are used to treat malignancy, although photons and electrons predominate in routine clinical practice. Radiation is usually delivered to tumours from outside the body (external-beam radiotherapy; EBRT), but sealed and unsealed radioactive sources may also be directly applied to a tumour inside the body (brachytherapy).

Table 1

Types of cellular damage[2]

Type of Damage	Frequency (per cell per Gray)
DNA-protein cross-links	1000
Altered DNA bases	3000
Single-strand DNA breaks	1000
Double-strand DNA breaks	20-40

Radiotherapy Planning

Photon (X-ray) beams are generated by a Linac (Figure 2) and directed toward the target in the patient as defined by the Clinical Oncologist. Cross-sectional imaging from a dedicated non-diagnostic CT scanner is required for accurate identification of this target in advance. To reduce the risk of causing damage in adjacent organs, careful planning is given to the direction, shape and intensity of the beams. Diagnostic imaging and, increasingly, planning MRI scans are carried out in the treatment position to assist definition of the target volume(s) and organs at risk (OARs). This process, known as radiotherapy planning, usually takes 2-3 weeks; however, the planning time required varies with the treatment indication and complexity (Table 2).

Delivery of Radiotherapy

When a treatment plan has been finalised, therapeutic radiographers coordinate the delivery of radiotherapy, with input from clinicians, medical physicists and clinical engineers as required. A session of radiotherapy takes approximately 15 minutes to deliver. Replicating the treatment planning position takes several minutes, and delivering the fraction usually takes up to five minutes. The delivery process does not involve undue noise, light, heat or pain. Patients do not pose any risk as a radiation hazard and are unlikely to experience significant immediate side-effects, and treatment is usually delivered on an outpatient basis.

Dose of Radiotherapy

Until recently, most patients treated with potentially curative (radical) radiotherapy for cancer were treated with conventional dose-fractionation schedules, delivering a dose of 1.8-2Gy daily over many weeks. Recently, there has been a move towards shorter, hypo fractionated schedules that allow delivery of a biologically equivalent dose of radiation over a shorter period. This, in a more pronounced form, is the basis of stereotactic ablative body radiotherapy (SABR), which is increasingly used in the treatment of early lung and prostate cancer and in the treatment of oligometastatic disease. Palliative treatments to improve symptoms are delivered as a limited number of fractions of radiotherapy, with larger daily doses than conventional treatment (although not as large as SABR).

Table 2

Indications for radiotherapy

Indication	Intention of Treatment
Radical	To eradicate potentially curable cancer
Adjuvant	To reduce risk of locoregional recurrence after radical surgery
Neoadjuvant	To reduce tumour volume prior to radical surgery
Palliative	To reduce symptoms of incurable cancer (metastatic or locally advanced)
Emergency	To prevent acute clinical deterioration, usually from an incurable cancer

The risk of late toxicity in normal organs can be reduced by optimising the radiation dose distribution using two advanced technologies:

Linacs capable of intensity-modulated radiotherapy (IMRT) produce beams of X-rays that vary in shape dynamically whilst X-rays are being delivered. The most modern Linacs produce IMRT from hundreds of angles in rapid succession in a single circular plane, in a technique called volumetric arc therapy (VMAT).

Imaging hardware built into modern Linacs is used to verify target location relative to the original treatment plan each day, known as image-guided radiotherapy (IGRT). High-quality patient alignment on the treatment couch by radiographers means the lowest radiation exposure possible is received by adjacent organs, as modelled using complex software

during the planning process. When satisfied with the patients' position using measurements and wall-mounted lasers, manual and automated cone beam CT imaging processes confirm the target location with high precision.

Fig2. A modern linear accelerator (Model shown is Varian TrueBeam©)

Unlike systemic anti-cancer therapies, radiotherapy side-effects are restricted to the anatomical region being irradiated - except for fatigue. The early side-effects of treatment (onset within 3 months of completing treatment) tend to occur towards the end of a course of radiotherapy and can continue for weeks to a few months. Clinicians regularly assess radiotherapy reactions during and after treatment and tailor supportive treatments accordingly. Guidance is available online from the NI Cancer Network (NICAN) for other doctors who encounter the early side-effects. [3] Late side-effects of radiotherapy (apparent after three months to many years) are identified during later follow-up. Although they are becoming less frequent as techniques improve, sometimes side-effects occur many years after treatment (e.g. valvular heart disease, myelitis, urethral stricture and radiation-induced malignancy). As more people are cured of their cancer this is assuming greater significance.

PROSTATE CANCER TREATMENT PRINCIPLES

Background

The management of localised prostate cancer with radiotherapy is based on the risk of relapse, as inferred from histopathology, tumour markers and imaging – Gleason grade, baseline PSA and MRI of pelvis. [4] As well as surgical and conservative options, localised disease is considered for radiotherapy to the prostate gland. For many patients, radical radiotherapy provides cure rates comparable to prostatectomy, in excess of 80%. [5] Of note, the entire prostate gland is targeted due to the malignant 'field change' seen in the prostate. Alternatives to radiotherapy may include active surveillance, radical (robotic) prostatectomy and brachytherapy.

Conventionally, prostate radiotherapy comprised 7-8 weeks of daily treatment, totalling a dose of 74-78Gy. Clinical trials have recently introduced shorter equivalent, hypo-fractionated schedules of 60Gy over a period of 4 weeks.[6,7,8] In selected high-risk cases, 78Gy delivered over 8 weeks remains the preferred strategy. Prophylactic treatment of the at-risk pelvic lymph nodes may also be offered.[7]

The common early side-effects of treatment are fatigue, urinary frequency, nocturia, dysuria, diarrhoea and rectal irritation. Later side-effects include altered bowel habit, rectal bleeding, and sexual dysfunction. Pelvic fistulae are rarely seen. Patients with intermediate- and high-risk localised prostate cancer treated with radical radiotherapy may also be offered concomitant androgen-deprivation therapy, which also affects sexual function (in addition to other potential toxicities) and can be employed in the both neoadjuvant and adjuvant settings.

Example Case

Mr A, 63 years old, was diagnosed with intermediate-risk, localised prostate adenocarcinoma (Gleason 3+4, T2a N0 M0, initial PSA 9ng/ml). Apart from mild lower urinary tract symptoms, his medical history was limited to bilateral total hip replacements.

Referral

The Urologist presented his case at the weekly cancer multidisciplinary meeting (MDM), and Mr A was seen by the Clinical Oncologist one week later. After discussion of the treatment options, the patient expressed a preference for EBRT (60Gy in 20 fractions over 4 weeks) rather than implanted radioactive seeds or surgery and LHRH agonist subcutaneous implants were arranged via his family doctor.

Radiotherapy Clinic

Mr A visited the planning clinic 8 weeks later, allowing time for the cytostatic effects of ADT to develop. PSA was satisfactory at <0.01ng/ml. The rationale for radiotherapy was discussed in detail with Mr A, illustrating this on the radiology system with the patient's own baseline anatomy. Baseline symptom assessment was documented and supportive medications were prescribed. He was counselled on bladder-filling and bowel preparation by a therapeutic radiographer working in the same clinic.

Planning Scan

Mr A had a CT planning scan later that afternoon, following a first attempt at bladder and bowel preparation. This was performed in the radiotherapy delivery position with the patient supine and flat on the scanner assisted by head and knee rests, and without IV contrast (lymph nodes not for treatment). Automated artefact-removal techniques removed metallic hip prostheses artefact (Figure 3), an increasingly important aid, given the aging demographic of the population diagnosed with cancer. Mr A subsequently had MRI imaging carried out in the treatment position which was co-registered with his planning CT facilitating optimal interpretation of the pelvic anatomy (Figure 4, not Mr A).

Treatment Planning

The Oncologist delineated the target volumes and OARs on tablets (Figure 5) using the fused images. Additional

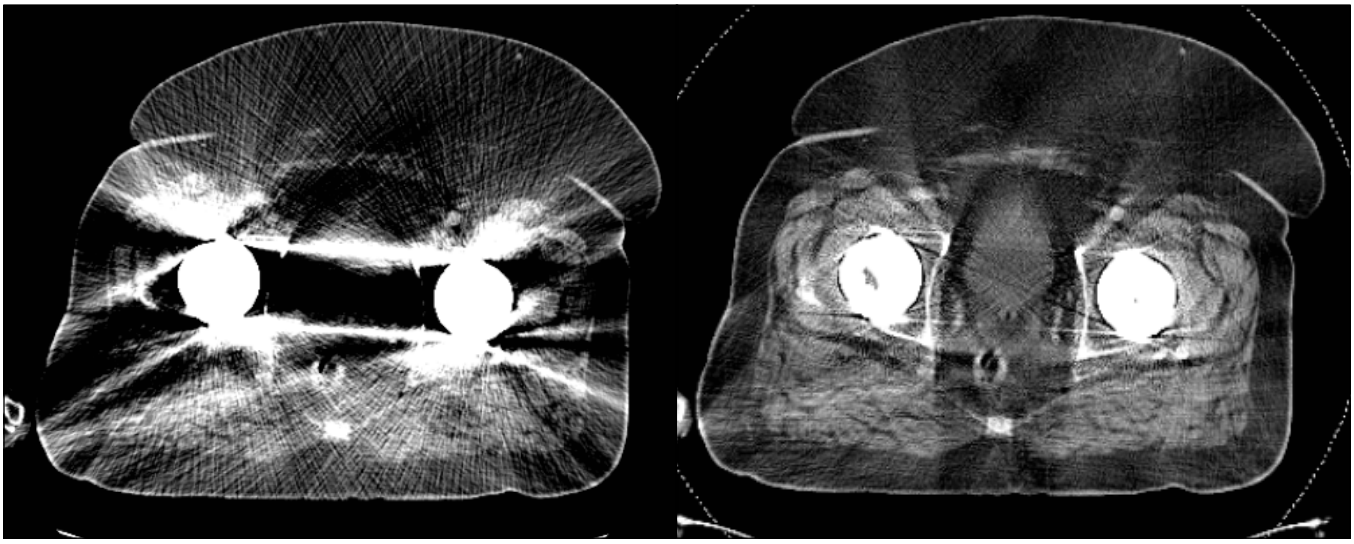


Fig 3. Axial appearances of the pelvis before (left) and after (right) the dual-energy CT artefact removal technique, with significantly clearer images of the bladder and bowel when artefact from the metallic hips is removed.

diagnostic-quality monitors at the workstation enabled the clinician to simultaneously refer to a planning atlas and the patient's electronic medical record. The physics team determined the optimal beam arrangements to achieve the dose prescribed by the Oncologist in their shared workspace. Finalised plans were forwarded to the treatment radiographers.

Treatment Delivery

The location of the prostate, between the bladder and the rectum, prevents complete sparing of normal organ irradiation. Standardisation of bladder filling and rectal emptying prior to treatment allows more accurate targeting the prostate and reduces potential side-effects. Integrated cone-beam CT scanning carried out immediately prior to each treatment facilitated daily review of bladder, rectum and prostate size and position. [9] Within 40 minutes of arriving in the building, Mr A had usually completed his VMAT-delivered fraction. He was reviewed by the treating team weekly to assess symptoms and early toxicity. Clinical documentation and onward referrals to radiotherapy nurses or physiotherapists was completed electronically, as were discharge letters to the family doctor.

Follow-up

Six weeks following treatment, Mr A was reviewed in the radiotherapy department. The urology team were updated regularly and Mr. A remained on regular follow-up with the Oncology team. One year after completion of radical radiotherapy, Mr A stopped androgen deprivation therapy and reported no significant sequelae from radiotherapy and had maintained an excellent biochemical response to treatment.

BREAST CANCER TREATMENT PRINCIPLES

Background

Wide local excision and post-operative whole-breast radiotherapy is equivalent to mastectomy for early breast cancer in terms of local recurrence. [10] Adjuvant radiotherapy in this setting aims to kill any undetectable malignant cells that were not removed at surgery. If clinicopathological features justify post-operative chemotherapy, this is given prior to radiotherapy.

Historically, whole-breast radiotherapy comprised 5 weeks of daily treatment, totalling a dose of 50Gy. Clinical trials have introduced hypo fractionated schedules of 40Gy in 15 fractions. [11] In selected cases, an additional 'boost' dose is given to the tumour bed. [12] Similarly, ipsilateral supraclavicular fossa (SCF), internal mammary chain and post-mastectomy chest wall irradiation are reserved for specific higher-risk scenarios.

The common early side-effects of treatment are fatigue, skin reaction and mild breast swelling. The late side-effects include altered breast texture, skin changes (telangiectasia and discolouration), pneumonitis and cardiac toxicity (left-sided cancers).

Example Case

Mrs B was a 61-year-old post-menopausal woman with a symptomatic left-sided breast cancer (T1 N2 M0, grade II ductal cancer, (ER-positive, PR-positive HER2-negative), who was referred for consideration of adjuvant therapy following wide local excision and axillary node clearance.

Referral

The breast MDM consensus was that chemotherapy, radiotherapy and endocrine therapy should be offered to reduce the risk of recurrence. The rationale for these adjuvant therapies was discussed in depth when Mrs B was seen jointly by the Oncologist and Breast Care Nurse.

Radiotherapy Clinic/Planning Scan

Mrs B attended radiotherapy planning clinic just before her fifth chemotherapy cycle. Having provided written consent,

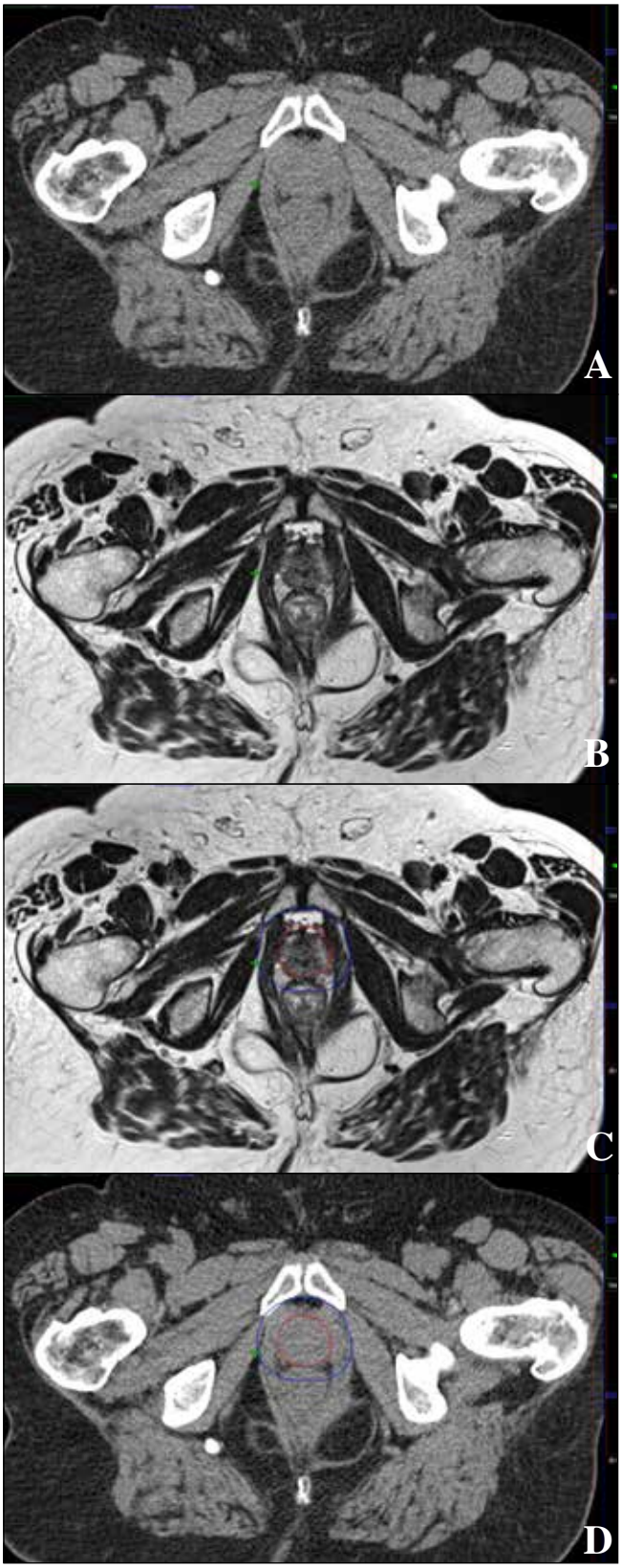


Fig 4. poorly visualised pelvic anatomy on CT scans (A) such as target organs like prostate (red) plus a margin of safety (blue) and organs at risk such as bowel (purple) may be better visualised on MRI images (B) so Oncologists use the latter to define organs (C) and transfer these to the CT images using CT-MRI co-registration (D).

three pin-point reference tattoos were applied (over the sternum and in the mid-axillary line on each side) to aid positioning during treatment, after her planning CT scan.

Treatment Planning

All breast radiotherapy in the NWCC is planned based on individually delineated target volumes, which is a significant enhancement over our earlier practice of conventional field-based planning. The Oncologist delineated the breast and nodal volumes with reference to international contouring guidelines. A Consultant Radiologist with a special interest in breast radiology joined the Oncologist to agree the defined SCF volume prior to generation of the optimal individualised treatment plan.

Fig 5. Contouring workstation

Treatment Delivery

Treatment began 3 weeks after her final chemotherapy cycle. Each day the patient was placed in the treatment position and imaged immediately prior to each fraction. Automated image matching was performed using bone landmarks and surgical clips (in the tumour bed), to optimise alignment. In-vivo dosimetry allowed verification of the delivered dose. Mrs B reported no side-effects and she tolerated her endocrine treatment without difficulty.

Follow-up

At twelve weeks following treatment completion Mrs B had no evidence of radiotherapy-related toxicity and proceeded to the self-directed aftercare programme.

LUNG CANCER TREATMENT PRINCIPLES

Background

Radical radiotherapy is offered to patients diagnosed with stage I-III non-small cell lung cancer (NSCLC) or limited stage small cell lung cancer (SCLC) who have a good performance status. Thoracic radiotherapy is the treatment of choice for patients who decline, or are unsuitable for surgery and is combined with concurrent chemotherapy if possible. [13]followed by central collection, checking, and reanalysis of updated individual patient data. Results from trials were

combined using the stratified log-rank test to calculate pooled hazard ratios (HRs Advances such as stereotactic ablative radiotherapy (SABR) have comparable results to surgery for stage I lung cancer. [14] Radiotherapy can also control symptoms and disease progression in incurable lung cancer, which comprises over half of new cases of lung cancer diagnosed in Northern Ireland. [15] Radiotherapy may also be delivered to the area of the chest where a tumour was resected (adjuvant radiotherapy) or to the whole brain prophylactically.

Lung radiotherapy schedules vary greatly, lasting between 2 and 6 weeks in the radical setting. A smaller number of fractions (eg one to 13 daily treatments) is particularly effective for palliation of haemoptysis, pain, cough or dyspnoea. SABR is reserved for smaller and more peripherally located tumours (eg 54-55Gy in 3-5 fractions).

The common early side-effects of lung radiotherapy include fatigue, skin reaction, oesophagitis and cough, with some patients experiencing breathlessness due to pneumonitis after 3-4 months. Less common, late side-effects include long-term breathlessness (due to lung fibrosis), cardiac toxicity and, rarely, spinal cord damage (myelitis). Late side-effects are rare with the dose-fractionation schedules used in palliative radiotherapy.

Example Case

Mr C (67 years old) was diagnosed with a stage IIIA adenocarcinoma of the right lung following investigation of new dyspnoea and weight loss of 6 kg. Molecular tests for EGFR mutation, ALK rearrangement and PDL-1 expression were negative.

Referral

Following discussion between the Oncologists and Surgeons at the central lung MDM, radical chemoradiotherapy was advised. He was seen by the Clinical Oncologist, who discussed the diagnosis, staging and treatment options. The patient consented to 55Gy in 20 fractions over four weeks to commence with cycle 3 of chemotherapy.

Planning Scan

Having embarked on chemotherapy, Mr C proceeded to radiotherapy planning. A 4D-planning CT scan was carried out. This CT scan uses motion-tracking technology to track the tumour in all phases of the respiratory cycle.

Treatment Planning

The lung tumour target volume was delineated in all phases of respiration. Taking account of organ motion during each respiratory cycle allows more accurate targeting of the tumour and minimises the treated volume. The treatment plan was approved at peer review within two weeks of the planning scan.

Treatment Delivery

Cone-beam CT was performed daily to facilitate visualisation of the tumour and appropriate matching of the plan. Accurate localisation of the tumour increases adherence to the prospectively modelled doses, including the OARs such as the oesophagus, which is particularly important in patients with baseline weight loss. Progressive improvement of tumour-associated consolidation during treatment led to increasing difficulty in matching and prompted re-planning, which was achieved within one week. During treatment, Mr C reported only mild oesophagitis responsive to sucralfate and a proton pump inhibitor.

Follow-up

At subsequent appointments there were no symptoms of radiation-induced toxicity, and follow-up imaging demonstrated excellent clinical response.

CONCLUSIONS

Radiotherapy was first delivered at NWCC on 30th November 2016. The establishment of the North West Cancer Centre has brought the latest advances in radiotherapy to its population, previously disadvantaged by distance from established centres, for the treatment of genitourinary, breast, lower gastrointestinal, lung head/neck cancer and haematological cancers. At the time of publication, almost 1500 patients have received radiotherapy at NWCC.

Radiotherapy is a fast-changing field of medicine, and there has been much development over the last decade; treatment planning and delivery is becoming more complex and the absolute numbers of patients receiving radical and palliative treatment increases. The ultimate aim of treatment is that these advances translate into tangible improvements in overall survival and quality of life for patients living with – and beyond – cancer.

REFERENCES

1. Ahmad SS, Duke S, Jena R, Williams M V, Burnet NG. Advances in radiotherapy. *BMJ*. 2012;**345**:e7765.
2. Joiner MC, van der Kogel A. Basic clinical radiobiology. 4th ed. Abingdon, Oxon: CRC Press; 2009.
3. Northern Ireland Cancer Network (NICAN). Guidance for patients who become ill whilst receiving radiotherapy or within 6 weeks of radiotherapy. Belfast: NICaN; 2014. Available from: http://nican.hscni.net/content/guidance-management-patients-who-become-ill-whilst-receiving-radiotherapy-or-within-6-weeks. Last accessed March 2019.
4. D'Amico A, Whittington R, Malkowicz S, Schultz D, Blank K, Broderick GA, *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;**280(11)**:969–74.
5. Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, *et al*. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys*. 2004;**58(1)**:25–33.
6. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, *et al*. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;**17(8)**:1047–60.

7. Roach M, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, *et al*. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 1994;**28(1)**:33–7.

8. Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, *et al*. Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. *Radiother Oncol*. 2007;**84(2)**:121–7.

9. de Crevoisier R, Bayar MA, Pommier P, Muracciole X, Pêne F, Dudouet P, et al. Daily versus weekly prostate cancer image-guided radiotherapy: Phase 3 multicenter randomized trial. *Int J Radiat Oncol Biol Phys*. 2018; **102(5)**:1420-29.

10. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, *et al*. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;**347(16)**:1233–41.

11. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, *et al*. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. 2008; **371(9618)**: 1098-107.

12. Bartelink H, Horiot JC, Poortmans P, Struikmans H, van den Bogaert W, Barillot I, *et al*. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med*. 2001;**345(19)**:1378–87.

13. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, *et al*. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non–small-cell lung cancer. *J Clin Oncol*. 2010;**28(13)**:2181–90.

14. Bryant AK, Mundt RC, Sandhu AP, Urbanic JJ, Sharabi AB, Gupta S, *et al*. Stereotactic body radiation therapy versus surgery for early lung cancer among US veterans. *Ann Thorac Surg*. 2018;**105(2)**:425–31.

15. Queen's University Belfast: Research Centres: Northern Ireland Cancer Registry. Cancer in Northern Ireland 2015: Lung Cancer. Belfast; NI Cancer Registry: 2016. Available from: http://www.qub.ac.uk/research-centres/nicr/FileStore/OfficialStats2015/FACTSHEETS/Filetoupload,746050,en.pdf#search=lung%20cancer. Last accessed March 2019.

Ulster Med J 2019;**88(2):**98-101

Clinical Paper

Helicopter Emergency Medical Service (HEMS) in Northern Ireland: An Analysis of the First 100 Cases

Emma Boylan, Russell McLaughlin, Glenn O'Rorke, Robert Thorpe, Darren Monaghan

Accepted 3rd February 2019
Provenance: externally peer reviewed

Abstract:

Introduction: Northern Ireland (N.I) is the most recent region within the UK to establish a helicopter emergency medical service (HEMS) which became operational in July 2017.[1] We present descriptive data and discussion about the first 100 cases managed by this new trauma service. Some call-outs involved multiple cases. The data covers a period of 130 days from late July 2018 to late November 2018.

Methods: Information from all HEMS cases was captured manually and records retained for governance purposes. For the purpose of this paper we conducted a hand trawl of records relating to the first 100 cases managed by the HEMS team. Data was entered into a database for the purpose of analysis. Measured data included: location of incident, mode of dispatch, patient demographics, mechanism of injury, interventions provided, destination (hospital) and outcome at 24hours.

Results: Patients were treated in all counties of N.I., most frequently in Co. Antrim. 83% of patients were male. Age range was between 3 years old and 97 years old. The most common mechanism of injury was road traffic collision; others included fall from height, animal attacks, electrocution, drowning and burns. All cases were assessed by a consultant and paramedic. Interventions included: pre hospital anaesthesia using rapid sequence intubation (RSI), thoracostomies, enhanced drug therapy (EDT) for pain management, procedural sedation or fracture reduction (FR) and administration of hypertonic saline (HTS). Thirteen patients were declared deceased on scene. Five required no further transportation (medically or self-discharged). Of the remainder, 90% were alive at 24 hours.

Discussion: There has been considerable learning in the early stages and analysis of this data has indicated:

Since starting the service we have provided critical interventions to a wide variety of age groups throughout NI. Gender profile, mechanism of injury, vulnerable road users (defined as motorcyclists, pedal cyclists and pedestrians) and RSI rates are comparable to data published in the UK. [2,3,4,5] The Royal Victoria Hospital (RVH) emergency department (ED) was the receiving unit for most patients attended by HEMS. 90% of all patients transferred to hospital were alive at 24 hours.

INTRODUCTION

Northern Ireland is the most recent region within the UK to establish a Helicopter Emergency Medical Service. The service became operational in July 2017 and is a partnership between the Northern Ireland Ambulance Service (NIAS) and Air Ambulance Northern Ireland charity (AANI). Currently, the service responds only to trauma cases throughout the region. The daily operational crew consists of a pilot, one paramedic and one consultant grade doctor (Figure 1). Medical staff were recruited from emergency medicine, anaesthesia and intensive care medicine.

The purpose of this paper is to present an analysis of activity, patient demographics and clinical interventions relating to the first 100 cases – some call-outs involved multiple cases. We intended to assess the level of enhanced interventions provided uniquely by the team for example RSI, EDT.

Fig 1. Northern Ireland Air Ambulance crew respond to a Road Traffic Collision.

Air Ambulance Northern Ireland, Maze-Long Kesh, 94-b Halftown Rd, Lisburn BT27 5RC.

Corresponding author: Dr Darren Monaghan

E-mail: Dr.Darren.Monaghan@nias.hscni.net

There was also a need to explore patterns in demand/activity that would provide opportunities to develop operational aspects of the service.

METHODS

All HEMS cases were captured manually and records retained for governance purposes. For the purpose of this paper we conducted a hand trawl of records relating to the first 100 cases managed by the HEMS team. Data was entered into a database for the purpose of analysis. Measured data included: location of incident, dispatch mode, patient demographics, mechanism of injury, treatment provided, destination and outcome at 24 hours. As there were 100 patients in the study, numbers and percentages quoted are equivalent.

RESULTS

Geography and Dispatch

The largest number of cases were in Co. Antrim, 36% with the smallest number of cases in Co. Fermanagh, 4% (Figure 2).

The helicopter was used as the primary dispatch mode in 75% of missions. The dedicated rapid response car was the primary mode of dispatch in just under a quarter of missions (24%). On one occasion, a road ambulance was dispatched for operational reasons.

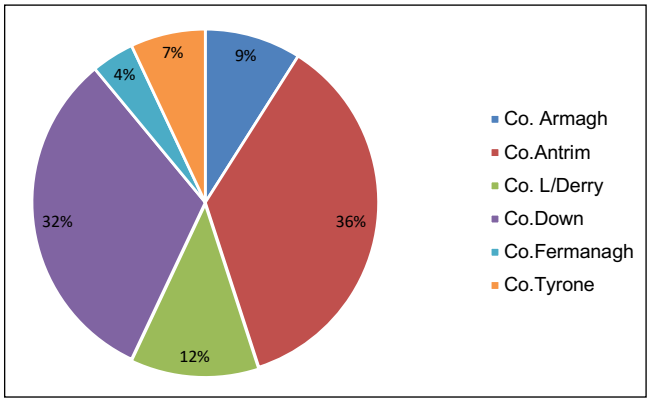


Fig 2. Location of call-out by county

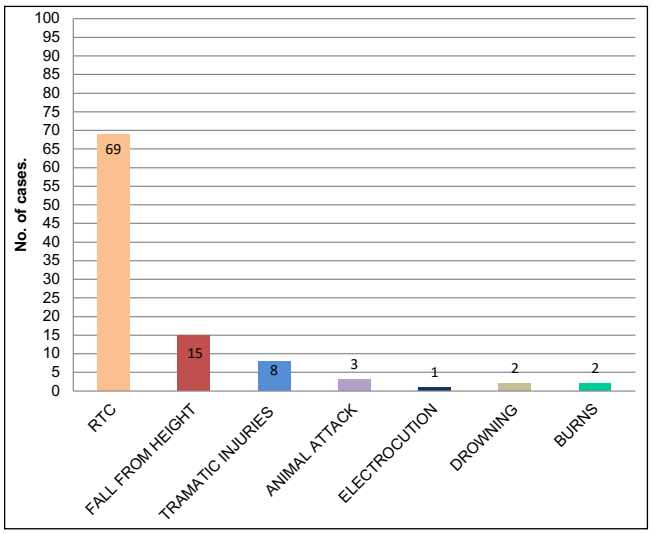


Fig 3. Mechanism of Injury

Patient demographics

Most patients (83%) were male. The disparity between genders in this sample of 100 cases is larger than in UK wide audit reports[1] but follows the trend that males are more likely be a victim of major trauma. [1,4]

The youngest patient was 3 years old and the oldest patient was 97. The mean population age was 45 years with a median of 43.5 and mode of 25.

Mechanism of Injury

RTC was the most common mechanism of injury at 69% (Figure 3).

Within the RTC category (Figure 4), motor vehicles included car, van or lorry. This group comprised 66% (44/69) of RTCs. Two-wheeled vehicles (motorcyclists and pedal cyclists) represented 22% (15/69) of those injured in a RTC.

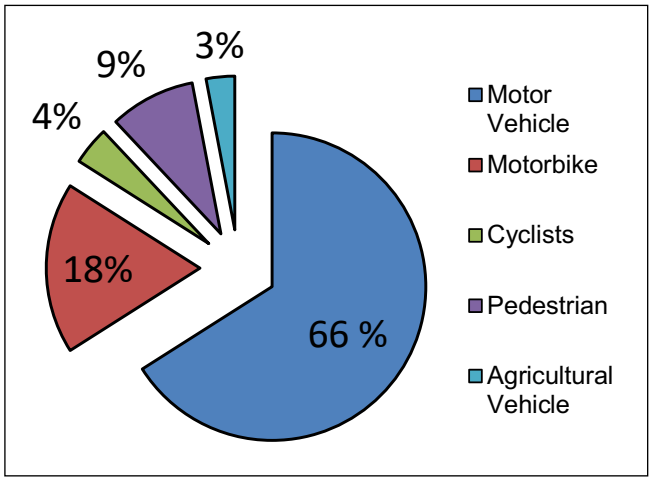


Fig 4. Types of road traffic involved in collision

Fall from height was the second largest percentage of mechanism causing injury, totalling 15. Ten of the 15 cases involved a fall ≥2 m (high energy transfer – high risk) with the remaining 5 cases involving a fall ≤ 2 m. Fall from height of ≤2 m, or low-energy fall, has been steadily increasing in published UK data since 1990 and has overtaken RTC as the most common mechanism of injury in major trauma.[3]

Interventions

In addition to the advanced skills and enhanced drug therapy

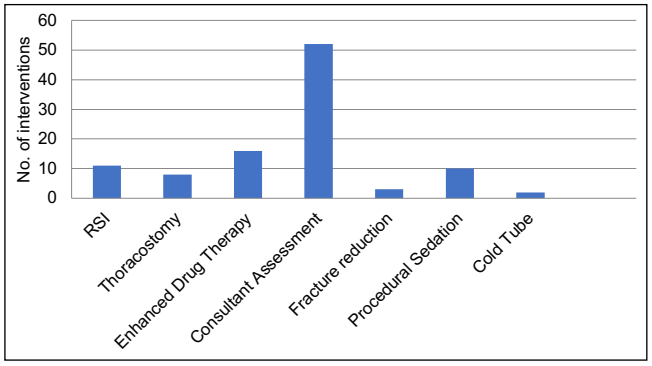


Fig 5. Advanced skills provided by the Air Ambulance

provided by the HEMS team (Figure 5 and Text Boxes 1-4) other outcomes were noted; which included the ability to redirect patients to the most appropriate receiving unit regardless of Trust boundaries.

BOX 1

RSI

- In total 11 RSIs were performed in the first 100 cases.
- Included in the 11 RSIs were:
- 2 RSI including thoracostomy
- 1 RSI including HTS
- 1 RSI including fracture reduction

BOX 2

Intubation without drugs referred to as 'Cold Tube'

- In total 2 cold tubes were performed.
- 1 x cold tube in conjunction with a thoracostomy.
- 1 x cold tube followed with HTS.

BOX 3

Thoracostomy

- In total 8 x thoracostomies were performed.
- In 5, airway was established by road crew prior to HEMS arrival.
- The remaining 3 thoracostomies were in conjunction with HEMS RSI or cold tube procedure (see box 1and 2).

BOX 4

Enhanced Drug therapy

- The use of EDT was recorded on 28 occasions within the first 100 cases.
- EDT includes medications not carried or administered by a road paramedic for example (but not limited to): Ketamine, midazolam, fentanyl.
- EDT was recorded in conjunction with 3 fracture reductions, 9 procedural sedations and 16 times for other reasons which included pain management.

Transport and Destination

Most patients were transferred to the RVH ED, however most other acute hospitals were utilised (Figure 6). A significant majority (67%) of patients were transported by road ambulance to the receiving hospital (Figure 7). Eighteen patients did not require further active transportation (13 deceased and 5 medically or self-discharged).

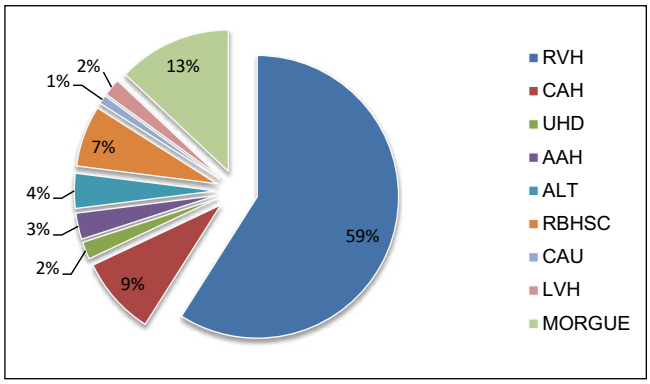


Fig 6. Destination Emergency Department

KEY
RVH: Royal Victoria Hospital
CAH: Craigavon Area Hospital
UHD: Ulster Hospital, Dundonald
AAH: Antrim Area Hospital
ALT: Altnagelvin Area Hospital
RBHSC: Royal Belfast Hospital for Sick Children
CAU: Causeway Area Hospital
LVH: Lagan Valley Hospital

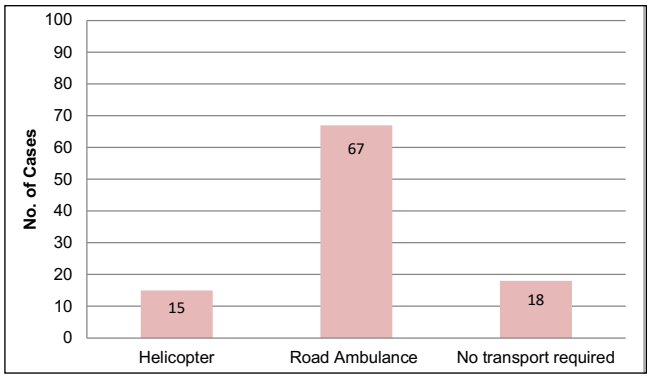


Fig 7. Mode of transport to receiving unit

Outcome at 24hours

90% of the 82 of patients transported to hospital were alive at 24 hours. 9% (n=8) of patients had died at 24 hours.

DISCUSSION

We have presented descriptive data relating to the first 100 cases treated by HEMS in N.I. Males are more likely to suffer major trauma in N.I in line with other published studies in the UK. [1] However, the percentage gap between male and female is larger in the first 100 cases; this may be due to the small sample size or for multiple, complex factors that would require in-depth analysis beyond the remit of this paper.

The mean age of patients in the first 100 cases was 45 years which is younger than UK figures collected in 2013. [1] Generally, the mean age of major trauma patients has been steadily increasing since 1990, according to Kehoe et al. [1] The most significant change in age profile percentage was in the over 75 years category; this tripled from 1990-2013.[1] In recent data collected by the Trauma Audit and Research Network (TARN) for England and Wales, patients aged 60 years and

over made up 53% of severely injuries registered on their database.[6] In addition, the most common mechanism of injury in this age group is a fall <2m. Falls were the second most common mechanism of injury in our population (15%), but falls from a significant height (>2m) were the most prevalent in our data. It is to be expected that a small sample size of 100 cases may not reflect every demographic or mechanism of injury national trend relating to trauma incidents.

We note a number of interesting findings:

Two-wheeled vehicles (motorcyclists and cyclists) made up 22% of those injured in a RTC in this sample. In terms of injury prevention, we feel that this area may warrant further study.

Based on the data from the first 100 cases, the rate of prehospital RSI is 11% (n=11) which is comparable to data published from Australia, England, Finland, Hungary, Norway and Switzerland. [2]

In the first 100 cases, we took a relatively low number of patients to hospital via helicopter. Some call-outs involved multiple patients – the helicopter can only carry one casualty. The lack of an operational helipad at the RVH means additional time is required to transfer a patient from the helicopter (landing at an alternative helipad i.e. Musgrave Park, Belfast) to a road ambulance for subsequent transport to the RVH by road. This factor, amongst others e.g. safety, weather, patient condition, interventions en route etc are considered at scene by the HEMS team when agreeing on the most suitable mode of transport. However, with the establishment of the helipad at the RVH we anticipate that this pattern will change in the future and more patients will be transported by helicopter.

In terms of destination hospital, although a majority of patients were brought to the de facto major trauma centre at the RVH, there was still a broad use of other acute hospitals within the province. With the establishment of a regional trauma network, it is possible that this pattern may also change.

In terms of outcomes we have only looked at the very binary measure of alive/dead at 24 hours.

At time of writing (early October 2018) we have attended 380 patients in 15 months and as our service is contributing to TARN, further detailed analysis will become available in due course.

REFERENCES:

1. Kehoe A, Smith JE, Edwards A, Yates D, Lecky F. The changing face of major trauma in the U., *Emerg Med J*. **32(12)**:911–5.
2. Sunde G, Heltne J, Lockey D, Burns B, Sandberg M, Fredriksen K, *et al*. Airway management by physician-staffed Helicopter Emergency Medical Services – a prospective, multicentre, observational study of 2,327 patients. *Scand J Trauma Resusc Emerg Med*. 23:**57**; 1-10.
3. Brake The Road Safety Charity. Driver gender. [Internet]. Huddersfield, UK: Brake Online. Available from: http://www.brake.org.uk/facts-resources/1593-driver-gender Last accessed March 2019.
4. GAIN: Guideline and Audit Implementation Network and The Regulation and Quality Improvement Authority. Northern Ireland Trauma Audit: February 2016. Belfast: GAIN; 2016. Available from: https://www.rqia.org.uk/RQIA/files/49/494ff427-9511-4311-bcca-db5fe7bc3eca.pdf Last accessed March 2019.
5. Great Britain. Department for Transport. Reported road casualties in Great Britain: 2017 annual report. London: Department for Transport; 2018. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/744077/reported-road-casualties-annual-report-2017.pdf Last accessed March 2019.
6. TARN: The Trauma Audi & Research Network. major trauma in older people: England and Wales. Manchester: The University of Manchester; 2018. Available from: https://www.tarn.ac.uk/content/downloads/3793/Major%20Trauma%20in%20Older%20People%202017.pdf Last accessed March 2019.

Ulster Med J 2019;**88(2):**102-104

Clinical Paper

Treatment of Infantile Haemangioma – Perspective of a Regional Surgical Centre

Weiguang Ho, Christopher Hoo, Claire Black

Accepted: 26th November 2018
Provenance: externally peer-reviewed

INTRODUCTION

Infantile haemangioma affects up to 1 in 10 infants, representing the commonest benign tumours of infancy[1]. It is commoner in people of Caucasian ethnicity, premature babies and those who underwent chorionic villous sampling[2,3].

Classification of vascular anomalies follows the International Society for the Study of Vascular Anomalies (ISSVA) classification of vascular malformations, which is based on the published work of Mulliken and Glowacki in 1982[4,5]. In this widely-accepted classification system, infantile haemangiomas are considered benign vascular tumours.

The natural course of haemangioma is reasonably well understood. Lesions typically present soon after birth and undergo rapid proliferation in the first year of life. This is followed by gradual involution in the following five to 10 years. Most haemangiomas are asymptomatic, spontaneously involute and do not require treatment, but they can cause significant issues with airway obstruction, ocular compression, ulceration, scarring or functional impairment[6].

Treatment with propranolol, a non-selective beta-blocker, was reported by Léauté-Labrèze et al in 2008[7]. Since then, further articles have reported its efficacy in inducing regression in the proliferative phase. McGee et al in 2013 demonstrated the safety and efficacy of propranolol therapy in the Northern Irish population, which at that time was reserved for problematic haemangiomas[8]. Marqueling et al published a systematic review finding treatment response in 98% of patients[9].

This study aims to investigate response to propranolol therapy and surgery in patients treated by our unit over a four-year period.

Since our previous publication, there have been no nationally agreed guidelines for the use of oral propranolol in the treatment of infantile haemangiomata[8].

METHODS

Medical records of all patients treated by the department of Plastic Surgery in the Royal Belfast Hospital for Sick Children were retrospectively reviewed between January 2013 and February 2017. A proforma was designed to collect relevant information on patient demographics, indication for propranolol, dosing regimen and observed outcomes. In addition, we collected data on referrals for surgical treatment and the types of surgical treatment undertaken.

A database was created from the information collected. This was used to delineate simple demographics, referral patterns, therapeutic efficacy of propranolol therapy and surgical treatment.

RESULTS

Demographics

37 patients with 50 haemangioma lesions were identified and all notes were retrieved. 7 were male and 30 were female, indicating a male:female ratio of over 1:4.3. Mean age at time of first appointment was 2 years and 1 month (range 1 month to 10 years and 7 months).

The majority of haemangiomas manifested in the head and neck region, followed by the trunk, upper limb, lower limb and external genitalia (Table 1). 10 patients had

Table 1

Patient and lesion demographics

		N (%)
Total patients		37
Mean age at first appointment (months, range)		25 (1-127)
Gender	Male	7
	Female	30
Region	Head and neck	31
	Trunk	11
	Upper limb	4
	Lower limb	2
	External genitalia	1
	Intraoral	1

Department of Plastic Surgery, Royal Belfast Hospital for Sick Children and Ulster Hospital, Upper Newtownards Road, Belfast BT16 1RH, United Kingdom

Correspondence to: Weiguang Ho

Email: weiguang.ho@setrust.hscni.net

haemangiomas in multiple locations, with seven patients in two locations and three patients in three locations.

Current practice

Propranolol therapy

The standard work-up prior to commencement of propranolol therapy has remained unchanged. All patients underwent this assessment and the decision for commencement of propranolol therapy was mutually made between clinician and patient's parents. They were monitored closely when starting therapy and at points of dose escalation.

Of the 37 patients, 28 were referred for assessment of treatment with propranolol therapy. Propranolol therapy was thought to be unsuitable for nine patients because the haemangioma had progressed beyond the proliferative phase. Hence, 19 patients received propranolol therapy.

The age at start of treatment was 9.4 months. The commencement dose was 1mg/kg in 15 patients and 2mg/kg in two patients.

Efficacy and duration of therapy

Objective response was observed in all patients by comparing clinical photographs during outpatient clinics. Three patients were on dose reduction after successful involution and seven patients had successfully stopped propranolol therapy at the time of the study. Five patients were currently still on treatment with propranolol. The mean duration from commencement of propranolol therapy until the decision for dose reduction was made was 372.4 days (n=9, range 133-651 days), requiring an average of 5.8 outpatient clinic appointments (range 2-13 appointments). The mean number of days required until dose reduction was 278.3 days (n=8, range 133-406 days). The total number of clinical appointments required until dose reduction was 3.9 (range 2-6 sessions).

Adverse effects

Oral propranolol therapy was prematurely stopped in two patients due to potential side effects; one patient was reported to have nightly wheeze and cough and another suffered from sleep disturbances. Alternate therapies commenced on these patients were topical Timolol and surgical excision and split skin grafting respectively.

Surgery

In our centre, patients are usually referred for surgical treatment in the event of poor response to propranolol therapy or if debulking is required after involution of haemangiomas. Within the study period, eight patients (24.3%) were referred for consideration of surgery (Table 2). Of these, five patients received surgery in the form of debulking. Conservative treatment was decided for the remaining three patients until they express concern or experience psychosocial harm due to the involuted haemangiomas. Two patients required a single-stage procedure, while two patients required two-stage and three-stage debulking excisions each. One patient was still awaiting surgery at the time of this study.

The mean age of patients who were referred for surgery was 5.3 years (range 3-10). The mean age of patients who underwent surgery was 5.4 years (range 3-10).

DISCUSSION

We found that patients who were older tended to be referred for and treated with surgery. This was consistent with the predictable course of IH, where 50% tended to regress by age 5 and 70% by age 7. With the increasing use of and body of evidence showing the safety and efficacy of propranolol therapy in encouraging accelerated involution, we can anticipate younger patients being referred for surgical treatment in the future.

As before, this case series contributes to the evidence of the efficacy and safety of oral propranolol therapy. We believe that this case series has also shed some light into the trend of surgical treatment of infantile haemangioma. This is consistent with recent findings by Tangtatco et al[10].

New nationally agreed guidelines have yet to emerge. Several regional guidelines, protocols and patient information booklets are readily available from a simple online search

TABLE 2

Summary of patient referred for surgery

Patient	Age (years)*	Reason for referral	Surgery offered?	Stages required	Patient satisfaction
27	5.1	Adverse effects to propranolol therapy	Yes	Awaiting surgery	Yes
28	5.2	Involuted	Yes	2	Yes
30	3.2	Involuted	Yes	3	Yes
33	5.9	Involuted	No	N/A	Yes
34	6.9	Involuted	No	N/A	Yes
35	4.5	No response to propranolol therapy	Yes	1	Yes
36	4.9	Involuted	No	N/A	Yes
37	10.8	Involuted	Yes	1	Yes

*Age at time of first outpatient appointment

including Great Ormond Street Hospital and Nottingham.[11,12] The American Association of Paediatrics published a conference consensus on the initiation and use of propranolol for Infantile Haemangiomas[13]. Consensus amongst dermatologists in Spain and paediatricians in South Australia have been published[14,15].

Treatment alternatives not frequently used in our centre include topical Timolol and laser therapy. The National Institute for Clinical Excellence (NICE) has produced guidance for the use of topical Timolol based on several studies finding positive response in reduction in redness, size and volume, with minimal adverse effects[16].

Chinnadurai et al systematically reviewed the use of a variety of lasers for the treatment of infantile haemangiomas[17]. This review highlighted the effectiveness of longer pulsed dye laser for cutaneous haemangiomas. Laser therapy alone and with beta-blockers were also found to have greater effects on mixed superficial and deep haemangiomas, compared with beta-blockers alone. The authors however found the strength of evidence to be insufficient to low. Limited conclusions were drawn on the effectiveness of neodymium-doped yttrium aluminium garnet (Nd:YAG) and carbon dioxide (CO2) lasers.

CONCLUSION

This study shows the efficacy of propranolol therapy with minimal adverse reactions. Limitations to this study are that this is a single centre study. Surgery, which was performed on a small number of patients, continues to be the mainstay of treatment in patients who do not meet indications for propranolol therapy or poor responders.

COI: The authors have no conflicts of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Zimmermann AP, Wiegand S, Werner JA, Eivazi B. Propranolol therapy for infantile haemangiomas: review of the literature. *Int J Pediatr Otorhinolaryngol*. 2010;**74(4)**:338–42.
2. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol*. 2010;**163(2)**:269–74.
3. Schwartz RA, Sidor MI, Musumeci ML, Lin RL, Micali G. Infantile haemangiomas: a challenge in paediatric dermatology. *J Eur Acad Dermatol Venereol*. 2009;**24(6)**:631–8.
4. Wassef M, Blei F, Adams D, Alomari A, Baselga E, Berenstein A, ISSVA Board and Scientific Committee. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics*. 2015;**136(1)**:e203–14.
5. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg*. 1982;**69(3)**:412–22.
6. Starkey E, Shahidullah H. Propranolol for infantile haemangiomas: a review. *Arch Dis Child*. 2011;**96(9)**:890–3.
7. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo J-B, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;**358(24)**:2649–51.
8. McGee P, Miller S, Black C, Hoey S. Propranolol for infantile haemangioma: a review of current dosing regime in a regional paediatric hospital. *Ulster Med J*. 2013;**82(1)**:16–20.
9. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. *Pediatr Dermatol*. 2013;**30(2)**:182–91.
10. Tangtatco JA, Freedman C, Phillips J, Pope E. Surgical treatment outcomes of infantile hemangioma in children: Does prior medical treatment matter. *Pediatr Dermatol*. 2018;**35(6)**:e418–9.
11. NHS Great Ormond Street Hospital. Treating haemangiomas with propranolol [Internet]. London: Great Ormond Street Hospital. Available from: http://www.gosh.nhs.uk/medical-information-0/medicines-information/treating-haemangiomas-propranolol. Last accessed March 2019.
12. Nottingham Children's Hospital Propranolol for Haemangiomas (OVER 3 months) [Internet]. Nottingham University Hospitals; 2014. Available from: https://www.nuh.nhs.uk/download.cfm?doc=docm93jijm4n711. Last accessed March 2019.
13. Drolet BA, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, Chiu YE, *et al*. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatr*. 2013;**131(1)**:128–40.
14. Baselga Torres E, Bernabéu Wittel J, van Esso Arbolave DL, Febrer Bosch MI, Carrasco Sanz Á, de Lucas Laguna R, *et al*. [Spanish consensus on infantile haemangioma]. *An Pediatr (Barc)*. 2016;**85(5)**:256–65. Spanish.
15. Department of Health, Government of South Australia. South Australian Paediatric Practice Guidelines: propranolol for infantile haemangioma [Internet]. Adelaide: Government of South Australia; 2013. Available from: https://www.sahealth.sa.gov.au/wps/wcm/connect/e1c9ef804233d33986aeeeef0dac2aff/propranolol+for+infantile+haemangioma.pdf?MOD=AJPERES. Last accessed March 2019.
16. NICE. Evidence Summary; ESU0M47. Infantile haemangioma: topical timolol. London: National Institute for Health and Care Excellence; 2015. Available from: https://www.nice.org.uk/advice/esuom47/chapter/full-evidence-summary. Last accessed March 2019.
17. Chinnadurai S, Sathe NA, Surawicz T. Laser treatment of infantile hemangioma: A systematic review. *Lasers Surg Med*. 2016;**48(3)**:221–33.

Ulster Med J 2019;**88(2):**105-110

Clinical Paper

Response to Therapy, Treatment Intolerance and Tyrosine Kinase Inhibitor Cessation Eligibility in a Real-World Cohort of Chronic Myeloid Leukaemia Patients.

RR McMullan[1*], C McConville[2], MF McMullin[1,3]

Provenance: externally peer reviewed
Accepted: 6th January 2019

Keywords: TKI, CML, intolerance, treatment cessation, real-world

ABSTRACT

Tyrosine kinase inhibitor (TKI) therapy has revolutionised chronic myeloid leukaemia (CML) management, it is however associated with significant side effects and economic burden. Recent studies have demonstrated that treatment free remission is possible in certain patients.

The aim of this study was to characterise a real-world population in terms of response to therapy, treatment intolerance and potential eligibility for stopping treatment.

Included were 105 CML patients diagnosed in Northern Ireland from March 2009-February 2018. Response to treatment was defined as per the 2009 and 2013 European Leukaemia Net guidelines. Potential for treatment cessation was assessed as per the 2017 UK Interim Expert Opinion on Discontinuing Tyrosine Kinase Inhibitor Treatment in Clinical Practice for Treatment-Free Remission in Chronic Myeloid Leukaemia.

Our cytogenetic data cohort had a 12-month complete cytogenetic response rate of 66% and the molecular data cohort had a 12-month major molecular response rate of 38%. Of those commenced on 2nd line TKI therapy 81% achieved an optimal response at 12 months. Twenty-two patients developed intolerance and required a change in TKI therapy. The commonest side effects were gastro-intestinal upset (18%), transaminitis (16%) and fluid retention (16%). In our cohort, 20% were considered eligible to stop TKI therapy. The commonest reason for ineligibility was insufficient duration of therapy (25%).

We observed that 1st and 2nd line TKI therapy are effective but problems with failure and intolerance persist. Additionally, this study identifies a cohort of patients who may attempt TKI cessation using the UK Interim Expert Opinion report on TKI therapy discontinuation.

BACKGROUND

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm with a reported incidence of 1-2 cases per 100,000 adults [1]. CML typically has three stages; chronic phase (CP), accelerated phase (AP) and blast phase (BP). As the disease progresses, cytogenetic abnormalities accrue, accompanied by symptomatic deterioration. The majority of patients are diagnosed during CP and most evolve into AP before BP. However, 20% of patients transit into an acute blastic process without AP warning signals [2].

Central to the pathogenesis of CML is the formation of the constitutively active tyrosine kinase, BCR-ABL1. This oncoprotein plays a key role in leukemogenesis by stimulating growth and replication by the manipulation of downstream signalling pathways and by generating a cytokine-independent cell cycle with aberrant apoptotic signals [3].

Identification of this critical pathway led to the development of targeted drug therapy, tyrosine kinase inhibitors (TKIs), which interfere with the interaction between BCR-ABL1 and adenosine triphosphate, thereby preventing proliferation of the malignant clone.

The IRIS trial was a seminal study confirming the significance of TKIs and led to the study drug, imatinib, being approved for first line treatment [4]. TKIs have improved the 10-year overall survival from approximately 20% to 80–90% [5]. A recent study by Bower *et al*. demonstrated that the life expectancy of CML patients is approaching that of the general population [6].

Despite this, long term TKI therapy is associated with a heavy economic burden which will increase as CML becomes more prevalent due to improved survival [7]. Furthermore, patients are frequently affected by significant and occasionally lethal side effects. Several studies have indicated that approximately half of patients who achieve a deep and sustained molecular

1 Department of Haematology, Belfast City Hospital, Belfast, Northern Ireland 2 Department of Haematology, Altnagelvin Hospital, Derry, Northern Ireland. 3 Centre for Medical Education, Queen's University Belfast, Belfast, Northern Ireland

*Corresponding Author

Correspondence: to Ross McMullan

Email; rmcmullan07@qub.ac.uk

response can safely and successfully stop TKI therapy and obtain treatment free remission (TFR) [8].

In patients with a molecular recurrence necessitating resumption of TKI therapy, the overwhelming majority retained their sensitivity to TKI therapy. In all major published trials to date, only one case has been identified where a patient progressed to BP despite therapy recommencement [9].

Although numerous trials have confirmed the safety and efficacy of TKIs, assessment of their real-world effectiveness and tolerance in a general CML population is scarce. Furthermore, identifying patients who may attempt to gain TFR is a relatively novel strategy.

The aim of this study was to provide a detailed description of the presentation and management of a real-world sample of CML patients. We sought to assess the effectiveness and tolerance of TKI therapy and evaluate what proportion of participants were deemed eligible to stop TKI therapy in an attempt to obtain TFR.

METHODS

This study included 105 CML patients diagnosed from March 2009 to February 2018 and managed by the Belfast City Hospital Haematology Department. This cohort was identified by interrogation of Consultant patient records. Patients not managed by this tertiary centre were not included. Data was collected using patient medical notes and electronic laboratory records.

TABLE 1:

Baseline Characteristics of the Study Population

Characteristic	Study Population
Number of Patients	105
Median Age (range)- years	61.5 (4-94)
Male sex- no. (%)	62 (59)
Palpable splenomegaly no. (%)	50 (48)
Median haemoglobin for males (range)- g/l	118.5 (67-155)
Median haemoglobin for females (range)- g/l	110 (64-148)
Median platelet count (range)- $x10^9$/l	96.8 (13.4-563)
Median white cell count (range)- $x10^9$/l	340 (84-2507)
EUTOS risk group-no. (%)	
Low	89 (85)
High	5 (5)
Unknown	11 (10)
Phase- no. (%)	
Chronic	99 (94)
Unknown	6 (6)

Cytogenetic analysis and BCR-ABL1 transcript analysis were performed at a single centre (Haematology Laboratory, Belfast City Hospital). Transcript analysis was conducted using quantitative polymerase chain reaction technology.

Results for response to treatment were expressed as per the 2009 and 2013 European Leukaemia Net (ELN) guidelines and applied retrospectively, depending on the date of diagnosis [10,11]. Potential for treatment discontinuation was assessed as per the eligibility criteria expressed by the 2017 UK Interim Expert Opinion on Discontinuing Tyrosine Kinase Inhibitor Treatment in Clinical Practice for Treatment-Free Remission in Chronic Myeloid Leukaemia [12].

Data were analysed using descriptive statistics and IBM SPSS® software was used.

RESULTS

Presenting Features

This study included 105 patients (62 males, 43 females) with a median age at diagnosis of 61.5 years. Baseline characteristics are shown in Table 1. The most common presenting symptoms were fatigue (32%), unintentional weight loss (24%) and night sweats (17%). 30% of patients were diagnosed as a result of an incidental finding. At diagnosis the majority of males and females were anaemic, 77% and 63% respectively. Moreover, 38% of patients were thrombocythaemic and 7% were thrombocytopenic.

Treatment and Response to Therapy

The majority of patients (74%) did not receive cyto-reduction prior to TKI initiation. However, 23% did receive hydroxycarbamide and 3% underwent leucopheresis. The most commonly prescribed 1st line TKI was imatinib (81%) with the remainder receiving 2nd generation TKI therapy, namely nilotinib (12%) and dasatinib (7%).

The response to 1st line TKI therapy was assessed, using cytogenetic data, in 57 patients in accordance with the 2009 ELN guidelines [10]. Cytogenetic data was not always available because of a lack of bone marrow biopsy data, probably arising from clinician reluctance to subject patients to an invasive procedure, especially if symptoms had resolved along with a downward trending *BCR-ABL1* transcript level. See Table 2 for availability at the various timepoints. In those with cytogenetic data available 79%, 72% and 66% achieved an optimal response to therapy at 3, 6 and 12 months respectively (Table 2). Whereas, 14%, 12%, and 6% of patients were determined to have a failure response to therapy.

The response to 1st line TKI therapy was assessed, using molecular data, in 47 patients in accordance with the 2013 ELN guidelines [11]. Due to a lack of compulsory monitoring molecular data was not always available (Table 3). In those with molecular data available, 50%, 43% and 38% achieved an optimal response to therapy at 3, 6 and 12 months respectively (Table 3). However, 9%, 22% and 15% of patients were determined to have a failure response to therapy.

TABLE 2:

Response to 1st Line TKI Therapy as Defined by the 2009 ELN Guidelines

	Response to Therapy						
	Optimal	Suboptimal	Failure	Unknown	Deceased	No Bone Marrow Biopsy	2nd Line Therapy Commenced
3 Months	11	1	2	2	1	40	0
6 Months	18	3	3	1	1	30	1
12 Months	23	7	2	2	1	19	3

TABLE 3:

Response to 1st Line TKI Therapy as Defined by the 2013 ELN Guidelines

	Response to Therapy						
	Optimal	Warning	Failure	Unknown	Deceased	Awaited	2nd Line Therapy Commenced
3 Months	17	14	3	9	1	3	0
6 Months	16	12	8	6	1	3	1
12 Months	15	11	6	4	1	3	7

TABLE 4:

Response to 2nd Line TKI Therapy as Defined by the 2013 ELN Guidelines

	Response to Therapy					
	Optimal	Warning or Failure	Unknown	Deceased	Awaited	3rd Line Therapy Commenced
3 Months	14	4	9	0	1	0
6 Months	18	3	5	1	1	0
12 Months	14	6	3	2	2	1

Monitoring was much more stringent in this cohort due to the less invasive sampling required for transcript analysis.

A total of 28 patients required a change in TKI therapy due to an inadequate cytogenetic and or molecular response. Subsequently, they were commenced on 2nd line therapy in an attempt to obtain disease control and to prevent progression. These patients were assessed for an optimal response to 2nd line therapy as defined by the 2013 ELN guidelines [11]. In those with molecular data available, 78%, 86% and 81% achieved an optimal response at 3, 6 and 12 months respectively (Table 4).

Treatment Intolerance

Initial TKI therapy was changed in 47% of patients due to inadequate response (26%), treatment intolerance (18%) and study completion (3%). Throughout their entire treatment regime 22 patients were identified who due to intolerance required a change in therapy. Among these 22 patients there were 38 instances of a change in TKI therapy, thereby highlighting that several patients experienced intolerable side effects to more than one agent. The most common side effects resulting in a change in therapy were gastrointestinal upset (18%), transaminitis (16%) and fluid retention (16%) (Figure 1).

Eligibility for TKI Discontinuation

The cohort of patients was assessed for eligibility to stop TKI therapy in accordance with a recently published UK Interim Expert Opinion on TKI discontinuation [12]. This report advises that TKI discontinuation may be attempted in adult patients with no prior history of AP or BP disease. Moreover, the patient must have been on TKI therapy for at least 3 years and have had a sustained response i.e. (*BCR-ABL1* ≤0.01%) throughout the last 2 years prior to attempted discontinuation[12].

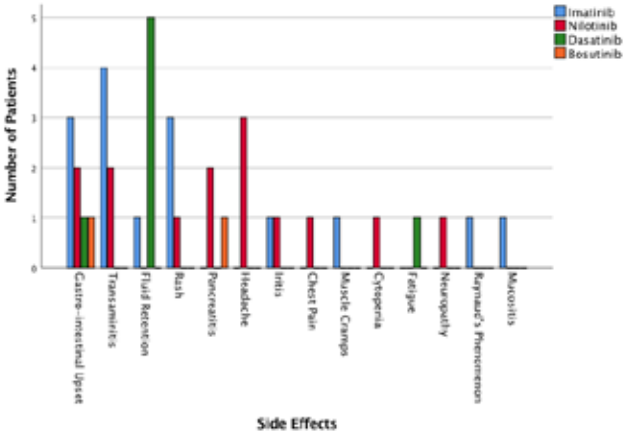


Fig 1; Side Effects Associated with Tyrosine Kinase Inhibitor Therapy Resulting In a Change in Therapy

In this cohort 20% were considered eligible to stop TKI therapy in an attempt to obtain TFR. Reasons for ineligibility included insufficient duration of therapy (25%), history of inadequate response to therapy (16%) and a *BCR-ABL1* transcript level ≥ 0.01 within the past 2 years (16%) (Figure 2).

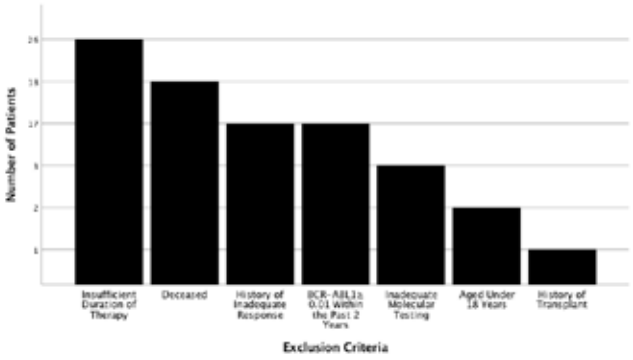


Fig 2. Reasons for Failure to Meet Eligibility Criteria as Defined by the 2017 UK Interim Expert Opinion on Discontinuing Tyrosine Kinase Inhibitor Treatment in Clinical Practice for Treatment Free Remission in Chronic Myeloid Leukaemia

Follow Up

This population of patients were followed up until March 2018. During follow up 18 out of 105 patients died, however, only 1 death was attributable to a CML blast crisis. One patient died from complications of a bone marrow transplant and a further patient died from acute liver failure attributed to imatinib therapy. Other common causes of death included sepsis and solid malignancy.

Annual *BCR-ABL1* transcript levels were assessed to determine what proportion of patients achieved a major molecular response (MMR). MMR is defined as a 3-log reduction in transcript levels from the standardised baseline or a transcript level of <0.1 in the International Scale [13].

Data suggests that the proportion of patients achieving and maintaining a MMR increases as time passes. Molecular follow up data at 2 years revealed that 63% achieved a MMR, at 5 years 83% achieved a MMR and at 8 years 100% of patients, still alive, had achieved a MMR. At the time of data analysis 8 patients had reached 8 years of follow up; all of whom had achieved a MMR.

DISCUSSION

Real-world data has important implications that inform clinical practice. The aim of this study was to provide such data on the presentation, management and outcomes of a CML population. We sought to highlight issues with treatment failure and intolerance and to identify a cohort of patients, using recently published guidance, who could stop therapy in an attempt to obtain TFR.

Advances in the understanding of the pathophysiology of CML have led to the development of targeted therapy which has changed management. However, a substantial number of patients suffer significant intolerance to TKI therapy. In this study 21% of patients experienced intolerance to one or more TKIs, necessitating a change in therapy. Side effects such as gastro-intestinal upset and transaminitis were common across the entire class of drugs. Certain characteristic side effects were coupled with particular TKIs as demonstrated by the relationship between dasatinib therapy and pleural effusions. It is essential that the clinician adopts a proactive stratagem to manage side effects. The association of side effect burden and poor medication adherence with a suboptimal disease response demands that side effects are managed aggressively. With unmanageable side effects it is appropriate to switch TKI therapy and with 3rd generation TKIs filtering into clinical practice, this will promote the therapeutic armoury available [14]. Our results mirror other real-world studies which have demonstrated that 41-44% of patients change TKI therapy due to treatment intolerance or failure [15,16].

Furthermore, TKI therapy is associated with substantial financial implications. As the life expectancy of CML patients now approaches that of the general population, the provision of life long therapy is expensive [6]. Consequently, TFR is an attractive therapeutic target for the health service. Analysis by Padula *et al*, suggests that the annual cost of imatinib therapy per patient in the United States was almost $80,000 per year and introduction of generic imatinib resulted in only a modest decrease in cost [17]. Therefore, safely stopping TKI therapy represents a substantial cost saving. However, it must be remembered that achievement of TFR will have its own unique costs. Patients will require closer monitoring and there is an argument for indefinite *BCR-ABL1* transcript analysis to safe guard against a delayed diagnosis of disease relapse and to help inform clinical practice regarding the long-term durability of TFR. Regardless, the standard cost of performing a transcript assay in our unit is £200, therefore, compared to one year of TKI therapy, regular molecular monitoring remains highly cost effective.

Our cytogenetic data cohort had a 12-month complete cytogenetic response (CCyR) rate of 66% and the molecular data cohort had a 12-month MMR rate of 38%; comparable to other population-based registries [15,18,19]. The EUTOS registry, one of the largest CML population-based registries, had a 12-month CCyR rate of 57% and a MMR rate of 41% [19]. Interestingly, our results compare favourably to Lucas *et al*., who using a surrogate end point CCyR equivalence (CCRe) which combined molecular expression data and cytogenetic data, revealed a 12-month CCyR equivalence rate of approximately 41% within a real-world UK population of CML patients treated with imatinib [20]. However, a proportion of patients in our study were treated with first line 2nd generation TKIs which have been demonstrated to induce earlier and higher rates of CCyR and MMR compared to imatinib [21,22]. This may partially account for the difference in 12-month response rates.

Stopping TKI therapy provides a novel opportunity to obtain TFR for approximately 40% - 60% of patients [8]. The STIM trial was one of the first studies to confirm the

possibility of achieving TFR. This study highlighted that most patients who relapsed did so within the first 6 months of treatment discontinuation and that all patients who relapsed remained sensitive to imatinib re-introduction [23]. The safety of imatinib discontinuation was re-affirmed by the TWISTER trial [24]. Moreover, interim analysis of the STOP 2G-TKI study revealed that discontinuation of 2nd generation TKIs yields promising TFR rates in addition to allowing effective re-introduction of TKIs without safety concerns [25]. The safety and stability of response in those who have successfully achieved TFR has been recently reaffirmed by the Australasian Leukaemia & Lymphoma Group (ALLG). The ALLG have previously demonstrated the persistence of BCR-ABL1-positive cells, even in patients with a sustained TFR [26]. They have now revealed that despite an absence of ongoing TKI therapy, there is an ongoing fall in minimal residual disease [27].

The exact pre-conditions for identifying patients suitable for TKI therapy cessation without fear of molecular relapse are currently unknown. However, several studies have begun to address this. The STOP 2G-TKI study identified that a history of TKI treatment resistance was predictive of potential molecular relapse, whereas the EURO-SKI trial highlighted that a longer duration of imatinib therapy was significantly associated with a higher probability of molecular relapse free survival [25,28].

The clinician must recognise the potential problems associated with TKI discontinuation. In addition to disease relapse, the psychological impact of stopping TKI therapy must be considered. An Italian survey revealed that almost 50% of patients had concerns over stopping TKI therapy due to potential disease relapse [29]. Moreover, a relatively new entity to emerge from discontinuation is the TKI withdrawal syndrome, affecting up to 60% of patients and typically manifesting as musculo-skeletal pain. It is often self-limiting but may persist for several months and require treatment with simple analgesia [30].

Little data exists on application of eligibility criteria in a CML population outside clinical trial milieux. Using the 2017 UK Interim Expert Report we identified that 20% of patients could stop TKI therapy, whereas, utilising the EURO-SKI criteria Geelen *et al,* only 11% of patients met the eligibility criteria [15].

There are limitations to our study. This was a population-based study and those involved were not monitored as strictly as during a clinical trial. The International Scale for reporting *BCR-ABL1* results was only recently available to our laboratory, therefore the majority of results were reported using the local assay.

CONCLUSION

In conclusion, our real-world observations show that 1st and 2nd line TKI therapy is effective, however problems with treatment intolerance and failure remain. Additionally, this study identifies a cohort of patients, using the recently published 2017 UK Interim Expert Opinion on Discontinuing TKI Treatment guidelines, who may attempt TKI therapy cessation. Our findings have revealed that criteria for an attempt to stop TKI therapy are met by one fifth of patients.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA: Cancer J Clin*. 2017;**67(1)**:7-30.
2. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2016 update on diagnosis, therapy, and monitoring. *Am J Hematol*. 2016;**91(2):**252-65.
3. Ren R. Mechanisms of BCR–ABL in the pathogenesis of chronic myelogenous leukaemia. *Nat Rev Cancer*. 2005;**5(3):**172-6.
4. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, *et al*. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;**348(11):**994-1004.
5. Deininger M, O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, *et al*. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with Imatinib. *Blood*. 2009; **114(22):** 1126
6. Bower H, Bjorkholm M, Dickman PW, Hoglund M, Lambert PC, Anderson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*. 2016; **34(24):**2851-7.
7. Ross DM, Hughes TP. How I determine if and when to recommend stopping tyrosine kinase inhibitor treatment for chronic myeloid leukaemia. *Br J Haematol*. 2014;**166(1):**3-11.
8. Kimura S. Current status of ABL tyrosine kinase inhibitors stop studies for chronic myeloid leukemia. *Stem Cell Investig* 2016 Aug 9;**3:**36.
9. Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, *et al*. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*. 2014;**32(5):**424-30.
10. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, *et al*. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol*. 2009;**27(35)**:6041-51.
11. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, *et al*. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;**122(6)**:872-84.
12. Clark R, Copland M, Goringe A, Huntly B, Milojkovic D, Mead A, *et al*. UK Interim Expert Opinion on discontinuing tyrosine kinase inhibitor treatment in clinical practice for treatment-free remission in chronic myeloid Leukaemia. Geneva: Novartis Medical Affairs and Medical Information; 2017. Available from: http://nssg.oxford-haematology.org.uk/myeloid/guidelines/TAS17-E010-final-uk-interim-expert-opinion-tfr.pdf. [Accessed Jan 2019.]
13. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, *et al*. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003;**349(15):**1423-32.
14. Deangelo D. Managing chronic myeloid leukemia patients intolerant to tyrosine kinase inhibitor therapy. *Blood Cancer J*. 2012;**2(10)**:e95.
15. Geelen IG, Thielen N, Janssen JJ, Hoogendoorn M, Roosma TJA, Willemsen SP, *et al*. Treatment outcome in a population-based, 'real-world' cohort of patients with chronic myeloid leukemia. *Haematologica*. 2017;**102(11)**:1842-9.

16. Castagnetti F, Di Raimondo F, De Vivo A, Spitaleri A, Gugliotta G, Fabbiano F, *et al*. A population-based study of chronic myeloid leukemia patients treated with imatinib in first line. *Am J Hematol*. 2017;**92(1)**:82-7.

17. Padula WV, Larson RA, Dusetzina SB, Apperley JF, Hehlmann R, Baccarani M, *et al*. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. *J Natl Cancer Inst*. 2016;**108(7): djw003.**

18. Hoglund M, Sandin F, Hellstrom K, Bjoreman M, Bjorkholm M, Brune M, *et al*. Tyrosine kinase inhibitor usage, treatment outcome, and prognostic scores in CML: report from the population-based Swedish CML registry. *Blood*. 2013;**122(7):**1284-92.

19. Hoffmann V, Baccarani M, Hasford J, Castagnetti F, Di Raimondo F, Casado L, *et al*. Treatment and outcome of 2904 CML patients from the EUTOS population-based registry. *Leukemia*. 2017;**31(3):**593-601.

20. Lucas CM, Wang L, Austin GM, Knight K, Watmough SJ, Shwe KH, *et al*. A population study of imatinib in chronic myeloid leukaemia demonstrates lower efficacy than in clinical trials. *Leukemia*. 2008;**22(10):**1963-6.

21. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boque C, *et al*. Final 5-year study results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients Trial. *J Clin Oncol*. 2016;**34(20):**2333-40.

22. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, *et al*. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*. 2016;**30(5):**1044-54.

23. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, *et al*. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010;**11(11):**1029-35.

24. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Yeung DT, *et al*. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*. 2013;**122(4):**515-22.

25. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-Bresler A, *et al*. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. *Blood*. 2017;**129(7):**846-54.

26. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Bartley PA, *et al*. Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. *Leukemia*. 2010;**24(10):**1719-24.

27. Ross DM, Pagani IS, Shanmuganathan N, Kok CH, Seymour JF, Mills AK, *et al*. Long-term treatment-free remission of chronic myeloid leukemia with falling levels of residual leukemic cells. *Leukemia*. 2018;**32**:2572–9.

28. Mahon F, Richter J, Guilhot J, Hjorth-Hansen H, Almeida A, Janssen JJJ, et al. Cessation of tyrosine kinase inhibitors treatment in chronic myeloid leukemia patients with deep molecular response: results of the Euro-Ski trial. *Blood* 2016; **128(22):**787

29. Breccia M, Efficace F, Sica S, Abruzzese E, Cedrone M, Turri D, *et al*. Adherence and future discontinuation of tyrosine kinase inhibitors in chronic phase chronic myeloid leukemia. A patient-based survey on 1133 patients. *Leuk Res*. 2015;**39(10):**1055-9.

30. Richter J, Soderlund S, Lubking A, Dreimane A, Lotfi K, Markevarn B, *et al*. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? *J Clin Oncol*. 2014;**32(25):**2821-3.

Ulster Med J 2019;**88(2):**111-114

Clinical Paper

Antibiotic Prophylaxis Protocols and Surgical Site Infection Rates in Trauma Surgery: A Prospective Regional Study of 26,849 Procedures.

Michael Warnock[1], Luke Ogonda[1], Peter Yew[1], Gerry McIlvenny[2]

Provenance: externally peer reviewed.
Accepted: 7th January 2019

ABSTRACT

Introduction Prophylactic antibiotics have been shown to reduce the rate of surgical site infection (SSI) [1], however there is little evidence supporting the effectiveness of one antibiotic over another. We have studied SSI rates and antibiotic prophylaxis protocols in Northern Ireland trauma surgery over a 10-year period to Identify the most effective antibiotic protocol associated with lowest rate of SSI.

Method Antibiotic prophylaxis protocols from 2004-2014 were sought from each of the region's 4 trauma hospitals and their dates of introduction recorded. For the same period, the number of trauma procedures carried out quarterly and the number of SSIs were recorded for each hospital from the return of prospectively collected SSI surveillance forms.

Results 26849 trauma procedures were included with an overall SSI rate of 1.34% (95% Confidence interval [CI] 1.21 to 1.49). Single dose flucloxacillin (2 grams) with single dose gentamicin (3mg/kg) was the most commonly used protocol used in 3 different hospitals for a combined 13.5 years covering 11445 procedures. The SSI rate was 0.72% (95% CI 0.58-0.89). Triple dose cefuroxime (1.5 grams) was used in 2 different hospitals for a combined 10 years covering 8864 procedures. The SSI rate for this regime was 2.46% (95% CI 2.16-2.80). Single dose cefuroxime (1.5 grams) was used in 2 different hospitals for a combined 8 years covering 6540 procedures. The SSI rate was 0.92% (95% CI 0.71-1.18).

Conclusion In this prospective observational cohort study prophylaxis using flucloxacillin and gentamicin was associated with the lowest SSI rate. Single dose cefuroxime was associated with a lower rate of SSI compared to triple dose ($p<0.001$). Identification of antibiotic regimes associated with the lowest SSI rates will promote the judicious use of antibiotics, improve antibiotic stewardship while allowing for continued benefit in the prevention of SSI in an era of ever-increasing antibiotic resistance.

INTRODUCTION

Surgical site infection (SSI) remains an important complication of surgical trauma care. It results in increased mortality, prolonged hospital stays, further revision surgery, increased antibiotic use and extended follow up and rehabilitation [2]. SSI is the second most common healthcare associated infection in Northern Ireland accounting for 19% of reported infections [2]. Overall risk of developing SSI following surgery for fractures of the hip has been reported to be 4.97% with a third of these cases representing a deep infection. The cost of treating one such patient has been estimated to be £31,164. An annual report published by Public Health England for 2016-2017 reported SSI rates in fracture surgery between 1-1.5% [3].

Prophylactic antibiotics have been shown to reduce the rate of SSI and their use has been integral to orthopaedic and trauma surgery practice in the prevention of SSI [1]. Despite the established strong evidence for prophylaxis there is little evidence supporting the use of one antibiotic over another or the use of single over multiple dose prophylactic regimes [4].

Staphylococcus aureus (*S.aureus*) and coagulase negative staphylococci such as *Staphylococcus epidermidis* are the most common causative organisms while gram negative bacilli can also be implicated. Cephlosporins (e.g. cefuroxime) offer cover against most *S.aureus* and some gram-negative organisms. They also have a good safety profile, long half-life and good penetration in bone, synovium and muscle. Despite this however their use in the UK has been limited by concerns over *Clostridium Difficile* infection (CDI) [4].

1. Ulster Hospital, South Eastern Health and Social Care Trust, Upper Newtownards Rd, Dundonald, Belfast, Northern Ireland
2. Public Health Agency, 12-22 Linenhall St, Belfast , Northern Ireland BT2 8BS

Correspondence to: Mr Michael Warnock

Email: michael.warnock@doctors.org.uk

Flucloxacillin is a penicillinase-resistant penicillin with good *S. aureus* cover. It has very commonly been combined with gentamicin for prophylaxis in both elective orthopaedic and trauma surgery. Indeed, this regime been used in up to 50% of NHS trusts in the UK for prophylaxis [5]. Gentamicin, an aminoglycoside, offers activity against gram-negative and gram-positive bacteria including *S.aureus*. Teicoplanin and Vancomycin, glycopeptides, have been reserved for prophylaxis in patients who are Methicillin Resistant *Staphylococcus aureus* (MRSA) positive or patients who have a penicillin allergy. Teicoplanin is usually favored over Vancomycin in penicillin allergic patients due to increased development of vancomycin resistance [6].

In an era of evolving antibiotic resistance, vigilant surveillance and judicious use of antibiotics for prophylaxis in trauma surgery is essential to ensure effectiveness as resistance and SSI pose a significant threat to future outcomes. In this prospective observational cohort study, trends in antibiotic prophylaxis and SSI rates in Northern Ireland trauma surgery are reported.

METHODS

The 3 most commonly used antibiotic prophylactic regimes over a 10-year period (2004-2014) were identified from each of the region's 4 trauma units as well as their dates of introduction to the nearest yearly quarter. For the same period, the total number of trauma procedures carried out and the number of SSIs, were provided by The Public Health Agency (PHA), the statutory custodian of all public health data. This data is collected prospectively from Surgical Site Infection Surveillance forms which are filled out immediately post operatively and returned. Only those with fully completed forms were included. Permission for access to each unit's data held by the PHA was sought and approved from the relevant clinical lead. Exclusion criteria included day case surgery, failure of return of completed surveillance form, invalid procedures (e.g. diagnostic) and spinal surgery. The antibiotic regime used in each trauma unit, time of use to the nearest yearly quarter, the total number of procedures and subsequent SSIs were recorded. Where the same antibiotic regimes were used across different sites and different times these along with their number of associated SSI were combined for analysis. SSI rates per 100 procedures was calculated and compared between antibiotic regimes. There was no individual patient data collected. Statistical analysis was performed using STATA (IC) Version 4 for Microsoft Excel and the Wilson method for calculating binomial confidence intervals [7].

RESULTS

The 3 different prophylactic regimes included single dose flucloxacillin (2 grams) with single dose gentamicin (3mg/kg), triple dose cefuroxime (1.5 grams) and single dose cefuroxime (1.5 grams). The protocols for MRSA positive and penicillin allergic patients were the same throughout all hospitals (initially Vancomycin 1 gram single dose then changed to Teicoplanin 10mg/kg single dose).

Flucloxacillin and Gentamicin was used across 3 out of the 4 different trauma units for a combined 13.5 years (total number of years used for each hospital combined). It was the most commonly used regime. Triple dose cefuroxime was used across 2 of the 4 trauma units for a combined 10 years and single dose cefuroxime was also used across 2 of the 4 trauma units for a combined 8 years. From the PHA and after screening for exclusion criteria a total of 26,849 procedures were included in the study. The number of procedures covered and the corresponding antibiotic prophylactic regime usage is shown in *Figure 1*.

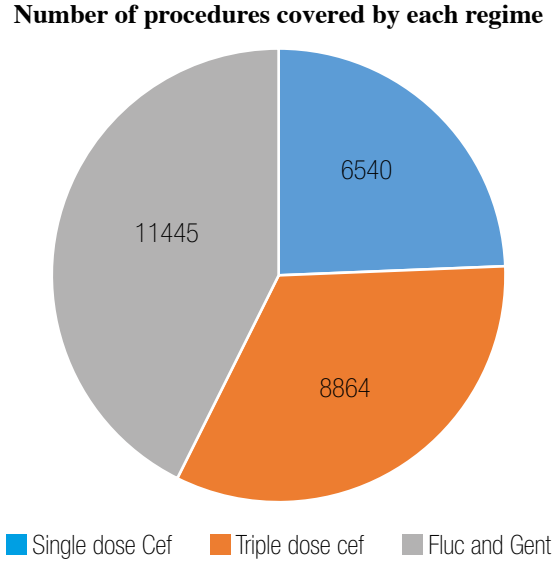


Fig 1. Pie chart showing number of procedures covered by each antibiotic prophylactic regime

Overall the SSI rate in trauma surgery in Northern Ireland for the 10 years was 1.34%. Flucloxacillin and Gentamicin regime covered 11445 procedures and 82 SSIs were recorded. Triple dose cefuroxime covered 6664 procedures with 218 SSIs and single dose covered 6540 procedures with 60 SSIs. Rate of SSI for each regime is shown in *Figure 2*.

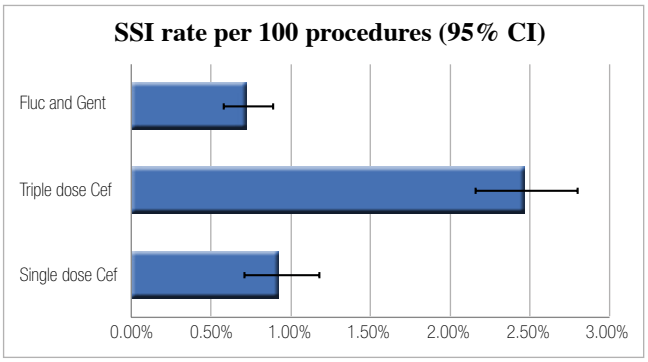


Fig 2. SSI rate (95% confidence interval) and antibiotic prophylactic regime

DISCUSSION

The development of SSI is a complex issue. It is multi-factorial and requires best practice to reduce modifiable risk factors. Prophylactic antibiotics are an integral part of trauma care and as such clinicians need to have an up to date

understanding of their indications, interactions and associated complications.

	Single dose Cef	Triple dose Cef	Fluc and Gent
Procedures	6540	8864	11445
SSI	60	218	82
SSI rate	0.92% (95CI 0.71-1.18)	2.46% (95% CI 2.16-2.80)	0.72% (95%CI 0.58-0.89)

Fig 3. Table of Procedures, Number of SSI and SSI rate

In this prospective observational cohort study, we have a single variable (prophylactic antibiotic regime) and a single outcome measure (development of SSI). This is a simplification of a very complex issue, but we believe important points are raised and the strength of the study is enhanced by the large numbers assessed. A clear weakness is not proving the different regimes are statistically similar in terms of other risk factors for development of SSI but it should be highlighted that in the region patient characteristics is unlikely to vary significantly between the different units and therefore the regimes.

In Northern Ireland, Flucloxacillin and Gentamicin is the most commonly used antibiotic regime which corresponds to that of the rest of the UK. It has a very favourable associated SSI rate and, in this study, the lowest. However, it should be noted that concern has arisen from use of this regime with regards to increased risk of acute kidney injury (AKI). Patients undergoing trauma surgery, and in particular, patients with a fractured hip are an at-risk population. Additional risk factors include older age, pre-existing renal impairment, dehydration and concomitant use of diuretics, antihypertensive and non-steroidal anti-inflammatory drugs (NSAIDs). In a large study from Dundee, Scotland [8] of 7666 orthopaedic patients, a change from cefuroxime to flucloxacillin and gentamicin antibiotic prophylaxis was associated with a 94% increase in AKI in orthopaedic trauma surgery and demonstrated that a higher proportion of patients with AKI died within 1 year of surgery than patients without AKI (20.8% versus 8.2% respectively). It is unclear which specific antibiotic is the cause or indeed if it is the combination. Flucloxacillin is associated with acute interstitial nephritis [9] and gentamicin is a direct tubular toxin. The risk of AKI has led to reconsideration of this regime in orthopaedic trauma surgery in Scotland.

Cephalosporins have reduced in use in the UK due to concerns about CDI [5]. CDI is an important healthcare associated infection. Antibiotics increase risk of CDI for at least 3 months [10] and even short courses of perioperative antibiotic prophylaxis have been associated with increased risk of CDI particularly in context of established outbreaks [11]. Third generation cephalosporins have been particularly implicated in CDI and one retrospective review of 625 trauma and orthopaedic patients receiving prophylaxis with cefuroxime compared with 706 patients receiving flucloxacillin and gentamicin showed reduction in CDI from 4% to 1% (p= 0.0004) [12].

In this study, multiple doses of cefuroxime (8864 patients, SSI rate 2.46%) has been associated with an increased risk of SSI compared to a single dose (6540, SSI rate 0.92%) (p<0.001). The reasons for this are not clear. What this study does is add weight to the evidence that there is no increased benefit of multiple dose antibiotic prophylactic regimes over single dose. In a refined meta-analysis reporting outcome for 921 patients who received either single or multiple doses of the same cephalosporin for prophylaxis in hip fracture surgery or closed fracture fixation no significant difference in overall SSI rate was demonstrated [13]. A recent review by *Bryson et al*. highlighted that evidence supporting single dose prophylaxis is not reflected in current practice [6]. This suggests a lack of knowledge of current research, fear of SSI or a general aversion to change has made clinicians reluctant to adopt single dose regimes. If there is an associated increase in SSI rate then why do we continue to prescribe multiple doses when there is, in addition, potential to promote resistance, increase risk of hospital acquired infection such as CDI and increase associated costs of intravenous antibiotics, including potential prolonged hospital stay?

One limitation of this study that has already been highlighted is that SSI is a multi-factorial problem and we have only assessed one variable. Additionally, the antibiotic regimes and their date of introduction are to the nearest yearly quarter and so there may have been some overlap when regimes changed. The PHA records do not make note of whether there is a compound injury or indeed if any patients are on antibiotics for a different reason preoperatively. These patient numbers should be very small however. It was not possible to accurately correlate the SSI surveillance form return rate as it was not available for all the years included and for all the units. The PHA previous estimates it to vary between 55-100% in orthopaedic trauma surgery. More consistent higher rates are achieved in elective orthopaedic surgery.

MRSA rates were not assessed in this study and the authors are keen to highlight any effective antibiotic prophylactic protocols are dependent upon robust and efficient pre-operative MRSA screening. The proportion of patients admitted to trauma and orthopaedics in Northern Ireland who are MRSA positive on screening is approximately 1%. [4] Indeed, it should be noted that MRSA and other antibiotic resistant bacteria are the very reason that studies such as this are important. The threat of increasing bacterial resistance to the future of effective prophylaxis in trauma and orthopaedic is very real. In the United States, at least two million illnesses and 23000 deaths a year are caused by antibiotic resistant bacteria and roughly two in every 100 people carry MRSA [14]. While the scale of the problem is not the same in the UK, it may well be in the future and this highlights the importance of judicious use of antibiotics.

CONCLUSION

In this prospective observational cohort study prophylaxis using flucloxacillin and gentamicin was associated with the lowest SSI rate. Although used in fewer procedures, single dose cefuroxime was associated with a lower rate of SSI compared to triple dose. Additional consideration must be given to side effect profiles not assessed in this study. Identification of antibiotic regimes associated with lower SSI rates will promote the judicious use of antibiotics and improve antibiotic stewardship while allowing for continued benefit in the prevention of SSI in an era of ever-increasing antibiotic resistance.

REFERENCES

1. Boxma H, Broekhuizen T, Patka P, Oosting H. Randomised controlled trial of single dose antibiotic prophylaxis in surgical treatment of closed fractures: The Dutch Trauma Trial. *Lancet*. 1996;**347(9009)**:1133-7.
2. Public Health Agency. *Northern Ireland point prevalence survey of hospital acquired infections and antimicrobial use*. Belfast: Northern Ireland Public Health Agency; 2012.
3. Public Health England. Surveillance of surgical site infections in NHS Hospitals in England. April 2016 to March 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/666465/SSI_annual_report_NHS_hospitals_2016-17.pdf. Last accessed: 26th January 2019.
4. Mackay DC, Harrison WJ, Bates JH, Dickenson D. Audit of deep wound infection following hip fracture surgery. *J R Coll Edinb*. 2000; **45(1)**: 56-9.
5. Edwards C, Counsell A, Boulton C, Moran CG. Early infection after hip fracture surgery; risk factors, costs and outcome. *J Bone Joint Surg Br*. 2008;**90(6)**:770-7.
6. Bryson DJ, Morris DL, Shivji FS, Rollins KR, Snape S, Ollivere BJ. Antibiotic prophylaxis in orthopaedic surgery. *Bone Joint J*. 2016;**98-B(8)**:1014-9
7. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*. 1927; **22**: 209-12.
8. Bell S, Davey P, Nathwani D, Marwick C, Vadiveloo T, Sneddon J, et al. Risk of AKI with gentamicin as surgical prophylaxis J Am Soc Nephrol. 2014;**25(11)**:2625-32.
9. Pusey CD, Saltissi D, Bloodworth L, Rainford DJ, Christie JL. Drug associated acute intersitital nephritis: clinical and pathological features and response to high dose steroid therapy. Q J Med. 1983;**52(206)**:194-211.
10. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for Clostridium difficile infection after exposure to antibiotics. *J Antimicrob Chemother*. 2012;**67(3)**:742-8.
11. Carignan A, Allard C, Pépin J, Cossette B, Nault V, Valiquette L. Risk of Clostridium difficile infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. *Clin Infect Dis*. 2008;**46(12)**:1838-43.
12. Al-Obaydi W, Smith CD, Foguet P. Changing prophylactic antibiotic protocol for reducing Clostridium difficile-associated diarrhoeal infections. *Orthop Surg (Hong Kong)* 2010;**18**:320–323.
13. Morrison S, White N, Asadodallahi S, Lade J. *SIngle versus multiple doses of antibiotic prophylaxis in limb fracture surgery. ANZ J Surg*. 2012;**82(12)**:902-7
14. Bingyun L, Webster TJ. Bacteria Antibiotic Resistance: New Challenges and Opportunities for Implant-Associated Orthopaedic Infections. *J Orthop Res*. 2018 Jan; **36(1)**: 22–32.

Ulster Med J 2019;**88(2):**115-117

Medical History/Education

Direct Ophthalmoscopy… Soon to be Forgotten?

Katherine McGinnity[1], Michael Williams[2]

Accepted: 26th January 2019
Provenance: Internally reviewed

Key words: Ophthalmoscopy, education, clinical skills

The direct ophthalmoscope was first developed in 1851 by Hermann Von Helmholtz (Figure 1).[1] Helmholtz noticed that the pupil normally appeared black, but under certain conditions seemed bright and red. He realised that the emitted light was *reflected* light, and advanced understanding by analysing how the emitted rays formed optical images. In order to obtain an image of the fundus he devised an instrument that would allow his own eye to be placed directly in line with the light rays entering and leaving the eye. Microscopic cover glasses served as mirrors to reflect light, and being transparent, allowed visualisation of the retina.[1]

Fig 1. An example of the first direct ophthalmoscope, Hermann von Helmholtz, 1851, held in the museum of the Royal College of Ophthalmologists' Collection, London, image courtesy of Mr Richard Keeler

His discovery transformed healthcare. Ophthalmoscopy became an integral part of the general medical examination as the new technology became generally adopted. Richard Liebreich produced an ophthalmoscope which offered a choice of correcting lenses, each held in turn in a clip behind the viewing mirror (Figure 2). It was first produced in the 1860s, and still available 80 years later. In 1880, Pickard and Curry produced an ophthalmoscope with a rotating disc of lenses, and a folding handle (Figure 3) and in 1886, the first ophthalmoscope with a built-in bulb, by Henry Juler, became available. Today technology is similarly developing in ways that would fascinate those who worked to improve the ophthalmoscopes of the 19th century. With little regard for the beauty of the original ophthalmoscopes however, debate exists as to whether the ophthalmoscope still has a place in healthcare education, given the likely advent of mobile retinal imaging systems.

Fig 2. An example of Richard Liebreich's ophthalmoscope, c1860, held in the museum of the Royal College of Ophthalmologists' Collection, London, image courtesy of Mr Richard Keeler.

Visualising the fundus is a critical skill as identification of retinal signs can be both life-saving and sight saving, as signs may have systemic relevance, for example swollen discs reflecting papilloedema, a retinal vein occlusion as the presenting manifestation of undiagnosed hypertension or a choroidal metastasis from a colorectal carcinoma. For medical students, it has been considered by some unrealistic to expect them to achieve a reliable level ophthalmoscopic proficiency during their course.[2] While identification of fundus signs is important, how it is done is not essential.

The direct ophthalmoscope instrument offers several advantages over alternative imaging methods. It gives a x15

1. Dr Katherine McGinnity, Northern Ireland Medical and Dental Training Agency. 2. Dr Michael Williams, Centre for Medical Education, Queen's University of Belfast

Correspondence to:Dr Michael Williams

E-mail: m.williams@qub.ac.uk

magnified view of the fundus, facilitating the appreciation of small changes in the retina, such as small fronds of new blood vessels. Being a 'live' imaging system, dynamic changes can also be seen, i.e. venous pulsation at the disc. The ophthalmoscope is widely available and is part of the culture of healthcare such that some medics maintain their ophthalmoscopy skills and can teach others. It is portable and inexpensive, and so can be part of the literal toolbox, for example during home visits where other modalities of ocular fundus examination are unavailable or impractical. It is also useful for patients with low grade nystagmus or unstable visual fixation.[3] Educationally, ophthalmoscopy reinforces understanding of ocular anatomy, taking advantage as it does of the accessibility of the eyes to direct visualisation. Also, learning how to perform ophthalmoscopy allows learning of a more generic skill: that of how to interact with patients in seeking their collaboration in what is quite an intimate examination, given the close proximity of patient and doctor during ophthalmoscopy. Thus, having medical students wield the ophthalmoscope allows them to rehearse negotiation with patients on the examination process.

Fig 3. Pickard and Curry's ophthalmoscope, c1880, held in the museum of the Royal College of Ophthalmologists' Collection, London, image courtesy of Mr Richard Keeler.

On the other hand, a fundus camera is relatively simple to use with minimal training, as demonstrated in the 'Fundus photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department' (FOTO-ED) study.[4] In this study 350 patients presenting to an ED had fundal photos taken by nurse practitioners. The nurse practitioners' training consisted of written materials, up to 30 minutes of direct training and a period of being observed. The images were then assessed by ophthalmologists. Eighty-three percent of patients had at least one eye with an image of gradable quality, and only 3% had no gradable images. The ease, comfort and speed of obtaining images was rated highly by nurses and patients alike.

The fundus camera has the added ability to zoom-in on areas of interest. A permanent objective record is created which can be kept on file and compared on re-attendance or compared to text books or images online. Lesions can be measured. Patients can be shown their pathology, useful for patient education.

As with radiology and dermatology, retinal photography does not necessarily require an ophthalmologist to be present with the patient, so images can be transmitted for review remotely. Fundus photography also facilitates teaching of signs, in that teaching time is not spent learning the skill of seeing the retina, with the teacher of ophthalmoscopy uncertain as to whether the student has seen the relevant sign or not. This was demonstrated in the 'Teaching Ophthalmoscopy To Medical Students study' (The TOTeMS Study) [5], a prospective randomised study comparing direct ophthalmoscopy with non-mydriatic fundus photography for examination of the retina by medical students. Fundal photographs were preferred by 77% of the 138 students, and diagnostic accuracy was significantly better when photographs were used compared to ophthalmoscopy, a difference that persisted when retested one year later. [6] From the patient's viewpoint, the fundus camera avoids light being shone in the eye for what may be a prolonged period of time during ophthalmoscopy. The disadvantages of ophthalmoscopy and photography are then self-evident.

Ophthalmoscopy is a difficult skill to master for several reasons. The view is time-limited as patients cannot tolerate the examination indefinitely. The view may be made more difficult by media opacities. The field of view is narrow (to visualize the entire retina it would require the clinician to systematically review 172 fields in order not to miss a sizeable lesion of 2 disc diameters). [7] Pharmacological dilatation makes retinal visualization easier but is time-consuming and uncomfortable for the patient. In a questionnaire-based study of 150 medical primary care practitioners, only 53% expressed confidence in using the ophthalmoscope. [8] Merely attempting ophthalmoscopy is said to be not good enough as ocular findings need to be reliably detected, and incompetent ophthalmoscopy may lead the practitioner to mistakenly exclude signs.[9] In the FOTO-ED study, comparing ophthalmoscopy to fundal photography in patients presenting to the ED, clinically important signs were missed with ophthalmoscopy.[10] Furthermore anecdotally, ophthalmoscopes are sometimes poorly maintained throughout hospitals.

Fundus cameras however, are expensive and not portable. This may all change as novel innovations such as the Peek Retina emerge (https://www.peekvision.org accessed November 2018). Peek Retina is a 0.35kg camera that is clipped onto a smartphone and allows non-mydriatric fundal photography. Validation is ongoing: agreement of cup to disc ratio measurement for example using images taken with the Peek Retina compared to standard fundal photographs has been demonstrated.[11] Making fundal photography accessible to all may transform ophthalmic examination, and may have particular impact in the developing world.

In conclusion however, it is the authors' view that until validation and wide availability of portable digital ophthalmoscopy occurs, direct ophthalmoscopy should still be taught to medical students, but must be done so in the context of its limitations and in the knowledge, that it may not always be the modality of choice for fundus imaging when they graduate. Studies are needed to determine the practice and preferences of medics with regard to fundal visualization.

None of the authors have any conflict of interest to declare.

No funding was sought or supplied for this project.

REFERENCES:

1. Pearce JM. The ophthalmoscope: Helmholtz's Augenspiegel. *Eur Neurol*. 2009;**61(4)**:244-9.
2. Ah-Kee E, Husni D, Khan A, Lim LT. An alternative to direct ophthalmoscopy. *Clin Teach*. 2016;**13(4)**:316.
3. Mackay DD, Garza PS, Bruce BB, Newman NJ, Biousse V. The demise of direct ophthalmoscopy: A modern clinical challenge. *Neurol Clin Pract*. 2015;**5(2)**:150-7.
4. Bruce BB, Lamirel C, Biousse V, Ward A, Heilpern KL, Newman NJ, *et al*. Feasibility of nonmydriatic ocular fundus photography in the emergency department: Phase I of the FOTO-ED study. *Acad Emerg Med*. 2011;**18(9)**:928-33.
5. Kelly LP, Garza PS, Bruce BB, Graubart EB, Newman NJ, Biousse V. Teaching ophthalmoscopy to medical students (the TOTeMS study). *Am J Ophthalmol*. 2013;**156(5)**:1056-61 e10.
6. Mackay DD, Garza PS, Bruce BB, Bidot S, Graubart EB, Newman NJ, *et al*. Teaching ophthalmoscopy to medical students (TOTeMS) II: A one-year retention study. *Am J Ophthalmol*. 2014;**157(3)**:747-8.
7. Orlans HO. Direct ophthalmoscopy should be taught within the context of its limitations. *Eye (Lond)*. 2016;**30(2)**:326-7.
8. Shuttleworth GN, Marsh GW. How effective is undergraduate and postgraduate teaching in ophthalmology? *Eye (Lond)*. 1997;**11 (Pt 5)**:744-50.
9. Purbrick RM, Chong NV. Direct ophthalmoscopy should be taught to undergraduate medical students--No. *Eye (Lond)*. 2015;**29(8)**:990-1.
10. Bruce BB, Lamirel C, Wright DW, Ward A, Heilpern KL, Biousse V, *et al*. Nonmydriatic ocular fundus photography in the emergency department. *N Engl J Med*. 2011;**364(4)**:387-9.
11. Bastawrous A, Giardini ME, Bolster NM, Peto T, Shah N, Livingstone IA, *et al*. Clinical validation of a smartphone-based adapter for optic disc imaging in Kenya. *JAMA Ophthalmol*. 2016;**134(2)**:151-8.

Ulster Med J 2019;**88(2):**124-127

Medical Education

The Long Case as a Formative Assessment Tool – Views of Medical Students

Claire Shama Masih, Claire Benson

Accepted: 19th February 2019
Provenance: Externally peer reviewed. Derived from MClinEd presented to QUB

INTRODUCTION

The long case has been valued for its authenticity and holistic patient assessment but due to contextual specificity and unreliability it has also been criticised.[1,2,3,4,5,6] Time is a defining characteristic of the "long" case but is also the major impediment to increasing its reliability by introducing more cases[5]. Attempts to improve reliability include adaptations into OSLERs and mini-CEXs allowing more direct observation.[7,8]

Despite awareness of limitations of the long case, our institution continues to use it for formative assessment of medical students undertaking musculoskeletal attachment. We undertook a largely qualitative study to ascertain the views of medical students on the value of the long case, with the specific question, "are medical students in favour of the long case as a formative assessment tool?"

A literature search of the Ovid® database using search terms 'Assessment', 'Long Case' and 'Medical Student' retrieved 70 relevant articles, only 3 of which included student opinion.[9,10,11] Our study adds to the extensive literature on reliability and validity of the long case by examining educational impact and acceptability.[12]

METHODS

The study was undertaken for a Masters in Clinical Education degree and ethical approval for all aspects was secured from the Medical School's Research Ethics Board. Anonymity of participants was ensured and voluntary informed consent was obtained with adherence to all required aspects of data protection as per University policy.

A questionnaire and a series of focus groups were used to assess the primary outcome - whether students were in favour of the long case as a formative assessment tool. Inclusion criteria were third year students undertaking musculoskeletal attachment in our Institution from September to December 2017. This comprised four sets of up to 30 students undertaking a 3 week attachment with a total of 106 students attending during the study. The small number of third year students who attended an alternative Institution was excluded.

Due to student numbers (30 every 3 weeks) there are insufficient suitable inpatients to allow individual long cases in rheumatology. Groups of up to five students are assigned a rheumatology inpatient for their long case on Monday and each student given a specific area on which to concentrate, for example history of presenting complaint or hand examination. Students prepare the case in their own time and present the case as a group at the bedside to a supervising tutor on the Thursday for formative assessment. Tutors give feedback to the group and may conduct further teaching on the case.

Questionnaires were completed by consenting students after their long case and collected from an assigned folder to ensure anonymity. Questionnaires from each student set were studied with coding of Likert question responses (Figure 1) and free text comments. Focus groups took place on the final day of the students' attachment, led by the principle investigator with conversations recorded and transcribed. Thematic analysis was undertaken of questionnaire and focus group data and representative quotations selected.

The study supervisor undertook an independent analysis of the data to provide rigour and independently agreed with the thematic analysis. It was planned to analyse questionnaires using a Chi squared test comparing categorical data on two levels but there were insufficient numbers to allow this. The alternative Spearman's ϱ-test was applied using the SPSS® (IBM Statistical Package for the Social Sciences) software package to compare ordinal variables.

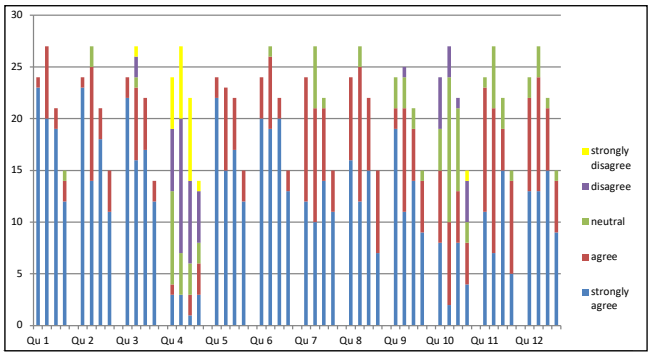
RESULTS

An 86% response rate to questionnaires was achieved which was appropriate for analysis. There was a trend for older students to have completed more previous long cases, which was statistically significant ($p<0.025$) and unsurprising. A proportion (10-15%) seemed to have spent less than 15 minutes with the patient either in preparation or presenting the case, which raises doubt about the validity of their experience as an example of a genuine "long case". Feedback from the doctor was positive or mixed in all cases except one who reported receiving no feedback. Feedback from the patient was more variable. No statistical correlation was found between time spent in preparation, feedback, age, or

Department of Rheumatology, Musgrave Park Hospital, Belfast Health and Social Care Trust, Northern Ireland, UK

Correspondence to: Dr Claire Masih

E-mail: clairemasih@doctors.org.uk



Qu 1: It was easy to make contact with the patient
Qu 2: The patient was available to meet at a suitable time
Qu 3: The ward allowed sufficient time and space to meet
Qu 4: I had reservations about interacting with the patient
Qu 5: The patient was happy to interact with me
Qu 6: I learnt new facts about the condition
Qu 7: The patient gave me clear and accurate information
Qu 8: I understood what it was like to live with the condition
Qu 9: The patient was at ease throughout
Qu 10: I learnt more from the long case than bedside teaching
Qu 11: The long case was an enjoyable way to learnt
Qu 12: The long case was good practice for starting work

Fig 1. Graphical representation of responses to Likert questions of questionnaire

Results for the four student sets are displayed for each question.

sex and whether students were in favour of the long case. Students reported an overall positive view of the long case in terms of organisation, patient and student acceptability, and educational impact. Response to one question ("I learnt more from the long case than other bedside teaching sessions") had a more varied response with most students reporting neutral response. Most students were in favour of the long case; (84 for, 3 against, 4 missing = 92% overall, or 97% valid answers). One student reported they found the long case *"repetitive and uninteresting"*, and strongly disagreed that they had learnt more from the long case than from bedside teaching sessions. The other students not in favour of the long case gave no free text reasons.

There were frequent free-text comments that the long case was *"good practice"*. Other comments reflected the depth of the long case as an advantage with phrases such as *"thorough"*, *"detailed learning"* and *"extra time"*. Students valued the opportunity for patient interaction with mention of improved confidence, communication, and understanding the patient's experience. Key words often repeated by students were *"real"* and *"integrated"*. There were references to *"real life"*, *"a real patient"*, *"realistic experience"* and linking lectures or textbooks to real cases. Regarding disadvantages of the long case, most students focussed on logistical problems. These included the patient being tired, occupied by meals, visitors and tests, feeling inconvenienced by teaching, students finding it hard to decide when to see the patient and feeling uncomfortable approaching the patient without an introduction. Four students found the presentation *"stressful"*, *"nerve-wracking"* or *"intimidating"*. Only 6 students made note of the disadvantage most mentioned in the literature, that the long case narrowly focusses on one encounter and knowledge gained in this encounter may not transfer to cases in general (contextual specificity). A phrase used which captures this point was, *"only so much to be learnt from one patient"*.

Only one dissenting voice chose "disagree" for question 3 ("The ward environment allowed me time and space to see the patient"). In fact it was clear that students had frequent difficulties in the ward and perhaps most students had not reflected in detail before answering this question, or felt disinclined to respond in a negative way concerning the ward.

We intended to hold 4 focus groups but insufficient numbers attended for the first focus group to be properly viable. Subsequent sets were successful with 6 students attending from sets 2 and 3, and 8 from set 4. Thematic analysis from focus group discussion revealed a breadth of both positive and negative views of the long case.

DIFFICULTIES UNDERTAKING THE LONG CASE

There was poor understanding of what was meant by a "long case" reflecting its declining use as a term. Requests for more guidance were common. Students also frequently commented on difficulties with the ward environment.

"it was like, a long case, what is that?"2D

"it could be a nightmare … you literally don't have a clue and no one really teaches you how to do them"3D

"It took so long to go through it all…it almost was causing hassle on the ward....like the lunch was sitting outside and it was just an absolute havoc..." 2B

"the patient's been away having tests or they're sleeping or people are there, and [we] found it quite stressful just being able to speak to the patient" 4H

THE LONG CASE WAS NOT A "FAIR" METHOD OF ASSESSMENT DUE TO CASE VARIABILITY

Students were able to identify the main disadvantage of the long case, namely the high contextual specificity. They frequently described the case as not "fair".

"it's hard to standardize because different patients have different levels of complexities…so like some of us might, may have a tougher time…so I guess it's good in the sense that it's formative and not, you know, summative."3E

"I just feel it's totally variable and not fair for everyone." 2A

"you're not getting the same exposure as everyone else and say that group's case came up in the exam you're kinda raging." 4E

AUTHENTICITY OF THE PATIENT ENCOUNTER

Students recognised this advantage of the long case which has been extensively discussed in previous literature.

"It grounds what you're learning in practice….it's actually really interesting to meet the patient and see what it looks like in practice."3C

"An OSCE is kind of fabricated, yeah, it's not real life." 4H

HOLISTIC "WHOLE PERSON" MEDICINE

This advantage of the long case has also been previously well recognised. The students used terms reflecting integration.

"in a long case you did everything, you see everything and you were able to tie it all together better" 4E

"you're not just focussing in, so you're getting an idea of the patient as a whole." 4H

EDUCATIONAL VALUE

The most varied views were on educational value of the long case. There are probably too many student, patient and tutor variables in each case to declare that the long case of itself is educationally valuable. Early detailed patient encounters are certainly memorable occasions which can help consolidate learning.

*"If I think of lupus I'll picture her so it makes the stuff easier to remembe*r." 3D

Encounters with real patients may be taken more seriously than simulated patients and this may improve the educational value of the long case.

"..preparing you for your exams then simulated patients are good but actually preparing you for being a doctor the patients on the ward is what you need." 2D

However other students did not feel preparing the long case was educationally valuable and required the presence of a tutor in order to feel that effective learning was taking place and tended to prefer bedside teaching.

"I learnt more by interacting more with the consultant."3C

"Having the consultant there and guiding me was definitely when I learnt."3E

As there is no summative testing on rheumatology during the musculoskeletal attachment it is difficult to know how well students genuinely retained the information from their teaching and we cannot make any objective comment on the true educational value of the long case. Some long case encounters are wonderful learning opportunities as stated by one student:

"I can clearly see that patient in my head and probably will do for the rest of my medical career now." 3F

Some are as stated in one questionnaire "*repetitive and uninteresting*".

STRENGTHS AND LIMITATIONS OF THE STUDY

By using both questionnaires and focus groups triangulation of methods was achieved and the study was able to include quantitative findings. Questionnaire return rate of 86% and focus group participation by 19% of the study population was achieved. Being aware of investigator reflexivity, the researcher kept a research diary. Participating students were sent a copy of the study write-up for comment to ensure respondent validation had occurred.

Due to time restrictions, a convenience sample was employed which is a weak sampling method. Students from a single academic year in one institution were sampled and only the first half of the year undertaking musculoskeletal attachment was included. As focus groups rely on volunteers, we acknowledge that a random sample of students may not have been achieved as participants may differ from non-participants. Investigator reflexivity is a potential limitation to all qualitative research as analysis can be subjective and prone to bias. The fact that the lead investigator had an interest in the long case and has spent time researching it may predispose her in favour of the long case.

DISCUSSION

Students were able to correctly identify the accepted advantages of the long case in terms of its authenticity and holistic nature. Their language did not include the standard terminology but they spoke of the long case "integrating" many aspects and involving a "real" patient encounter. The questionnaires demonstrated an understanding of these advantages and aligned well with the more detailed views expressed in focus group discussions. Concerning disadvantages of the long case, the brief comments on the questionnaires were more superficial and mainly included practical difficulties faced conducting the long case, some of which might have been specific to our long case set-up. It took the more detailed discussion in the focus groups to allow the issues surrounding "fairness" to surface, but these were also strongly felt. Again, the students used layman's language to describe this recognised problem of "reliability" in the long case.

The opportunity for feedback was mentioned as an advantage of the long case in questionnaire responses. In the focus group discussions, requests for better feedback emerged as a strong theme.

"It's the feedback you need; you need feedback to improve and I just think that's the most important thing" 3D

In this study, a single doctor acting as tutor supervised each case and gave formative feedback. The tutors may not have had specific training in delivering feedback, and feedback was given in a group setting, potentially limiting what could be said to individual students. Interestingly one of the only three studies to look at medical student views also identified the quality of feedback as an important variable[13].

This study found that despite the disadvantages voiced, the vast majority of students were in favour of the long case. As well as supporting the existing literature, this study identified new themes regarding medical students' views on the long case, namely difficulties conducting a long case and importance of feedback. Previous studies on logistical issues are limited to costs when the long case is used for examinations, and do not cover other practical issues. [13] Our students had problems with their timetable, the ward environment, coordinating groups, understanding how to conduct the long case, and meeting the patient. While we want students to show initiative and adaptability and become familiar with the real ward environment, we also want to maximise teaching and learning opportunities. This study has shown the importance of these issues when it comes to medical students' experience of the long case, and if we want to improve we must address them wherever possible. We acknowledge that these issues depend to a great degree on the specific context and do not apply to long cases in general.

It should also be possible to modify our feedback arrangements for the long case, such as stating that feedback is being given, delivering fair and structured comments and issuing corrections where necessary, especially in examination technique. We have discussed how there was divergence of opinion among the students regarding whether the long case was educationally valuable. The educational value of the experience may have depended on the degree to which practical difficulties overshadowed the case and also the quality of feedback delivered afterwards.

In summary, the long case can be a useful tool for formative assessment as well as a rich source of learning for medical students. However, every long case is unique and amongst the variety there will be exciting cases that students recall throughout their careers as well as cases of poor educational value which students may not enjoy. In this way, long cases reflect the real world of medicine where some cases before us can be mundane or difficult but all are patients deserving of our attention and care.

REFERENCES

1. Wass V, van der Vleuten C. The long case. *Med Educ*. 2004; **38(11)**:1176-80
2. Ponnamperuma GG, Karunathilake IM, McAleer S, Davis MH. The long case and its modifications: a literature review. *Med Educ*. 2009; **43(10)**:936-41
3. Norcini J. The validity of long cases. *Med Educ*. 2001; 35(8):720-1.
4. van der Vleuten C. Making the best of the 'long case'. *Lancet*. 1996;**347 (3)**:704–5.
5. Harden RM. Revisiting 'Assessment of clinical competence using an objective structured clinical examination (OSCE)'. *Med Educ*. 2016; **50(4)**:376-9.
6. Wass V, Jolly B. Does observation add to the validity of the long case? *Med Educ*. 2001;**35(8)**:729–34.
7. Gleeson F AMEE Medical Education Guide No. 9. Assessment of clinical competence using the Objective Structured Long Examination Record (OSLER). *Med Teach*. 1997;**19(1)**:7-14.
8. Hill F, Kendall K, Galbraith K, Crossley J. Implementing the undergraduate mini-CEX: a tailored approach at Southampton University. *Med Educ*. 2009; **43(4)**:326-34.
9. Johnston JA, Hill M. Resurrecting the long case. ABN Abstracts. Abstracts from the Association of British Neurologists Annual Meeting 2011. *J Neurol Neurosurg Psychiatr*. 2012; **83(3)**:e1.
10. Price J; Byrne JA. The direct clinical examination: an alternative method for the assessment of clinical psychiatry skills in undergraduate medical students. *Med Educ*. 1994; **28(2)**:120-5.
11. Bleasel J, Burgess A, Weeks R, Haq I. Feedback using an ePortfolio for medicine long cases: quality not quantity. *BMC Med Educ*. 2016;**16(1)**:278
12. Van Der Vleuten CP. The assessment of professional competence: developments, research and practical implications. *Adv Health Sci Educ Theory Pract*. 1996;**1(1)**: 41–67.
13. Cookson J, Crossley J, Fagan G, McKendree J, Mohsen A. A final clinical examination using a sequential design to improve cost-effectiveness. *Med Educ*. 2011; **45(7)**:741-7.

Letters

HOW MUCH CARDIOTHORACIC SURGERY IS TAUGHT IN UK MEDICAL SCHOOLS?

Editor,

The National Undergraduate Curriculum in Surgery was created by the Royal college of Surgeons of England in 2015. The curriculum aimed to provide guidance for medical schools creating an evidence-based, clinically relevant and contemporary curriculum for all students.[1] However, Cardiothoracic Surgery (CTS) is not included in many U.K. medical schools' curriculum. Our study aimed to evaluate how much cardiothoracic surgery is taught in UK medical schools.

A questionnaire consisting of 8 questions was designed to evaluate student's experiences in CTS during their undergraduate studies. Two questions were focussed on teaching specifically in Aortic Dissection (AD). The questionnaire was then sent electronically to final year medical students and foundation year one doctor graduated in 2018. Medical schools with no intake of medical students before the 2013-2014 academic year were excluded from this study. [2,3]

Three hundred and six senior medical students and recent graduates completed the questionnaire. Students from 16 U.K. medical schools responded. Thirty-two (10.45%) had a placement in CTS during medical school. Three (18.75%) medical schools integrated CTS as part of the undergraduate curriculum. One hundred and twenty (39.22%) had received teaching in CTS, mainly through small group tutorials and online lectures. All students received teaching on AD. Method of teaching was mainly through lectures (79.33%)

Cardiothoracic Surgery is not included as part of the undergraduate curriculum in most U.K. medical schools. Student experiences in cardiothoracic surgery vary even in the same medical school. However, AD was taught in all surveyed medical schools. Further work should be done to improve student's experience in cardiothoracic surgery during their undergraduate study, especially for students who consider cardiothoracic surgery as their future career.

Jeremy Chan[1], Pushpinder Sidhu[2]

1. Foundation year 2 doctor, Wales Deanery, 2. Consultant cardiothoracic surgery, Royal Victoria Hospital, Belfast

Correspondence to:

Dr Jeremy Chan, e-mail: chanchunyu12@gmail.com

REFERENCES

1. Royal College of Surgeons. *National undergraduate curriculum in surgery*. London: Royal College of Surgeons; 2015.
2. General Medical Council. *The state of medical education and practice in the UK*. London: General Medical Council; 2018.
3. UK Foundation Programme. *2018 recruitment stats and facts report; England, Northern Ireland, Scotland, Wales*. London: UK Foundation Programme; 2018.

MYCOBACTERIAL ABSCESSES AFTER BCG VACCINATION

Editor,

A 25-year-old man was referred to the dermatology department with two lesions on his upper left arm. These were intermittently discharging pus and bleeding. There was no history of trauma and he was systemically well. He had no past medical history of note and was not taking medication. He was in the army and had been posted overseas to various countries including the middle east.

He recalled receiving a BCG vaccination to his left arm in 2014 with subsequent significant local reaction which resolved with scarring.

On examination, there were two erythematous nodular lesions on the lateral aspect of his left upper arm adjacent to the BCG scar. The superior lesion measured 20 x 10mm and the inferior lesion measured 12 x 13mm. There was no palpable axillary or cervical lymphadenopathy (Figure 1).

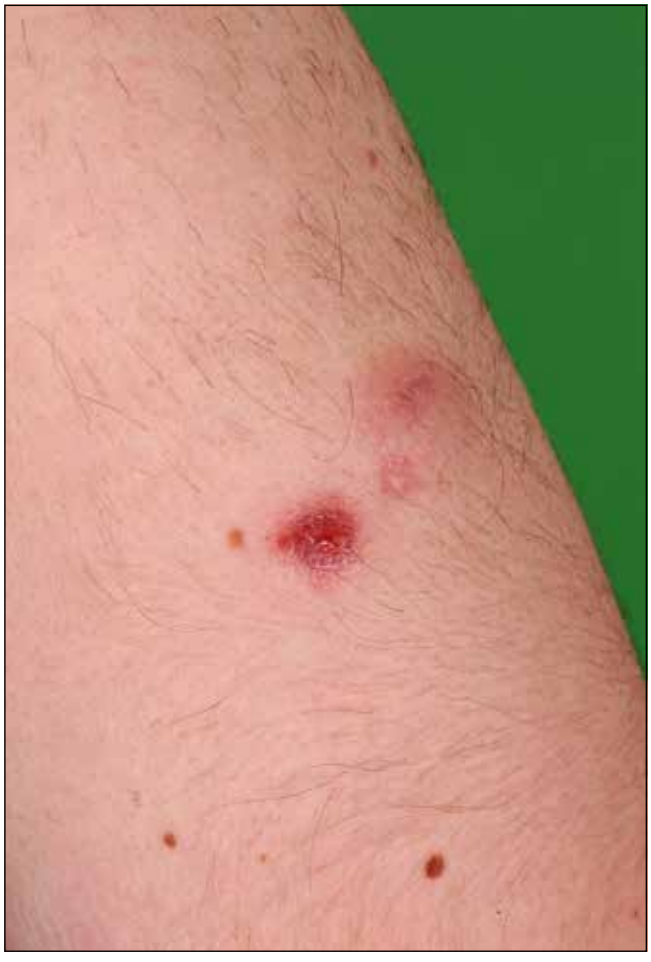


Fig 1.

Diagnostic punch biopsies were performed for histopathology and culture. Histopathology showed granulation tissue with two ill-defined microscopic granulomatous foci (Figure 2). MTB (Mycobacterium bovis) complex was cultured.

Additional PCR testing performed and confirmed a BCG strain.

The BCG strain was sensitive to Isoniazid, Ethambutol, Rifampicin and resistant to Pyrazinamide.

Other investigations included: Leishmaniasis serology negative, HIV negative, ESR, U&E, LFTs, CRP and Chest x-ray normal.

He was referred to infectious diseases clinic and prescribed Rifampicin, Isoniazid, Ethambutol and Pyridoxine for 9 months. At review after 2 months of treatment, the lesions were no longer itchy and were not discharging pus or blood. On examination, the lesions were less indurated and erythematous.

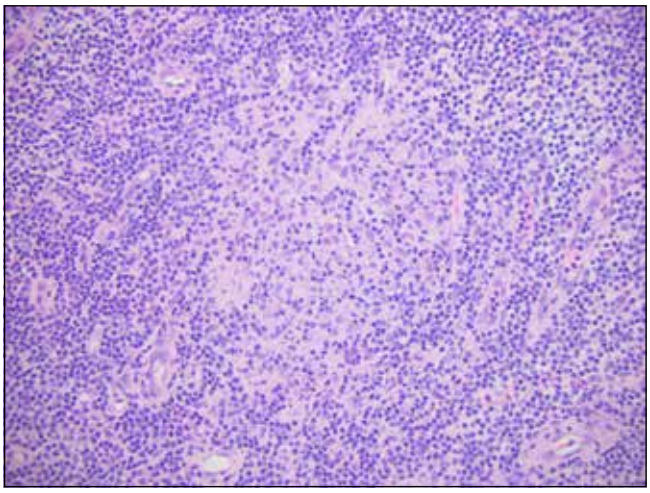


Fig 2.

The Bacille Calmette-Guérin (BCG) vaccine is a vaccine against Mycobacterium Tuberulosis infection which has been in use since 1921. BCG uses a strain of live attenuated Mycobactium Bovis.[1]

In the United Kingdom, the BCG vaccine was administered to all secondary school children until 2005 when a targeted programme for those at higher risk of TB was introduced.[1]

The BCG vaccine has been administered more than 4 billion times. Adverse events in BCG administration are rare. In a study of 117,533 vaccines abscesses were reported in 0.02% of patients[2] and in another study the incidence of BCG abscess of 0.05%.[3]

There are no large randomised control trials investigating treatment of BCG abscesses.

A random, open, group control study of 33 patients compared isoniazid vs isoniazid/rifampicin; the combination therapy showed a higher cure rate with acceptable side effect profile.[4] This was the case with our patient. There are case reports of surgical excision or observation

In summary, we report a case of BCG abscesses as a rare adverse reaction to the BCG vaccine in an immunocompetent individual. These abscesses are currently responding to treatment with anti-tuberculosis medications. This case highlights that MTB infection should be considered in patients who present cutaneous eruptions after receiving BCG vaccination.

R Brennan, K McKenna

Dermatology Department, Belfast City Hospital, Lisburn Road, BT9 7AB, Belfast, United Kingdom

Correspondence to: Dr Ronan Brennan

E-mail: ronan_brennan@hotmail.co.uk

REFERENCES

1. World Health Organisation. BCG vaccines: WHO position paper – February 2018. *Wkly Epidemiol Bull*. 2018; **93(8)**: 73-96.
2. NHS. [Internet]. Vaccinations: BCG (TB) vaccine side effects. 2016. Available from:: https://www.nhs.uk/conditions/vaccinations/bcg-tb-vaccine-side-effects/#bcg-injection-scar [Accessed Feb 2019].
3. de Souza GR, Sant'Anna CC, Lapa e Silva JR, Mano DB, Bethlem NM. Intradermal BCG vaccination complications – analysis of 51 cases. *Tubercle*. 1983;**64(1)**:23-7.
4. Hendry AJ, Dey A, Beard FH. Adverse events following immunisation with bacille Calmette-Guérin vaccination: baseline data to inform monitoring in Australia following introduction of new unregistered BCG vaccine. *Commun Dis Intell Q Rep*. 2016;**40(4)**:E470-E474.

NOTIFIABLE VIRAL INFECTIOUS DISEASES: IDENTIFYING PATTERNS OF LEARNING IN CLINICAL DECISION SUPPORT

Editor,

Notifiable viral infectious diseases are a significant public health risk and it is important for frontline healthcare professionals to correctly detect and diagnose patients with these diseases. Healthcare professionals can use online clinical decision support resources to ensure that their knowledge of these diseases is evidence-based, practical and current.[1] However, there are few analyses on *how* doctors use clinical decision support tools at the point-of-care or how they use them in specific specialties - such as the field of infectious diseases.[2,3] The purpose of this report is to attempt to fill this gap in the literature by analysing the usage of a point-of-care decision support tool - BMJ Best Practice - in the field of viral infectious diseases.

In December 2018, we conducted an analysis of patterns of use on BMJ Best Practice related to notifiable viral infectious diseases over the previous 12 months.[4] We looked to see which of the notifiable viral infectious diseases generated the most usage on the clinical decision support tool and also which sections of the content were most used.

We found that the most common notifiable viral infectious diseases are the most used. The most viewed diseases include measles, hepatitis C, Ebola virus infection, hepatitis B, and mumps. With the exception of Ebola, these are amongst the most common notifiable viral infectious diseases worldwide.[5] Thus, it is not surprising that these are well-used. However, this also suggests that the content is being used to guide practical and common decisions that doctors and healthcare professionals take every day. The exception is Ebola – this is still a rare disease. However, it has received a great deal

of public attention and this may account for some of its popularity.

We also looked at what sections of the topics received most views. The sections of the topics with the most page views suggest a clear pattern of usage. The top two sections include the topic homepage and the "highlights-summary" page. However, this is to be expected as these are the first pages that users land on when they go to a topic.

Where they go next is of more interest; and here there are clear messages from the data. Six of the next ten most popular sections relate to diagnosis – these include the sections on "approach to diagnosis", "history and examination", "differential diagnosis", "investigations", "diagnosis: step-by-step" and "case history".[4] Of the remaining, three relate to issues in management. These include the sections on "treatment options", "treatment details", and "approach to management".

The data suggests that users are utilising the clinical decision support tool to aid their decisions in diagnosis and management of notifiable viral infectious diseases and that they need help in the basics of taking a history, conducting an examination, ordering tests and ruling in or out differential diagnoses.[5] Equally it may be that they want to confirm what they are doing is correct. The usage behaviour is largely related to the clinical workflow and suggests that users are using the tool at the point-of-care and not as a referential source that they might look at after the clinical event.

Kieran Walsh, Lilah Basil, Lalitha Bhagavatheeswaran

Corresponding author: Kieran Walsh, Clinical Director, BMJ Best Practice and BMJ Learning, BMA House, Tavistock Square, London WC1H 9JR

Email: kmwalsh@bmjgroup.com

Sources of funding: None

Conflicts of interest: KW works for BMJ which produce a range of resources in infectious and non-infectious diseases.

Ethical approval: This was not sought as this was not a trial.

REFERENCES

1. Kwag KH, González-Lorenzo M, Banzi R, Bonovas S, Moja L. Providing doctors with high-quality information: an updated evaluation of web-based point-of-care information summaries. *J Med Internet Res*. 2016;18(1):e15.
2. Walsh K. Online clinical decision support: how it is used at the point-of-care. *BMJ Simul Tech Enhanc Learn*. 2017;3(2):73-4
3. Islam R, Weir CR, Jones M, Del Fiol G, Samore MH. Understanding complex clinical reasoning in infectious diseases for improving clinical decision support design. *BMC Med Inform Decis Mak*. 2015;15:101.
4. Gov.Uk [Internet]. Guidance: Notifiable diseases and causative organisms: how to report. London: Public Health England; 2019. Available from: https://www.gov.uk/guidance/notifiable-diseases-and-causative-organisms-how-to-report#list-of-notifiable-diseases [Accessed Feb 2019]
5. Gov.Uk [Internet]. Research and analysis: notifiable diseases: historic annual totals. Cases of infectious diseases: annual total figures from 1912 to 2017. London: Public Health England; 2018. Available from: https://www.gov.uk/government/publications/notifiable-diseases-historic-annual-totals. [Accessed Feb 2019]

ANTIMICROBIAL PROPERTIES OF NATIVE ULSTER MACROFUNGI (MUSHROOMS AND TOADSTOOLS) TO CLINICAL PATHOGENS

Editor,

Previously, our research group has reported in the *UMJ* on various traditional Ulster cures and remedies (January 2009)[1] and on the physiological basis of the antibacterial activity emulating such cures and remedies (January 2009)[2]. In addition, we have examined the antimicrobial properties of sphagnum moss and its role in the Great War 1914-1918, relating to bandage preparation and wound dressings.[3] To date, we have not examined the antimicrobial properties of native macrofungi, namely the mushrooms and toadstools and therefore, it was the aim of the current study to examine the activity of native Ulster macrofungi on clinical bacterial and fungal pathogens.

Fig1a Coprinus comatus: Dick Culbert, B.C., Canada

Twenty-two species of native macrofungi were collected from woodlands throughout Northern Ireland (Table 1). *Lentinula edodes* (Shiitake mushroom) was also examined, given its popularity as a constituent of Asian (mainly Japanese) cuisine. Formal identification of all macrofungi examined was made by PCR-DNA techniques, employing fungal 18S rDNA universal ITS 1 and ITS 4 primers (ITS1: TCC GTA GTT GAA CCT GCG G and ITS4: TCC TCC GCT TAT TGA TAT GC). Aqueous and protein extracts (approx.1mg/ml) were obtained from freeze-dried preparations of each fungus. Six bacterial and one fungal pathogen were examined

in this study (Table 1), including the Gram-positive bacteria (*Bacillus cereus, Listeria monocytogenes, Staphylococcus aureus* (methicillin-sensitive), *Staphylococcus aureus* (methicillin-resistant), the Gram-negative bacteria (*E. coli* O157, *Klebsiella aerogenes*, *Pseudomonas aeruginosa*) and the fungal pathogen, *Aspergillus flavus*. All isolates were obtained from the HSC MicroARK Northern Ireland Microbiology Repository, located at the Northern Ireland Public Health Laboratory, Belfast City Hospital (www.microark.com). Antimicrobial properties were determined on each fungal extract/pathogen combination by standard disk diffusion assay.

All native fungi, except for *Agaricus bisporus* (the common mushroom) demonstrated antimicrobial activity against at least one of the extracts to one of the clinical pathogens tested (Table 1). Two native fungi, *Coprinus comatus* and *Leucopaxillus tricolor* were active against all of the pathogens tested. *Lentinula edodes* (Shiitake mushroom) was also active against all of the pathogens tested. Overall, aqueous extracts were more antimicrobial than the protein extracts examined.

Coprinus comatus is commonly seen in Northern Ireland (Figure 1a) and is sometimes known as shaggy ink cap, lawyer's wig, or shaggy mane, due to the white cap of the fungus being covered in scales. Other recent studies have also shown this fungal species to exhibit potent antimicrobial properties.[4] *Leucopaxillus tricolor* (Figure 1b) is found

TABLE 1:

Antimicrobial activity of aqueous and protein extracts of 23 macrofungi against clinical pathogens

	Aqueous Extract	PPER* Extract
Agaricus augustus		*Listeria monocytogenes*
Agaricus bisporus		
Amanita sp.	*Staphylococcus aureus, MRSA***	
Boletus chrysenteron	*Staphylococcus aureus*	*Listeria monocytogenes*
Clitocybe sp.	*Staphylococcus aureus, MRSA*	*Listeria monocytogenes*
Coprinus comatus	*Bacillus cereus, E. coli O157, Klebsiella pneumoniae Listeria monocytogenes, MRSA, Pseudomonas aeruginosa*	
Gymnopilus junonius	*Klebsiella pneumonia, Listeria monocytogenes, MRSA*	*Listeria monocytogenes*
Gymnopus confluens		*Listeria monocytogenes*
Hygrocybe nigrescens		*Listeria monocytogenes, Aspergillus flavus, E. coli O157*
Hypholoma fascicularis	*Listeria monocytogenes*	
Inocybe geophylla	*Staphylococcus aureus*	*Listeria monocytogenes, Aspergillus flavus*
Laccaria amethystine	*Staphylococcus aureus, MRSA*	
Lentinula edodes	*Aspergillus flavus, Bacillus cereus, E. coli O157, Klebsiella pneumoniae, Listeria monocytogenes, MRSA, Pseudomonas aeruginosa*	
Leucopaxillus tricolor	*Bacillus cereus, E. coli O157, Klebsiella pneumoniae, Listeria monocytogenes, MRSA, Pseudomonas aeruginosa, Staphylococcus aureus*	*Aspergillus flavus Listeria monocytogenes*
Mycena rosea	*MRSA, Staphylococcus aureus*	*Aspergillus flavus, E. coli O157, Listeria monocytogenes*
Mycena sp.		*E. coli O157, Listeria monocytogenes*
Psathyrella candolleana	*Bacillus cereus*	
Pseudotrametes gibbosa	*MRSA, Staphylococcus aureus*	
Russula cyanoxantha		*Aspergillus flavus, Listeria monocytogenes*
Russula nigricans	*MRSA, Staphylococcus aureus*	
Russula parazurea		*Listeria monocytogenes*
Russula sp.		*Listeria monocytogenes*
Trametes versicolor	*MRSA, Staphylococcus aureus*	

Where no value is recorded there was no inhibition in any of the clinical pathogens tested
*PPER = Plant Protein Extraction Reagent
**MRSA = methicillin-resistant Staphylococcus aureus

growing in woodland litter and is composed of three coloured components, namely a brown cap, yellow gills and a white stem, hence the epiphet name, *tricolor*. *Lentinula edodes* (Figure 1c) is a common constituent of Asian cuisine and has been shown previously to have antimicrobial properties.

Fig 1b Leucopaxillus tricolor: Eva Skific (Evica)

Antimicrobial resistance (AMR) has now emerged as a major global public health problem. Locally in Northern Ireland, the extremes of AMR manifest as multi- and pan-resistant Gram-negative respiratory infections in patients with cystic fibrosis (CF), particularly associated with *Pseudomonas aeruginosa* and *Burkholderia cenocepacia,* which can cause a treatment dilemma due to a shortage of active antibiotics.

In conclusion, this study has identified extracts from native local macrofungal species to have an antimicrobial activity against several clinical pathogens. Given the need to search for novel antimicrobial compounds coupled with the agrarian background of Northern Ireland's economy, further work should be undertaken to identify other local sources of antimicrobials and a mechanism established amongst the relevant government agencies, academia and patient groups, to help such novel compounds enter into the drug discovery pathway, so that any potential medicinal value can be fully exploited.

Nelson D[1*], Moore JE[2], Millar BC[2], & Rao JR[1]

[1] Plant Pathology Research Division, AgriFood & Biosciences Institute (AFBI), Newforge Lane, Belfast, BT9 5PX, Northern Ireland, UK.,

[2] Northern Ireland Public Health Laboratory, Department of Bacteriology Belfast City Hospital, Lisburn Road, Belfast, BT9 7AD, Northern Ireland, UK.

Fig 1c Lentinula edodes: Fankenstoen from Portland, Oregon, USA

Correspondence to: Dr. David Nelson

Email: david.nelson@afbini.gov.uk

REFERENCES

1 Ballard LM. An approach to traditional cures in Ulster. *Ulster Med J*. 2009;**78(1)**:26-33.

2 Woods-Panzaru S, Nelson D, McCollum G, Ballard LM, Millar BC, Maeda Y, *et al*. An examination of antibacterial and antifungal properties of constituents described in traditional Ulster cures and remedies. *Ulster Med J*. 2009; **78(1):**13-5.

3 Moore PJ, Rao JR, Nelson D, McCollum G, Ballard LM, Millar BC, *et al*. Examination of the antibacterial properties of sphagnum moss (Sphagnum spp.) and its significance with turf burning in Ireland. *Br J Biomed Sci*. 2012;**69(4):**178-80.

4 Stojković D, Reis FS, Barros L, Glamočlija J, Ćirić A, van Griensven LJ, *et al*. Nutrients and non-nutrients composition and bioactivity of wild and cultivated *Coprinus comatus* (O.F.Müll.) Pers. *Food Chem Toxicol*. 2013;**59**:289-96.

Ulster Med J 2019;**88(2):**133-135

Abstracts

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

Wednesday 3 April 2019, Wellcome-Wolfson Institute for Experimental Medicine

OVERVIEW

QUB Scrubs hosted the Student Research Symposium providing a forum for medical and dental students to present research conducted during student summer studentships and intercalated degrees. Fourteen students submitted abstracts for moderated poster presentations that were judged by Professor Roy Spence and Professor Peter Maxwell. Speakers at the symposium discussed mentoring (Professor Jayne Woodside, QUB), intercalated degrees (Mr Sagar Kanabar, Final Year Medical Student, QUB), career paths (Professor Peter Maxwell, QUB) and clinical academic training (Dr Gerard Walls, ICAT fellow). The four prize winning abstracts were presented by medical students Michelle Doherty, James Cutlan & Rachael Allen, Chris Madden-Kee and Patrick McAleavey. The symposium was organised in collaboration with staff from the School of Medicine, Dentistry and Biomedical Sciences and was made possible by support from Queen's University Belfast, the Medical Defence Union and the Wesleyan company.

FIRST PRIZE

Trends of Prostate-Specific Antigen (PSA) testing in a UK region

Michelle T Doherty, Eileen Morgan, Gerard Savage, Anna T Gavin

Northern Ireland Cancer Registry, Queen's University Belfast.

Background: The increase in prostate cancer incidence in Northern Ireland has been linked to a rise in the use of PSA testing despite this test not meeting the standards for cancer screening.

Aim: To determine the trends and patterns of General Practice use of PSA testing in Northern Ireland (NI) using population-based data.

Patients and methods: Data were collected on PSA tests in NI 1993 to 2016. Annual rates of PSA testing were calculated for age, test result and source. A sub-analysis of patients tested 2010-2016 by source, first tests and PSA result was performed.

Results: Over a million (1,391,509) PSA tests were performed in NI 1993-2016, increasing from 44 in 1993 to 93,108 in 2016. Over the past decade (2007 – 2016) PSA tests with levels <4ng/ml have increased 1.37 fold. Between 2010-2016, 608,036 PSA tests were performed on 190,755 patients. Over two thirds were requested from GP. Of first tests 39.2% ordered in GP occurred in men under 50 with 29.9% over 80 years. The majority (87.3%) of patients having a first PSA test requested by their GP had a result <4 ng/ml.

Conclusions: PSA testing has increased significantly in N. Ireland since 1993 with findings indicating testing in asymptomatic males and those considered outside the advised age ranges. The majority of demand for PSA testing is originating from primary care, mainly those receiving a PSA test for the first time. Consequently, prostate cancer is now being detected at earlier stages however with no change in mortality rates there is potential to create a large burden on men's health and wellbeing and also on the Health Service.

SECOND PRIZE

The use of a digital learning platform in improving medical student clinical skills in prescribing fluids

Rachael Allen, James Cutlan, Alexander Davey

Queen's University Belfast and Belfast HSC Trust

Objectives: To pilot and assess the potential educational value of a high-fidelity education tool for prescribing intravenous (IV) fluids with Medical Students.

Introduction: Currently, IV fluid prescribing is a routine task in clinical practice but remains poorly understood by Medical Students and Junior Doctors alike. There is an unmet need to redesign the way that this complex topic is addressed in undergraduate teaching. We are aiming to introduce an online, case-based learning environment as a widely available method of education in fluid management. Improving knowledge and experience in IV fluids will help improve clinical outcomes and patient safety.

Methods: Forty Queen's University Belfast Medical Students in years 3, 4 and 5 were invited to attend a fluid prescribing teaching event hosted by the Scrubs society.

The event included a brief presentation, followed by three clinical case studies accessed via the digital learning platform "Efluid chart", developed by a Consultant Anaesthetist. The case studies included hypotensive shock, small bowel obstruction and pancreatitis. The platform allows users to view a clinical synopsis, observation chart and fluid balance chart for each case, then create a fluid management plan. Once submitted, immediate and individual feedback is given on the prescription made based on the rate, volume, type of fluid used and additives. Summaries of the relevant clinical guidelines are also included.

The students that took part were invited to fill out surveys before and after the session. The questions in the pre-teaching survey focused on knowledge, experience and confidence in making fluid management plans and the methods by which students have attained their current knowledge of fluid prescribing. The post-teaching survey asked about knowledge, experience and confidence again, as well as if they felt that the session had improved their knowledge in the area.

Results: *Pre survey:* Prior to the event, 57.89% students said they had 'room for improvement' in their prescription of IV fluids. *Post survey:* Following the event, 73% of students reported that the event improved their knowledge of prescribing IV fluids.

Case examples: In relation to the severe, acute pancreatitis case, students showed a 10% positive improvement in reported lack of knowledge and/or experience in prescribing IV fluids.

Discussion: E-learning is a still developing area that has the potential to make learning resources widely available. The use of case-based learning with immediate constructive feedback can bridge the gap between theoretical study and clinical practice for Medical Students and Junior Doctors. This could be a useful tool in preparing the clinical community for digital transformation.

While the results of the survey have shown an improvement in the students perceived skills in fluid management, more development of the Efluid chart platform is required to maximise the learning potential. A larger and more varied case base would make the platform more accessible and useful to a wider range of healthcare professionals and undergraduates. Future development with nursing staff and clinical biochemists could make the platform useful for inter-professional learning.

Fig 1. SCRUBS Research Symposium Prize winners (L-R) Chris Madden-Kee, Patrick McAleavey, Michelle Doherty, Rachael Allen and James Cutlan

JOINT THIRD PRIZE

Use of Progestins in BRCA1 mutation carriers – are we increasing the risk of breast cancer?

Christopher T.J. Madden-McKee, Kienan I. Savage, Stuart A. McIntosh

Centre for Cancer Research and Cell Biology, Queen's University Belfast, United Kingdom

Background: Hormonal contraceptives containing synthetic progestins are routinely prescribed at a young age in women carrying mutations in the breast cancer susceptibility gene-1 (BRCA1). Progestins have been associated with increased breast cancer risk in BRCA1 mutation carriers but the biological mechanism of this association is poorly understood. The aim of this study is to investigate the effects of progestins on malignant transformation in BRCA1 heterozygous breast cells.

Methods: A BRCA1 heterozygous MCF10A normal breast epithelial cell line was treated with the progestin R5020 along with oestrogen for 12 weeks and monitored for changes in cellular proliferation, anchorage-independent growth, mutational status of TP53 and PTEN, DNA damage and cellular morphology.

Results: BRCA1 heterozygous cells had a significantly higher ($p<0.001$) number of double-strand break foci after 12 weeks of hormone treatment versus wild-type controls. There were also differences in cellular proliferation, anchorage-independent growth and cellular morphology but no features of true malignant transformation.

Discussion: This study provides further evidence that BRCA1 heterozygous cells are haploinsufficient for DNA damage repair. Better models are required to investigate the effects of progestin signalling on malignant transformation in BRCA1 heterozygous breast tissue, especially with regard to both RANKL signalling and androgen receptor interactions.

JOINT THIRD PRIZE

Haemophagocytic Lymphohistiocytosis-like syndrome reduces survival in patients with ARDS

Patrick McAleavey, Andrew Boyle, John Conlon, Cecilia O'Kane, Danny McAuley

Centre for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom, Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, United Kingdom

Table 1.

** p <0.05 compared to control*

Group	Control (n = 416 [81.4%])	High ferritin (n = 58 [11.4%])	High IL-18 (n = 54 [10.6%])
SOFA score	8.0 [6.0 - 10.0]	9.0 [8.0 - 12.0]*	11.0 [8.5 - 13.0]*
Ventilator-free days	15.0 [0.0 - 22.0]	0.0 [0.0 - 14.5]*	7.5 [0.0 - 21.0]
Mortality at 28 days	21%	38%*	35%*
Mortality at 12 months	32%	52%*	44%

Background: Haemophagocytic Lymphohistiocytosis (HLH) is a rare hyperinflammatory condition. Ferritin and IL- 18 are elevated in cases of HLH, however their role in the pathogenesis of HLH is not understood. Plasma ferritin and IL-18 are recognised biomarkers for HLH. In patients with sepsis, an HLH-like syndrome (HLH-LS) has been reported [1]. However, it is unknown if a similar HLH-like syndrome co- exists in patients with ARDS, and if it modifies outcomes in patients with ARDS.

Hypothesis: We hypothesised that an HLH-LS occurs in patients with ARDS, and that its presence is associated with increased mortality.

Methods: A post-hoc analysis of the HARP-2 clinical trial was undertaken. HARP-2 was a randomised, controlled clinical trial evaluating simvastatin in 540 patients with ARDS. Baseline plasma samples obtained were analysed for ferritin and total IL-18 using an enzyme-linked immunosorbent assay. Ferritin >4000 ng/mL or a total IL-18 >2500 pg/mL have been reported to have a high sensitivity and specificity for the diagnosis of HLH-LS. Patients with high ferritin or high IL-18 values were compared to a control group with normal ferritin and IL-18 values.

Results: 511 patients where baseline samples were available were included. High baseline ferritin was present in 58 (11.4%) patients. These patients had a higher baseline SOFA score, fewer ventilator free days (VFDs) and higher 28-day and 12-month mortality. High baseline IL-18 was identified in 54 (10.6%) patients. These patients had a higher baseline SOFA score and higher 28-day mortality. Although these patients also had fewer VFDs and higher 12-month mortality, these findings were not statistically significant (Table 1).

Conclusion: This post-hoc analysis demonstrates that an HLH-LS, identified by high ferritin or high IL-18, occurs in patients with ARDS. Furthermore, the presence of an HLH-LS with ARDS is associated with worse clinical outcomes. Identification of this co-existing HLH-LS might offer an opportunity to improve outcomes for this group of patients with ARDS.

THE ULSTER MEDICAL JOURNAL

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

NOTICE TO CONTRIBUTORS

The Ulster Medical Journal is an international general medical journal with contributions from all areas of medical and surgical specialties relevant to a general medical readership. It retains a prime focus on material relevant to the health of the Northern Ireland population. The Journal is indexed on *PubMed Central* and *Index Medicus*.

The Journal's links with the Ulster Medical Society and Queens University Belfast are reflected in regular publication of Medical History and Medical Education articles. **The front cover** of the journal usually includes an image related to an article within, but the editor is keen to consider publishing images that reflect "**Ulster medical life**" in a broader context. Please contact the editor for further details.

Papers, case reports and letters should be sent to the Editor by e-mail at editor@ums.ac.uk. The preferred format is **Microsoft Word**.

Manuscripts should be accompanied by a covering letter **signed** by all the authors agreeing to publication and stating that the work has not been published elsewhere; and stating that they have been actively involved in the preparation of the paper and outlining their contribution to the paper. Any conflict of interest should be declared.

A **PDF** copy of the printed and signed covering letter is ideal for electronic submission.

A Consultant or GP Principal (or equivalent) is required to act as guarantor of the manuscript (usually as a co-author) in case of any issues that may arise after publication.

If e-mail submission is not possible, A CD or memory stick containing the manuscript, tables, images and covering letter can be sent to the Editor at: Dr John Purvis, Consultant Cardiologist, Cardiac Unit, Altnagelvin Hospital, Londonderry, BT47 6SB, Northern Ireland.

Articles submitted for consideration should be typewritten in single spacing, with wide margins, preferably in Times (New) Roman 12pt font. They should be fully corrected and alterations in proof may be disallowed or charged to the authors.

Colour images and tables are encouraged and there is currently no charge for colour reproduction.

Images and tables should be included as separate high resolution .jpg or .tif files and NOT embedded in the Word manuscript file. Images should be appropriately annotated and labelled.

Dr Purvis will be pleased to advise on the preparation of manuscripts on request.

After editorial checks, all manuscripts are independently refereed. The editor may request revision to a manuscript before it goes to the referee, e.g., embedded images, annotation of unlabelled images or poor quality of English.

After peer review by the referee, a manuscript may either be accepted for publication, accepted with minor or major revisions requested within a deadline or rejected. The Referee's and Editor's decisions are final and not open to negotiation. A manuscript may not be re-submitted after rejection.

1. For full or short papers, the text should indicate the purpose of the paper, and should include an introduction, sections on materials and methods, results, and a discussion relevant to the findings. A brief factual summary/abstract should be provided at the beginning of the paper along with up to six key words. For case reports, these should be **novel** or particularly important cases and *not just good teaching points*, with a maximum of 10 references and appropriate patient consent for publication of photographs.
2. Letters to the editor should be less than 500 words with up to 5 references and 1 table and/or figure.
3. Audits are eligible for publication as letters to the editor but will not be considered as original papers.
4. Scientific measurements should be in SI units (DN Baron. *Units, Symbols and Abbreviations. A Guide for Medical and Scientific Authors*. 5th ed. London: Royal Society of Medicine, 1994). Blood pressure may be expressed in mmHg and haemoglobin concentration as g/dl.
5. References should be restricted to those really necessary and useful. This journal uses the "Vancouver" style. See Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org/recommendations/) for full details and advice. Text references are numerical and each article reference should include:
    1. a list of all authors when six or less (when seven or more only the first six should be listed followed by *et al*).
    2. the title of the article.
    3. the title of the journal *in italics* (abbreviated to the form published by the National Library of Medicine, www.ncbi.nlm.nih.gov/nlmcatalog/journals).
    4. the year.
    5. volume number and issue number (in brackets) **in bold**.
    6. first and last pages.

- *Example:* Devlin LA, Price JH, Morrison PJ. Hereditary non-polyposis colon cancer. *Ulster Med J* 2005;**74(1)**: 14-21.
- Book references should give the author, title, edition, town of publication, name of publisher, year of publication, and, where appropriate, volume and page numbers.

6. Reprints can be obtained from the printers, Messrs Dorman & Sons Ltd, Unit 2, 2A Apollo Road, Boucher Road, Belfast BT12 6HP - telephone (+44) 028 9066 6700, email info@dormans-print.co.uk - who should be approached directly. For reprint information in the United States contact: International Reprint Corporation (IRC), 287 East H Street, Benecia, California, 94590 USA. Telephone (707) 746-8740, fax (707) 746-1643.
7. Fellows and Members of the Ulster Medical Society receive the journal free. Individuals may subscribe directly. Institutional subscriptions are for a calender year. The journal has three issues per year and is published in January, May and September with a circulation of 1,000 hard copies. The journal contents are covered by *Current Contents/Clinical Practice, Index Medicus, Excerpta Medica, PubMed, PubMed Central*, and *Index Copernicus*. The journal is available in 16mm and 35mm microfilm and 105mm microfiche from UMI, 300 North Zeeb Road, PO Box 1346, Ann Arbor, MI 48106-1346, USA.

The journal attempts to conform to the International Committee of Medical Journal Editors (ICMJE) and authors should consult the ICMJE website for details of policies not specifically outlined below and particularly for research on animals and other ethical considerations. In addition, the journal is a member of the Committee On Publication Ethics (COPE).

Volume 88 No. 2 **May 2019**
ISSN 0041-6193

Front cover: Lentinula edodes, a native Ulster mushroom is a common constituent of Asian cuisine and has been shown previously to have antimicrobial properties.