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- CFTR Gene in Northern Ireland
- Acute Kidney Injury
- Perceptions of Obesity & Bariatric Surgery

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Ulster Med J 2025;**94(2):**61-63

Editorial

Introductions

James Lucas

It is a great privilege to assume the role of Honorary Editor of the Ulster Medical Journal from my predecessor, Professor David Armstrong. In doing so, it is important to mark his contribution to the Journal. During his tenure, David oversaw the publication of an eclectic mix of original papers, covering history, ethics and clinical medicine. His thought-provoking and erudite editorial pieces were crafted with literary flair. As I have recently come to appreciate, the role of editor involves considerable tenacity with regards to the independent peer-review process, a careful eye for detail and the skills of a diplomat. David is a busy clinician, and it could not have been easy to juggle an additional commitment as demanding as this one.

The success of the UMJ flows, in no small part, from the wisdom of its Editorial Board. My colleague, Professor Peter Maxwell, opens a series of Guest Editorials, below, with a discussion on the challenges facing clinical academics in the workforce. I hope that policy makers will give careful consideration to the solutions that he proposes.

A longstanding and steadfast supporter of this Journal, Professor John Hedley-Whyte, who is the David S. Sheridan Professor of Anaesthesia and Respiratory Therapy at Harvard University, has recently stepped down from the Editorial Board. His contribution as an author, particularly to the Medical History Section of this Journal, has been immense and continues in this Issue, on the subject of Hugh Percy, 10th Duke of Northumberland. Professor Hedley-Whyte's colleagues on the Editorial Board have asked me to thank him for his many years of service and to wish him well for the future.

My satisfaction in seeing this Issue of the Journal take shape over the summer was considerably tempered by the news of Professor Barry Kelly's death, in June. To describe Barry simply as a 'former editor' of this Journal hardly does justice to his contribution. I am grateful, therefore, to Professor Patrick Morrison, who has penned a fitting and moving obituary to a great thinker, whose loss will be felt far beyond his family, friends and colleagues.

Clinical Academics in the NHS workforce – down but not out!

Peter Maxwell

The future for clinical academic doctors is dependent upon solving multiple challenges. These include providing clear training opportunities, sustainable career paths and a thriving environment for academic clinicians to conduct research, provide medical education and engage in clinical practice. Over the last 15 years, clinical academic numbers in the UK have fallen as a proportion of the NHS workforce.[1,2] This change reflects the sustained investment to expand the numbers of NHS consultants and general practitioners whereas, in contrast, there has been no substantial change in funding for clinical academic posts. This has resulted in a significant reduction in the number of clinical academics within the NHS medical workforce (now only 3%)[2]. These demographic changes are reducing the visibility of clinical academics as role models in the overall NHS workforce and act as a deterrent to choosing a career in clinical academia. This situation is not unique to the UK with reported declines in clinical academic numbers in many countries.[3,4]

Solutions are needed to help mentor doctors interested in research and teaching, to improve and expand clinical academic training opportunities and to provide more support (including job security) for individuals willing to make the sustained commitment to a clinical academic career.

Some of the challenges faced by clinical academics are obvious such as balancing the many competing demands of clinical duties and academic roles (research, teaching, supervision). Clinical academic training is typically much longer than 'run through' NHS training and will usually involve time 'out-of-programme', to complete a PhD or MD degree, followed by further efforts to obtain funded post-doctoral research fellowship experience. This post PhD/MD training will enhance an individual's competitiveness for a tenured clinical academic post. Issues of pay disparity, funding uncertainties and lack of clear career paths for clinical academic trainees (compared to their full time NHS colleagues) are also disincentives.

For the future sustainability of the clinical academic workforce, it is important to have robust funding mechanisms that will support a much larger and more flexible training pipeline and additional funding to expand the number of early- and mid-career tenured clinical academic posts. This would help to promote diversity and increase the representation of women and underrepresented groups (which includes primary care researchers) in clinical academia. General practitioners typically have much shorter clinical training paths than hospital consultants therefore innovative routes are needed to provide GPs with clinical academic development opportunities after completing their training.

Clinical academics have critical roles in undertaking research aimed at improving human health. High profile medical scientific breakthroughs are often newsworthy and may lead to further inward investment into the life sciences sector with benefits to the wider UK economy.

Clinical academics are also well placed to contribute to the longer-term multidisciplinary research focused on reducing health inequalities, improving access to healthcare, developing disease prevention strategies and testing the utility of early detection methods (including cost effectiveness of screening programmes). This is valuable research contributing to the overall public health and it is ultimately also beneficial to the wider economy to have healthier working age and older age populations.

Despite the challenges, the current clinical academic workforce remains resilient and can respond rapidly to need e.g. during the COVID-19 pandemic, the rapid establishment of the UK's RECOVERY trial, led by clinical researchers, permitted prompt assessment of multiple therapeutic options.[5]

During their careers, clinical academics can look forward to embracing a broad portfolio of work and arguably have greater autonomy in what they choose to investigate (research) or how they educate (teaching). Local, national and international collaborations, with a wide range of investigators and educators, can lead to lifelong friendships that help sustain joy in working through the ups and downs of a busy clinical academic career.

The UK Office for the Strategic Co-ordination of Health Research recently commissioned a report entitled "Clinical researchers in the United Kingdom: Reversing the decline to improve population health and promote economic growth".[6] This provides a comprehensive overview of difficulties facing clinical research allied to a number of important recommended actions including establishing a common national clinical research framework, ensuring the national training pathway is flexible and faster than currently, provision of visible leadership and mentorship by established researchers, and providing equitable rates of pay for clinical academics compared to NHS colleagues

The Irish Clinical Academic Training (ICAT) programme[7] was established in 2016 on an all-island basis and has been well-funded by multiple partners including the Health Research Board, Public Health Agency R&D Division, postgraduate deaneries and all of the participating universities in both Northern Ireland and the Republic of Ireland. The ICAT programme has been hugely successful in providing opportunities for medical, dental and veterinary trainees to have structured research training pre-, during, and post-PhD with further encouragement for the trainees to have supervisors drawn from different institutions and wider disciplinary backgrounds. The alumni from the ICAT programme are now beginning to establish themselves in tenured clinical academic posts in Ireland and beyond. The ICAT programme has demonstrated that high quality clinical academic training is achievable with sustained investment, collaborative working and imaginative leadership from senior academics.

The Northern Ireland Clinical Academic Training Programme (CATP)[8] is a partnership between the Queen's University Belfast (QUB), Ulster University (UU) and the Northern Ireland Medical & Dental Training Agency (postgraduate deanery). The CATP provides dedicated time for academic training. The CATP scheme oversees recruitment into the Academic Foundation Programme with 4-month posts in Year 2, Academic Clinical Fellowship (ACF) posts (75% clinical /25% academic) and Academic Clinical Lecturer (ACL) posts (50% clinical /50% academic). The ACF posts are held prior to undertaking a postgraduate research degree (PhD/MD) and the ACL posts are for higher specialist trainees in medicine or dentistry who have a research degree. The CATP scheme has been successful in encouraging trainees to move up the clinical academic training ladder with CATP alumni obtaining tenured posts in Northern Ireland and beyond. However, the CATP scheme, as a training pipeline, is currently too small to sustain or expand the local clinical academic workforce.

Northern Ireland now has two medical schools (QUB & UU) helping to educate the next generations of clinicians, researchers and medical educators. The total number of students enrolled in both medical schools is more than double the number of medical students in Northern Ireland 25 years ago. This increased enrolment is necessary for current and future NHS workforce plans.

In parallel, an urgent expansion in clinical academic training is required to meet the needs (for researchers and educators) within Northern Ireland's dental and medical schools. It is also essential that many more clinical academic posts are created to help realise the exciting research opportunities and health economic benefits afforded by initiatives like iReach Health[9] (derived from the Belfast City Region Deal) and the new School of Medicine/Personalised Medicine Innovation Centre[10] (supported by the Derry/Londonderry & Strabane City Region Deal).

Professor Peter Maxwell
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Dr Caren Walsh graduated from Queen's University Belfast in 2002 and initially trained in general medicine before moving into General Practice. She completed her GP training in Northern Ireland and has been a GP partner at Grosvenor Road Surgery in West Belfast since 2014. Alongside clinical practice, she works as a Medical Adviser to the Strategic Planning and Performance Group (SPPG) and is the Quality Improvement Lead for RCGP Northern Ireland. Her professional interests include population health, tackling health inequalities, and embedding quality improvement approaches across primary care.

UMS Lecture/Meeting Dates

Date	Lecture	Speaker & Subject	Venue	Time
Thursday 2 Oct	Presidential Address	Dr Caren Walsh *GP Partner Grosvenor Road Surgery* **'Stand up, speak up, step forward'** **https://www.eventbrite.co.uk/e/presidential-address-tickets-1427234931099?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 23 Oct	UMS	Dr Margaret O'Brien *Assistant Director of Primary Care / Head of General Medical Services, SPPG* Dr Brendan O'Brien *Former CCIO NHS National Services Scotland and before that CCIO for the HSCB* **'Navigating the turbulent data ocean of the cradle to grave records in Northern Ireland'** **https://www.eventbrite.co.uk/e/navigating-the-turbulent-data-ocean-of-the-cradle-to-grave-records-in-ni-tickets-1503382400229?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 6 Nov	UMS/QUB/NIMDTA Joint Meeting	**Trainee Research Day**	Wellcome Wolfson, QUB	9.30am – 3pm
Thursday 13 Nov	Robert Campbell Oration	Professor Andy Knox MBE *Medical Director NHS Lancashire and South Cumbria Integrated Care Board, GP Partner Ash Trees Surgery Carnforth and Honorary Professor Lancaster University Management School* **'Love and Power'** **https://www.eventbrite.co.uk/e/love-and-power-tickets-1503517714959?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 27 Nov	Gary Love Lecture	Dr Anne Kilgallen, Mr Bernard Lee and Professor Emerita Mary Frances McMullan **'An Evening with….'** **Contact administrator@ums.ac.uk to reserve a place**	Members only (restricted numbers) UMS Rooms	Canapes 6pm Lecture 6.30pm
Thursday 11 Dec	UMS	Dr Keith Grimes *Founder and CEO of Curistica, Healthtech Innovation Consultancy* **'An introduction to Generative AI in Healthcare'** **https://www.eventbrite.co.uk/e/an-introduction-to-generative-ai-in-healthcare-tickets-1503540182159?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 8 Jan	Joint meeting with Ulster Obs and Gynae	Dr Suzy Todd *Consultant in Genitourinary Medicine* **'Genitourinary Medicine & HIV'** **https://www.eventbrite.co.uk/e/genitourinary-medicine-hiv-tickets-1503550482969?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 22 Jan	Sir Thomas and Lady Edith Dixon Lecture	Professor Lucy Easthope *Director, Whatever Next* **'When the Dust Settles - lessons from a life in disaster'** **https://www.eventbrite.co.uk/e/when-the-dust-settles-lessons-from-a-life-in-disaster-tickets-1503551556179?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 5 Feb	Joint meeting UMS with BCH	Professor Mark Taylor *Consultant HPB Surgeon at BHSCT and Visiting Professor at Ulster University* **'The NHS: Sink or Swim'** **https://www.eventbrite.co.uk/e/the-nhs-sink-or-swim-tickets-1503563341429?aff=oddtdtcreator**	BCH Postgraduate Centre	Buffet 6.30pm Lecture 7.30pm
Thursday 19 Feb	Desmond Whyte Lecture	Marie McGrath *Director FutureSpark Coaching* **'Team culture matters – a recipe for team resiliency'** **https://www.eventbrite.co.uk/e/team-culture-matters-a-recipe-for-team-resiliency-tickets-1503626510369?aff=oddtdtcreator**	Centre of Medical & Dental Education & Training, Altnagelvin Area Hospital	Buffet 6.30pm Lecture 7.30pm
Thursday 5 Mar	UMS	Mike Farrar *Permanent Secretary* **https://www.eventbrite.co.uk/e/mike-farrar-tickets-1503638125109?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 26 Mar	UMS	Ruth Jordan *Spread and Scale Programme Director, Dragon's Heart Institute and Fellow of the Billions Institute* Paul Twose *Consultant-Level Therapist, Cardiff and Vale UHB and Honorary Lecturer, School of Healthcare Sciences, Cardiff University.* **'Redefine Possible: Spread and scale your impact with the Model for Unleashing'** **https://www.eventbrite.co.uk/e/redefine-possible-spread-scale-your-impact-with-the-model-for-unleashing-tickets-1503638546369?aff=oddtdtcreator**	BCH Postgraduate Centre	7.30pm
Thursday 23 April	UMS	Annual General Meeting	UMS Rooms and online	5pm
Friday 15 May	UMS	Annual Dinner	The Great Hall, QUB	7pm

All lectures can be booked via:
Eventbrite https://www.eventbrite.co.uk/o/ulster-medical-society-52479713363 or by emailing administrator@ums.ac.uk

Ulster Med J 2025;**94(2):**64-76

Clinical Paper

Mutation characterisation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in people with cystic fibrosis in Northern Ireland

Philippa J. Blevings,[1] John E. Moore[1,2,3], John McCaughan,[4,5] Alastair Reid,[5] Jacqueline C Rendall,[3] and Beverley C. Millar[1,2,3*]

ABSTRACT

Background

Cystic fibrosis (CF), which is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene is the most common life-limiting autosomal recessive genetic disease in Northern Ireland. Currently, Northern Ireland has approximately 520 people with CF (PwCF) (312 adults, 208 children) and a defective gene carrier rate of 1 in 22 persons, with approximately 86,507 carriers within the general population. Advances in DNA sequencing technology has allowed for better genetic characterisation of CFTR mutations. The aim of this project was to (i) examine current CFTR mutation frequency and type in paediatric and adult CF populations in Northern Ireland, (ii) examine CFTR mutational trends in relation to CF patients' age groups, (iii) compare Northern Ireland CFTR most common allele frequencies with those documented globally and (iv) establish a reference/baseline of CFTR mutation information prior to the effect of CFTR modulator therapy.

Methods

Anonymised data comprising of birth year, sex, and known alleles of adult and paediatric individuals (n=520) from the Northern Ireland CF population was examined. Alleles were recorded according to legacy, protein and cDNA name and organised by mutation class and type, in accordance with CFTR2 database nomenclature. Individual known alleles frequencies from the complete Northern Ireland CF population (n=1005) were calculated and compared with the CFTR2 database, globally with CFTR data obtained from CF national registries.

Results

Within the Northern Ireland CF population, there were 61 different CFTR mutational variants identified in a population of 1005 alleles. In descending occurrence, the most common was F508del with 626 alleles (62.3%), followed by R117H (8.9%), G551D (5.0%), G542X (3.3%), R560T (2.8%) and P67L (2.2%). The remaining alleles were present at a frequency of <2.0%. The six most frequently detected CFTR mutations accounted for 84.4% of all alleles. Over approximately two and a half decades (1996-2021), 23 CFTR mutations remain shared. Six alleles, which were described in the 1996 CFTR analysis, were absent from the 2021 data, whilst there were additional descriptions of 39 allelic mutations, which occurred in the 2021 analysis, but which were not described in the 1996 analysis.

Conclusion

Characterisation of CFTR mutation alleles from people with cystic fibrosis provides essential information to help predict disease severity and effect of targeted CFTR modulator therapy. These 2021 data provide a valuable genetic update from the 1996 data and a reference point on the status of the Northern Ireland CFTR mutation types and frequencies. CFTR modulator therapy has the potential to indirectly alter the current *status quo* and distribution of CFTR mutation types amongst children of PwCF, due to improved clinical status and fecundity. Revisiting this in a decade from now will allow an estimation of the indirect influence of CFTR modulator therapy on CFTR mutation evolution.

Keywords: allele; cystic fibrosis; CF; CFTR; F508del; mutations; Northern Ireland

Introduction

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease in Caucasians, with a prevalence

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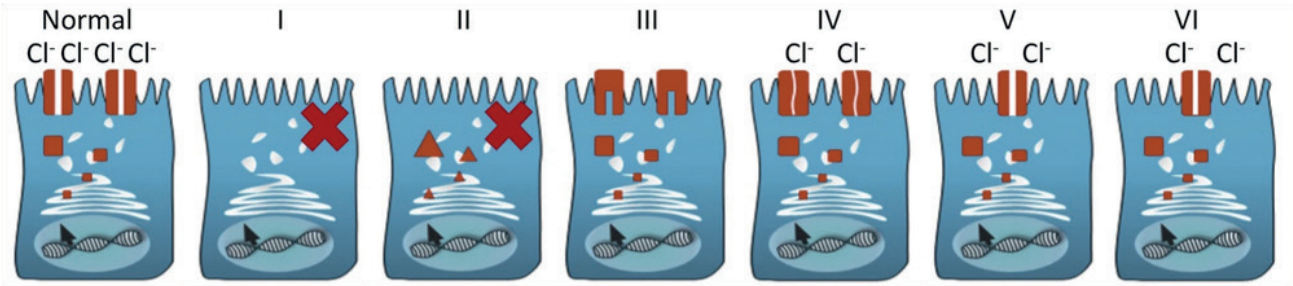
of 1 in 2,500 live births in Europe.[1] Both life span and quality are affected with devastating multi-system involvement, particularly with the respiratory and gastrointestinal systems.[2,3] CF is caused by cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations, and greater than 2,000 variants are now recognised, grouped into six classes (Figure 1).[4] Despite wide allelic diversity, one mutation F508del, involving a phenylalanine deletion at CFTR residue 508, accounts for approximately 70% of alleles worldwide.[5]

The CFTR gene encodes a chloride channel, regulating fluid, pH and electrolytes in mucosal membranes and is important in lung antimicrobial defence.[6] Altered CFTR function has wide-ranging detrimental effects, resulting in a progressive pathophysiological cascade, including pancreatic insufficiency, meconium ileus, defective mucociliary clearance, inflammation, pathogen colonisation and ultimately, respiratory failure.[6-8] The leading cause of morbidity and mortality is lung disease, initiated by inflammation, infection, and accumulated mucus obstructing pulmonary parenchyma.[7] CF lungs are conducive to microbial colonisation, especially with environmental bacteria and fungi, including *Pseudomonas aeruginosa* and *Aspergillus fumigatus*.[9] Additional bacterial pathogens can include *Staphylococcus aureus* (SA), *Haemophilus influenzae* and the non-tuberculous mycobacteria (NTMs).[10] Microorganisms exploit CF lung environment niches

Figure 1: Molecular defects of the cystic fibrosis transmembrane conductance regulator (CFTR) mutations and therapeutic approaches developed

CFTR, cystic fibrosis transmembrane conductance regulator
Drugs already in use by CF patients are noted in bold.
* Read through compounds promote the read through of premature termination codons in CFTR mRNA.
** correctors improve the processing with delivery of functional CFTR protein to the cell surface
*** potentiators increase the function of CFTR channels on the cell surface.

(Reproduced from Deletang K, Taulan-Cadars M. Splicing mutations in the CFTR gene as therapeutic targets. *Gene Ther*. 2022;**29**:399–406. https://doi.org/10.1038/s41434-022-00347-0 under a Creative Commons Attribution 4.0 International (CC BY-NC 4.0) Licence (https://creativecommons.org/licenses/by-nc/4.0/)



Molecular defect	No CFTR synthesis (mRNA or protein)	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced CFTR synthesis	Decreased CFTR stability
Prevalence	10%	88%	4%	< 2%	Rare	
Type of mutations	Nonsense Frameshift Canonical splice	Missense Aminoacid deletion	Missense Aminoacid change		Splicing defect Missense	Missense Aminoacid change
Mutation examples	G542X W1282X R553X R1162X	F508del I507del N1303K M1101K	*G551D* G551S S1255P G178R	R117H R347P R334W R1070W	A455E 3272-26A>G 3849+10kb C>T	4326delTC Gln1412X 4279insA
Therapeutic approach	*Read through** compounds, ELX-02; **kalydeco®** (Ivacaftor)	*Correctors** *(+potentiators***)* **Orkambi®** (Lumacaftor +Ivacaftor); **Trikafta®**; GLP222 **; ABBV-3067*	*Potentiators (+correctors)* **kalydeco®**; **Trikafta®** (Elexacaftor + tezacaftor + Ivacaftor); **Symdeko®** (tezacaftor-Ivacaftor)		*Splicing modulators* Antisense oligonucleo-tides; **kalydeco®**; **Trikafta®**	*Stabilizers*

Table 1: Sources of CFTR mutation frequency data

Databases & Registries	Available at:
CFTR2	http://cftr2.org
ECFSPR (2018)	https://www.ecfs.eu/sites/default/files/general-content-files/working-groups/ecfs-patient-registry/ECFSPR_Report_2018_v1.4.pdf
Dutch CF Registry (2020)	https://ncfs.nl/onderzoek-naar-taaislijmziekte/dutch-cf-registry/
French CF Registry (2017)	https://www.vaincrelamuco.org/sites/default/files/french_cf_registry_2017_annual_data_report.pdf
Belgian CF Registry	https://www.sciensano.be/en/projects/belgian-cystic-fibrosis-registry
CFF Registry (2021)	https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf
Canadian CF Registry (2018)	https://cysticfibrosis.ca/canadian-cystic-fibrosis-registry
Irish CF Registry	https://cfri.ie/annual-reports/
Brazilian CF Registry (2017)	http://www.gbefc.org.br/ckfinder/userfiles/files/REBRAFC_2017_EN.pdf
South African CF Registry (2019-20)	https://sacfa.org.za/wp-content/uploads/SACFA-CF-RegistryAnnualReport2019-2020.pdf
Australian CF Registry (2020)	https://www.cfsa.org.au/acfdr-2020-annual-report/
Asian CF data	https://pubmed.ncbi.nlm.nih.gov/26437683/
UK CF Registry (2020)	https://www.cysticfibrosis.org.uk/about-us/uk-cf-registry/reporting-and-resources

following initial colonisation of the lower respiratory tract, leading to infection with these organisms, which can become chronic.[9,10]

The last formal publication of CFTR mutations types in the Northern Ireland CF population was approximately 27 years ago in 1996.[11] Advances in DNA sequencing technology combined with a requirement to know each CF patient's CFTR allelic mutations, in order to access the recently licenced CFTR modulator therapies, including ivacaftor and elexacaftor-tezacaftor-ivacaftor (ETI), has produced high quality mutational information, which is now beginning to be published for each country, in order to build up a global picture of CFTR mutation classes and their geographical distribution. The aim of this project was to (i) examine current CFTR mutation frequency and type in paediatric and adult CF populations in Northern Ireland, (ii) examine CFTR mutational trends in relation to CF patients' age groups, (iii) compare Northern Ireland CFTR allele frequencies with those documented globally and (iv) establish a reference/baseline of CFTR information prior to the effect of CFTR modulator therapy.

Methods

Anonymised data comprising of birth year, sex, and known alleles of 312 adult and 208 paediatric individuals (n=520) from the Northern Ireland CF population as of December 2021, were examined. Alleles were recorded according to legacy, protein and cDNA name and organised by mutation class and type, in accordance with CFTR2 database nomenclature (www.cftr2.org). Individual known alleles frequencies from the complete Northern Ireland CF population (n=1005) were calculated and compared with the CFTR2 database, globally with CFTR data obtained from CF national registries (Table 1).

Results

Names, characteristics, and frequencies of the mutations identified in the Northern Ireland CF population showing the adult and paediatric data combined are shown in Table 2. In the adult Northern Ireland CF population, there was 312 PwCF and 591 alleles. The Northern Ireland CF paediatric population had 208 PwCF and 414 alleles. Altogether, there was 520 PwCF and 1005 known alleles. Sixty one

Table 2: Names, characteristics, and frequencies of CFTR mutations identified in the Northern Ireland CF population.
The six most frequently occurring alleles are listed in descending order. The remaining alleles (<2% frequency) are listed in alphabetical order.

Variant Legacy Name	Variant cDNA Name	Variant Protein Name	Mutation Type	Mutation Category	Mutation Class	Allele Frequency (%)	
						NI	CFTR2
F508del	c.1521_1523delCTT	p.Phe508del	Deletion, CFTR protein abnormal and destroyed by cell before reaching cell membrane	CF causing	II	62.29	73.08
R117H	c.350G>A	p.Arg117His	Missense mutation, CFTR protein reaches cell membrane but channel does not move chloride effectively	Varying clinical consequence	IV	8.86	2.04
G551D	c.1652G>A	p.Gly551Asp	Substitution, CFTR protein reaches cell membrane but channel is blocked	CF causing	III	4.98	3.28
G542X	c.1624G>T	p.Gly542X	Nonsense, no functional CFTR protein made	CF causing	I	3.28	3.92
R560T	c.1679G>C	p.Arg560Thr	CFTR protein abnormal and destroyed by cell before reaching cell membrane	CF causing	II	2.79	0.38
P67L	c.200C>T	p.Pro67Leu	CFTR protein abnormal and destroyed by cell before reaching cell membrane	CF causing	II	2.19	0.27
1078delT	c.948delT	p.Phe316LeufsX12	No functional CFTR protein made	CF causing	I	<2.0%	0.21
1154insTC	c.1021_1022dupTC	p.Phe342HisfsTer28	No functional CFTR protein made	CF causing	I	<2.0%	0.24
1248+2T->A	c.1116+1G>A	No protein name		CF causing		<2.0%	
1461ins4	c.1327_1330dupGATA / c.1326_1329dupAGAT / c.1329_1330insAGAT	p.Ile444ArgfsX3		CF causing		<2.0%	0.06
1717-1G->A	c.1585-1G>A	No protein name	No functional CFTR protein made	CF causing	I	<2.0%	1.35
1898+1G->A	c.1766+1G>A	No protein name		CF causing		<2.0%	0.47
2184insA / 2185insA	c.2052dupA / c.2052_2053insA	p.Gln685ThrfsX4	Insertion, no functional CFTR protein made	CF causing	I	<2.0%	0.36
2751+2T->C	c.2619+2T>C	No protein name	Splicing mutation			<2.0%	
2789+2insA	c.2657+2_2657+3insA	No protein name	Insertion	Unknown significance		<2.0%	0.09
2789+5G->A	c.2657+5G>A	No protein name	Substitution, CFTR protein made and works but quantity is insufficient	CF causing	V	<2.0%	1.11
3120G->A / Q996Q	c.2988G>A	p.Gln996Gln996	CFTR protein made and works but quantity is insufficient	CF causing	V	<2.0%	0.09
3272-26A->G	c.3140-26A>G	No protein name	CFTR protein made and works but quantity is insufficient	CF causing	V	<2.0%	0.52

3659delC	c.3528delC	p.Lys1177SerfsX15	No functional CFTR protein made	CF causing	I	<2.0%	0.59
3849+10kbC->T	c.3718-2477C>T, c.3717+10kbC>T, c.3717+12191C>T	No protein name	CFTR protein made and works but quantity is insufficient	CF causing	V	<2.0%	1.24
3850-1G->A	c.3718-1G>A	No protein name	mRNA splicing defect, CFTR protein made and works but quantity is insufficient	CF causing	V	<2.0%	0.01
5T	c.1210-12T[5]	No protein name		Varying clinical consequence		<2.0%	0.56
5T;TG12	c.1210-33_1210-6GT[12]T[4]	No protein name		CF causing		<2.0%	0.2
5'UTR to exon 9						<2.0%	
621+1G->T	c.489+1G>T	No protein name	mRNA splicing defect, no functional CFTR protein made	CF causing	I	<2.0%	1.45
711+2T->C						<2.0%	
711+3A->G	c.579+3A>G	No protein name	mRNA splicing defect, CFTR protein made and works but quantity is insufficient	Varying clinical consequence	V	<2.0%	0.07
A349V	c.1046C>T	p.(Ala349Val)		Unknown significance		<2.0%	0.01
D1152H	c.3454G>C	p.Asp1152His	CFTR protein reaches cell membrane but channel does not move chloride effectively	Varying clinical consequence	IV	<2.0%	0.62
E60X	c.178G>T	p.Glu60Ter	Nonsense	CF causing		<2.0%	0.33
F508C	c.1523T>G	p.Phe508Cys	Substitution	Varying clinical consequence		<2.0%	0.01
G576A	c.1727G>C	p.Gly576Ala	CFTR protein reaches cell membrane but channel does not move chloride effectively	Non CF causing	IV	<2.0%	0.08
G85E	c.254G>A	p.Gly85Glu	Missense, substitution, CFTR protein abnormal and destroyed by cell before reaching cell membrane	CF causing	II	<2.0%	0.66
I37R	c.110T>G	p.Ile37Arg	Missense, CFTR protein reaches cell membrane but channel is blocked		III	<2.0%	
I507del	c.1519_1521delATC	p.Ile507del	CFTR protein abnormal and destroyed by cell before reaching cell membrane	CF causing	II	<2.0%	
L206W	c.617T>G	p.Leu206Trp	CFTR protein abnormal and destroyed by cell before reaching cell membrane/CFTR protein reaches cell membrane but channel is blocked	CF causing	II-III	<2.0%	0.37
L967S	c.2900T>C	p.(Leu967Ser)		Varying clinical consequence		<2.0%	0.02

M1210K	c.3629T>A	p.Met1210Lys		CF causing		<2.0%	
N1303K	c.3909C>G	p.Asn1303Lys	Missense / CFTR protein reaches cell membrane but channel is blocked	CF causing	II	<2.0%	2.41
No legacy name	c.4035_4038dup	p.S1347Pfs*13	Protein change			<2.0%	
No legacy name	c.869+1G>C	No protein name		CF causing		<2.0%	
Q493X	c.1477C>T	p.Gln493Ter	Nonsense, no functional CFTR protein made	CF causing	I	<2.0%	0.32
R1070P	c.3209G>C	p.(Arg1070Pro)				<2.0%	
R1070W	c.3208C>T	p.Arg1070Trp	Missense, CFTR protein abnormal and destroyed by cell before reaching cell membrane/CFTR protein reaches cell membrane but channel is blocked	Varying clinical consequence	II/III	<2.0%	0.04
R1158X	c.3472C>T	p.Arg1158Ter	Nonsense, no functional CFTR protein made	CF causing	I	<2.0%	0.19
R1162X	c.3484C>T	p.Arg1162X		CF causing		<2.0%	0.69
R1239R/3849G->A	c.3717G>A	p.Arg1239Arg	Abnormal splicing	CF causing		<2.0%	0
R134S	c.402F>T	p.(Arg134Ser)	Missense			<2.0%	
R297Q	c.890G>A	p.Arg297Gln	Substitution, missense			<2.0%	
R334Q	c.1001G>A	p.Arg334Gln	Missense			<2.0%	0.01
R347H	c.1040G>A	p.Arg347His		CF causing		<2.0%	0.22
R352Q	c.1055G>A	p.Arg352Gln	CFTR protein reaches cell membrane but channel is blocked	CF causing	III	<2.0%	
R751L	c.2252G>T	p.Arg751Leu				<2.0%	
S1159P	c.3475T>C	p.Ser1159Pro		CF causing		<2.0%	0.01
S549N	c.1646G>A	p.Ser549Asn		CF causing		<2.0%	0.21
TG12T5			CFTR protein reaches cell membrane but channel does not move chloride effectively/CFTR protein made and works but quantity is insufficient	CF causing	IV/V	<2.0%	
V520F	c.1558G>T	p.Val520Phe	CFTR protein abnormal and destroyed by cell before reaching cell membrane	CF causing	II	<2.0%	0.17
W1282X	c.3846G>A	p.Trp1282X	Nonsense, no functional CFTR protein made	CF causing	I	<2.0%	1.75
W361R	c.1081T>C	p.Trp361Arg	Missense			<2.0%	
Y1092H	c.3274T>C	p.Tyr1092His	Substitution, missense			<2.0%	
Y1092X	c.3276C>A / c.3276C>G	p.Tyr1092X		CF causing		<2.0%	0.25
Y563N	c.1687T>A	p.Tyr563Asn	Missense, CFTR protein reaches cell membrane but channel is blocked	CF causing	III	<2.0%	0.04

different variants were identified in the Northern Ireland CF population from 1005 alleles. In descending occurrence, the most common was F508del with 626 alleles (62.3%), followed by R117H (8.9%), G551D (5.0%), G542X (3.3%), R560T (2.8%) and P67L (2.2%). The remaining alleles were present at a frequency of <2.0%.

Northern Ireland CF alleles are shown along with CFTR2 database mutation frequencies. Total number of mutations in the CFTR2 database was 89052, as of 2021. The countries that make up this data base are Australia (n=3,414), Belgium (n=1,281), Brazil (n=1,211), Bulgaria (n=16), Canada (n=5328), Chile (n=27), Cyprus (n=42), Czech Republic (n=629), The European CF Society [Austria, Denmark, Germany, Greece, Hungary, Israel, Italy, Latvia, Portugal, Moldova, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden & Switzerland] (n=16,124), Estonia (n=49), France (n=1,986), Ireland (n=1,083), Japan (n=15), Lithuania (n=22), Macedonia (n=109), Mexico (n=121), The Netherlands (n=1,453), Palestine (n=33), Republika Srpska (n=16), Saudi Arabia (n=<10), South Africa (n=155), South Korea (n=<10), Turkey (n=282), UK (n=9,421), US (n=46,183), Ukraine (n=31) and Venezuela (n=<10). Some mutations identified were not found in the CFTR2 database which contains 466 listed mutations, but not all known variants, as some are found in only a few individuals worldwide and some information on class category is missing as CFTR2 only contains information on the 322 most common variants. Over 1,300 alleles have been reported as CF causing, with other less common alleles putative effects unknown.[12]

Table 3 compares the frequency of F508del homozygous, F508del heterozygous and others within the countries of the British Isles, as well as with a further eight countries. F508del prevalence varies globally and despite geographical proximity, differs markedly in Northern Ireland compared to Ireland and Great Britain. Northern Ireland has the highest frequency of F508del heterozygous and lowest F508del homozygous frequency, from the European countries shown. F508del is the most common allele in all countries analysed and has a higher frequency in Europe, USA, South Africa, and Canada than in Northern Ireland and a lower frequency in South America and Asia. Other non-F508del mutations increase in frequency in India, Iran, and Brazil. Figure 2 shows a comparison of the four most common CFTR alleles identified in the Northern Ireland CF population with other global regions. Table 4 compares the CFTR mutations described in the Northern Ireland population previously in 1996 with those described in the Northern Ireland CF population from 2021. Figure 3A shows the prevalence of CFTR mutations by year of birth, Figure 3B shows the frequency of F508del mutations by age and Figure 3C shows the frequency of F508del mutations in 2021 by frequency in the Northern Ireland adult and paediatric CF populations. Figure 4 compares the six most common CFTR mutations in Northern Ireland in 1996 and 2021.

Table 4: Comparison of the CFTR mutations described in the Northern Ireland population previously in 1996 with those described in the Northern Ireland CF population from 2021.
Footnote: Data sources: 2021- current study; 1996[11]

CFTR mutation in 1996	Shared CFTR mutations (1996 & 2021)	CFTR mutations in 2021
3849 G>A	1154insTC	1078delT
557delT	2789+5G->A	1248+2T->A
M1L G>T	3120G->A/Q996Q	1461ins4
Q2X	3659delC	1717-1G->A
V562L	3849+10kbC->T	1898+1G->A
Y917C	3850-1G->A	2184insA / 2185insA
	621+1G->T	2751+2T->C
	711+3A->G	2789+2insA
	E60X	3272-26A->G
	F508del	5T
	G542X	5T;TG12
	G551D	5'UTR to exon 9
	I507del	711+2T->C
	L206W	A349V
	N1303K	D1152H
	P67L	F508C
	R1162X	G576A
	R117H	G85E
	R297Q	I37R
	R560T	L967S
	V520F	M1210K
	W1282X	No legacy name (c.4035_4038dup)
	Y563N	No legacy name (c.869+1G>C)
		Q493X
		R1070P
		R1070W
		R1158X
		R1239R/ 3849G->A
		R134S
		R334Q
		R347H
		R352Q
		R751L
		S1159P
		S549N
		TG12T5
		W361R
		Y1092H
		Y1092X

Discussion:

CFTR allele epidemiology in paediatric and adult CF populations in Northern Ireland.

Northern Ireland's CF epidemiological profile and gene pool has changed considerably with time, as illustrated in Figure 3A, Figure 3B and Figure 4. Allelic variation and individuals per year-group has increased steadily from 1980, with greater mutation variation in younger groups contributing to historic gene pool dilution and diversification, reflecting improved life expectancy. Increased diversity aligns with the end of "The Troubles" in 1998, where increasing immigration could have potentially resulted in allelic diversity and vertical passing of different variants. Between 2000-2010, almost 122,000 people immigrated to Northern Ireland,[13] potentially introducing different mutations into Northern Ireland's CF gene pool. Most immigrants were from Eastern Europe, potentially explaining N1303K's increase from 1.18% at its first appearance in 1980's to 2.61% after 2010, as this allele is the third most common in the Lithuanian CF population.[14] 3849+10kbC->T and G542X are noted in the CF population after 1990, most frequent in Lithuania and Latvia respectively.[15] 3120+1G->T is noted in the current Northern Ireland CF population born after 1980 and is predominantly an African variant.[16] Although historically predominately a Caucasian disease, from 2010-2020, the percentage of Indian, Pakistani, African, and other ethnicities with CF have risen in the UK, possibly due to improved diagnosis.[17] Additionally, improvements in molecular analyses, particularly sequencing, may have concurrently aided with the detection of rarer mutation types, as well as other influencing factors, including CF birthrate, family planning and prenatal testing and fertility procedures, relating to assisted reproductive technology (*in vitro* fertilisation and intrauterine insemination) and pre-implantation genetic screening.[18]

Changes in F508del prevalence are noted in various age groups, illustrated in Figure 3A and Figure 3B. In older Northern Ireland CF age groups, F508del heterozygous individuals' prevalence is higher and F508del homozygous lower i.e., 35.7% in the 20-23-age group and 82.6% in >55-year-olds (heterozygous F508del), and 50.0% in the 20-23-age group to 4.3% in >55-year-olds (homozygous F508del). F508del homozygous individuals often have severe disease phenotypes, dying younger and those with severe mutations have a ten-year-lower estimated median survival age than those with mild mutations,[5] possibly explaining lower incidences in older age groups. F508del heterozygous individuals may live longer due to less severe disease, especially when combined with a mild second mutation, resulting in the dominant phenotype.[5] Scotet and colleagues reported a similar finding to this current study in relation to a lower proportion of F508del homozygous individuals with increasing age[5]. Likewise, a similar trend was noted in Dutch CF Registry reports, where a lower homozygous frequency in over 48-year-olds was recorded than in 12-17-year-olds i.e., 20.0% and 65.0% respectively.[19]

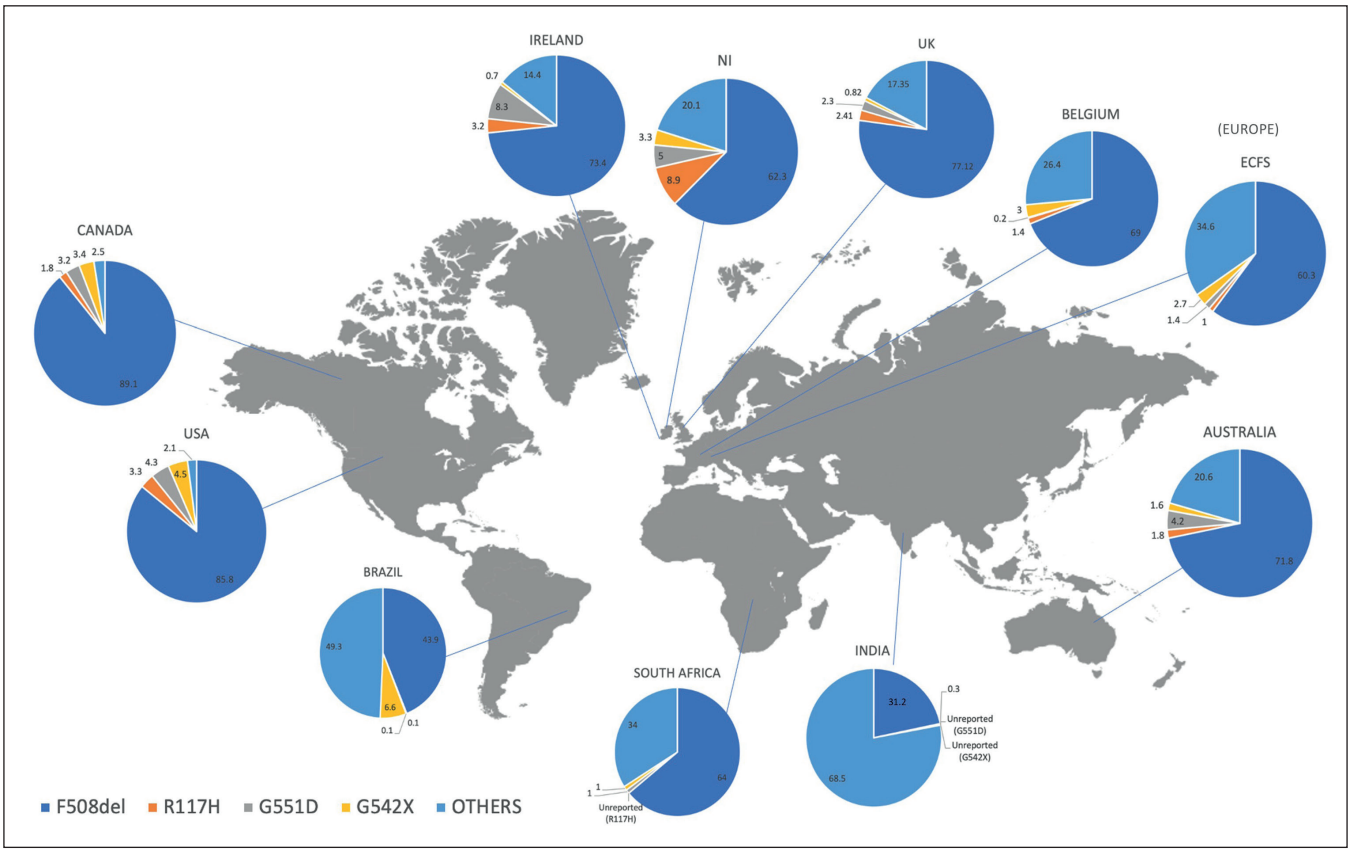
Comparison of Northern Ireland CFTR allele frequencies with other countries.

There is wide CF mutational heterogeneity worldwide, with mutation spectrum and frequency highly influenced by ethnic background and geographical location.[20] CFTR mutation rates are highest in European Caucasian populations at 1 in 2,500 live births.[21] Incidence is less common in native Africans (1 in 17,000), and in Asian UK migrants (1 in 10,000 - 12,000),[7] with prevalence increasing from the Mediterranean basin to Northern Europe.[5] Few mutations reach worldwide frequencies above 0.1%[20] and frequencies vary due to genetic drift, changes in allele frequency over generations due to random parental population allele proportion fluctuations,[17] isolation, and the founder effect - an extreme version of genetic drift occurring when individuals become isolated from a larger population.[5] The four most common Northern Ireland CFTR variants compared worldwide and with countries within the British Isles are shown in Table 3 and Figure 2.

Northern Ireland's CFTR distribution of the F508del mutation is unlike any of its closest geographical neighbours, including Ireland, England, Scotland and Wales (Table 3 & Table 4). Northern Ireland has a lower proportion of F508del homozygous (34.2%) and a higher prevalence of F508del heterozygous (51.5%), than its neighbours. The F508del mutation is ubiquitous and the most common CFTR variant worldwide.[22] This is believed to have arisen in Europe over 52,000 years ago, spreading West to East, in chronologically distinct expansions, resulting in differential F508del frequencies in Europe and beyond.[22] It is hypothesised that F508del heterozygous individuals had a selective advantage due to high prevalence among native Europeans, possibly an increased resistance to intestinal diseases, known as heterozygous resistance,[23] explaining its high allelic frequency, however this benefit remains elusive.[24] From Table 3, it is evident that the frequency of mutations not in the Northern Ireland top four, increases further from Caucasian populations of America, UK, Europe, and Australia, reflected by high percentages of other mutations in India, Iran, and Brazil. The F508del mutation exhibits substantial regional variation from 27% of alleles in Turkey, 26% in Algeria, to 87% in Denmark.[25] In Northern Ireland, F508del frequency was 62.3%, and lower than the worldwide average of 73.1%, but similar to Europe's average of 60.3%. USA and Australian F508del frequencies are higher at 85.8% and 89.1%, respectively, suggesting prevalence may increase westward.

R117H was the second most common Northern Ireland CF allele at 8.9%, higher than the worldwide average of 2% and the European average of 1%, with highest frequencies reported in neighbouring Ireland at 3.2%[26] and Australia at 1.8%[27]. G551D was the third most common Northern Ireland

Figure 2: Comparison of the four most common CFTR alleles identified in the Northern Ireland CF population with other global regions.
Footnote: Data sourced from international cystic fibrosis registries as detailed in Table 1.



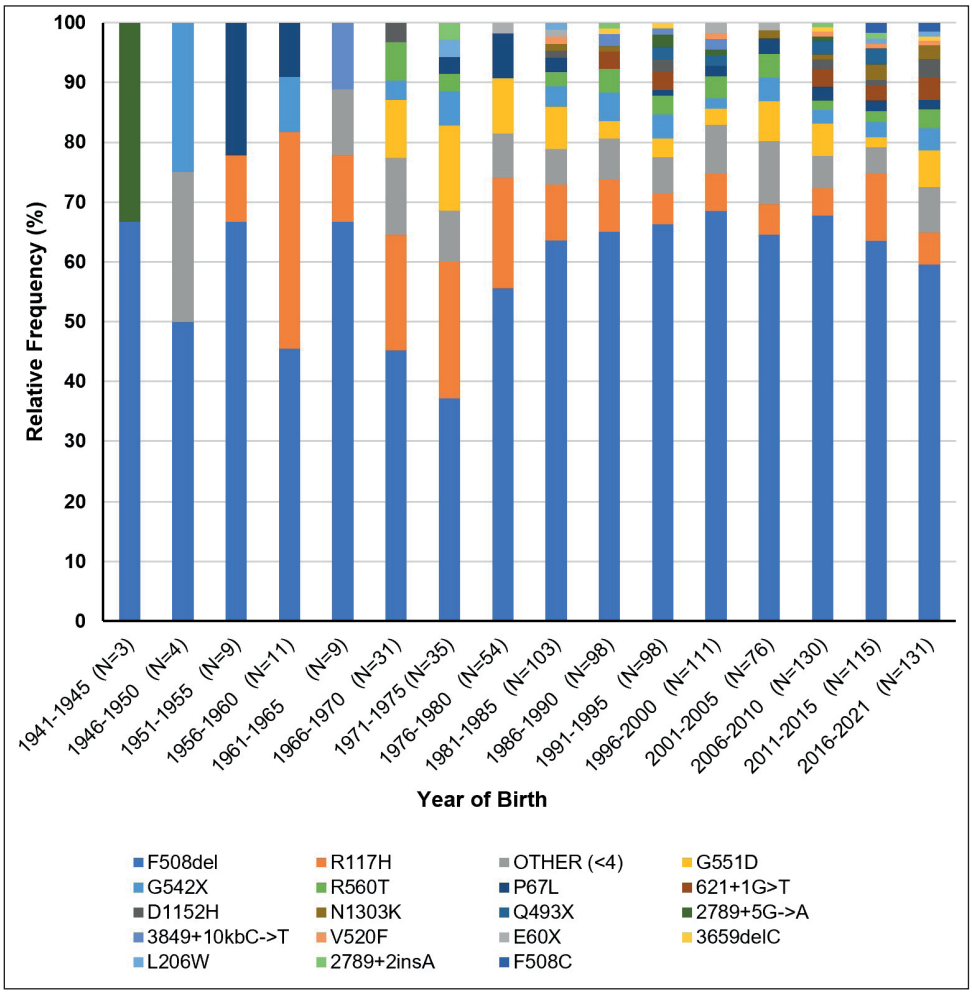
allele, and 5.0%, higher than the worldwide average of 3.3%. This mutation is most frequent non-F508del mutation in Ireland (8.3%)[26] and within many celtic cultures.

Such differences in the frequency of F508del mutations, particularly the ratio of homozygous to heterozygous populations, in the contemporary Northern Ireland population merits further reflection. A number of related interesting questions await an answer. Historically, one hypothesis relating to differences in CFTR gene frequencies is that CF gene mutations, particularly F508del was enriched due to the protective effect against secretory diarrhoeas which CF conferred on those with the condition, when exposed to pathogenic bacteria from domesticated cattle, which were transmitted zoonotically. This was particularly the case in populations in Northern Europe, which spread southwards in tandem with cattle pastoralism.[28] There is controversy regarding whether or not, wild oxen ever inhabited ancient Ireland. Scharff's treatise on the "*Origins of Irish Cattle*" suggests that this was the case and that cattle (*Bos longifrons*) were introduced to Ireland long ago, certainly pre-Christian times by early settlers.[29] Rutimeyer described three distinct lineages of cattle, namely *trochoceros, primigenius* and *brachyceros*, from archaeological remains, which had lived in Switzerland during the Stone Age.[30] It is interesting to note that *brachyceros* are ancestors of the modern Kerry breed of cattle today. Rutimeyer also noted that the same breed has been found in ancient archaeological deposits in Great Britain, Sweden, Holland and other parts of Europe.[30] This evidence of the early origins of cattle in Ireland may offer supporting evidence of a migration of domesticated cattle and a CFTR (F508del)-enriched population of herders coming to Ireland, as part of the expansion of cattle pastoralism across European. Certainly, by the 7th and 8th centuries, the presence of cattle in Ulster is documented in Gaelic literature, as documented in *An Táin Bó Cúailgne* (*The Cattle Raid of Cooley*), narrating the story of the theft of Donn Cuailnge (the brown bull of Cooley) from his owner, Dáire MacFiachna, by Queen Medb of Connacht. However, the geographical isolation of Ireland as an island, sitting west of its neighbouring island, Great Britain, which sits west of continental Europe, may suggest that ethnic diaspora of people and their domesticated livestock may have been limited due to the island effect, physically limiting their free movement.

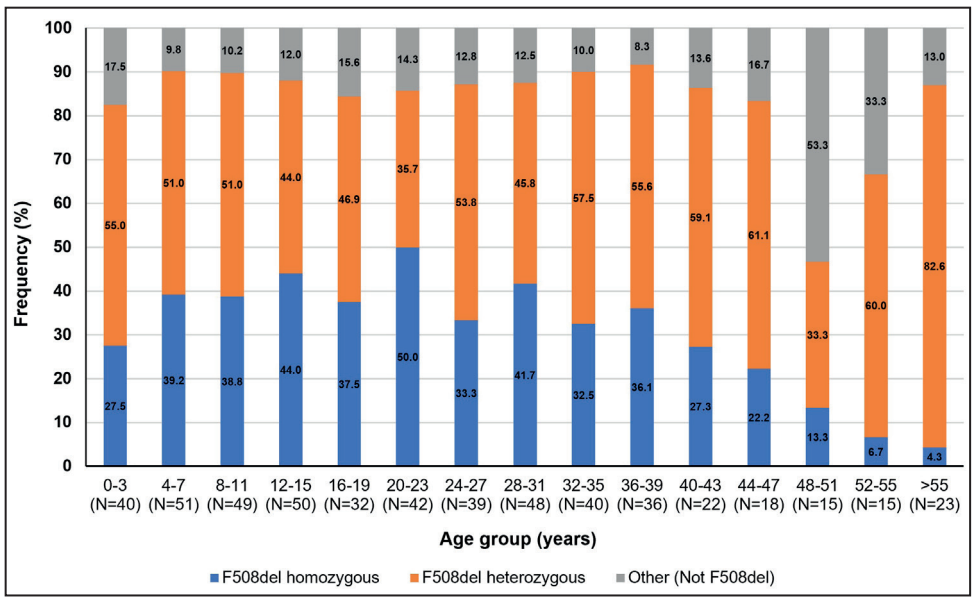
Historically in Ulster (*circa* to the 19th century), the island effect, the effect of limited movement of people, limited travel opportunities, poor modes of transportation, a relatively poor infrastructure and a lack of social mobility, combined with political, religious, social and cultural factors, may have limited the diversity and richness of the provincial gene pool. The importance of consanguinity data in human genetic studies has been previously stressed.[31] There are

Figure 3:

A Frequency of CFTR alleles (>4) in the Northern Ireland CF population (adults and paediatrics) relative to year-of-birth
CFTR, cystic fibrosis transmembrane conductance regulator



B Frequency of CFTR mutation groups in relation to current age of the Northern Ireland CF population.
CFTR, cystic fibrosis transmembrane conductance regulator



C F508del distribution within the Northern Ireland adult and paediatric CF populations
Footnote: "Key: Blue F508del homozygous; Orange F508del heterozygous; Grey Others"

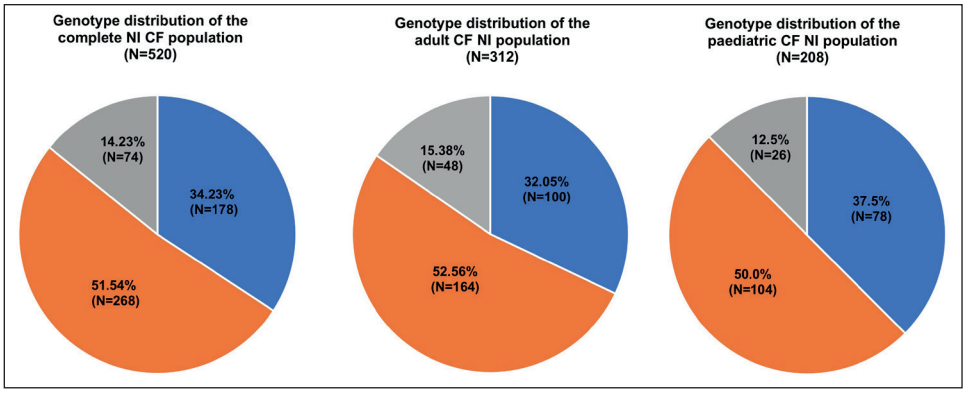


Figure 4: Comparison of the six most common CFTR mutations in the Northern Ireland CF population in 1996 and 2021
Footnote: Data sources: 2021- current study; 1996[11]

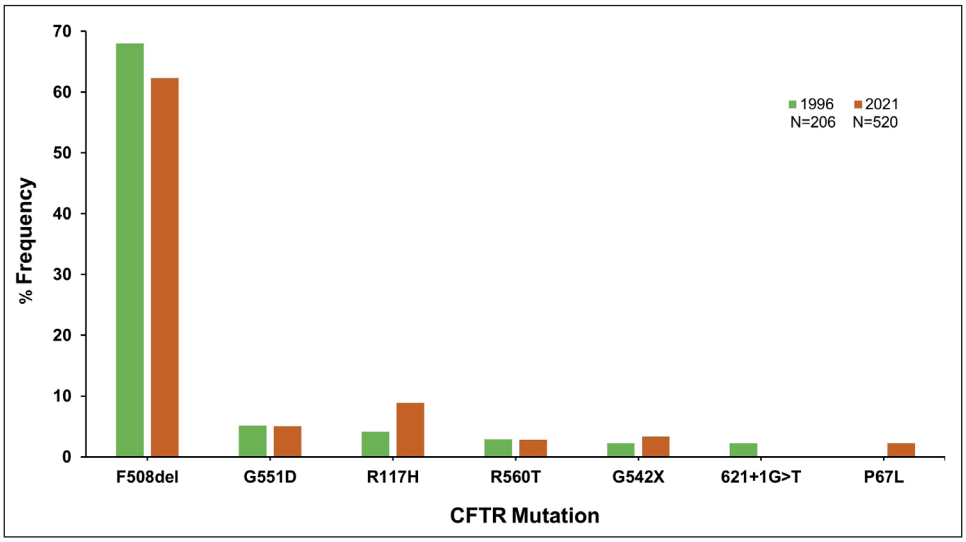


Table 3: Comparison of the prevalence of the F508del mutation in Northern Ireland with other countries within the British Isles and globally.
Footnote: Data sourced from international cystic fibrosis registries as detailed in **Table 1**.

Genotype Country	F508del homozygous (%)	F508del heterozygous (%)	Other (includes missing or inconclusive) (%)
NI	34.2	51.5	14.2
Ireland	55.5	36.5	8.0
England	49.2	40.0	10.8
Scotland	42.1	47.6	10.3
Wales	44.2	45.0	10.8
Netherlands	55.5	35.3	9.2
France	41.4	41.2	17.4
Australia	47.2	40.5	12.4
USA	44.5	41.2	14.2
Canada	47.2	40.5	12.4
Brazil	23.9	27.5	48.6
Belgium	45.8	38.3	15.9
South Africa	47.0	33.0	20.0

two historic reports dealing with consanguinity in Ireland, where in 1883, Cameron reported that in 7,567 persons investigated, 43 (0.57%) were or said they were children of first cousins.[32] A latter study in 1955 by Kilpatrick and colleagues reported that it was unlikely that the full-cousin marriage rate in Northern Ireland was as much as 1%.[33] A further study published in 1970 by Masterson indicated a first-cousin marriage rate in Catholic marriages during the period 1959-1968, of 0.032% for the dioceses of Derry, 0.069% (Down and Connor), 0.066% (Armagh), 0.075% (Clogher) and 0.000% (Dromore).[31] Masterson concluded that the incidence of first cousin marriages during the study period was lower and possibly lower than those reported by Freire-Maia, for most European countries.[31] These data therefore suggest inverse proportionality and a counter-support for consanguinity in relation to the relatively high incidence of CF in Ireland.

The effects on the CFTR mutational gene pool on mass historical migrations into Ulster requires analysis. Two mass migrations into Ulster dominate this social anthropological landscape.[34] These would have had a significant redistribution of the *status quo* of CFTR genotypes, but to what extent remains unknown. Firstly, the migration of the Hugenots from France to Ireland following the Revocation of the Edict of Nantes by Louis XIV in 1685, saw approximately 5,000 Hugenots settle in Ireland.[35] In Ulster, they settled mainly in Lisburn, as well as in Castleblaney, Co. Monaghan and Killeshandra, Co. Cavan.[35]

Secondly, the mass migration of Scottish and English settlers to Ulster, as part of the Plantation of Ulster, is of particular significance.[34] The majority of the Ulster plantation occurred from 1609 and by the mid 1600s, after the Cromwellian conquest of 1652, Gaelic clan chiefs had been crushed and their lands seized for plantation with predominantly Scottish Lowland planters, as well as with English settlers. Scottish immigrants to Ulster continued and increased in frequency due to famine in Scotland, during the Seven Lean Years in the 1690s.[34] It is estimated that the population of Ulster in 1630 was 240,000 comprising of 200,00 Irish and 40,000 British with the Irish figure taken from the Muster Rolls for circa 1630.[36] From 1650 to 1700, 100,000 settlers have been estimated to have migrated from Britain to Ulster, of which half of them were English.[34] Additionally, in the 20 years following William III's victory in 1690, it is estimated that approximately 50,000 Scots arrived in Ulster. This represents a significant dilution of the existing gene pool with predominantly Scottish, as well as English CFTR mutational genes. The frequency of F508del homozygous, as well as heterozygous genotypes from Northern Ireland, align most closely with Scottish values, compared to Irish and English frequencies, as shown in Table 3.

It is interesting to note the dynamics of CFTR genotype stability within the Northern Ireland CF population (Table 4). Over approximately two and a half decades (1996-2021), 23 CFTR mutations remain shared. The six most frequently detected CFTR mutations accounted for 84.4% of all alleles. Six alleles, which were described in the 1996 CFTR analysis, were absent from the 2021 data, whilst there were additional descriptions of 39 allelic mutations, which occurred in the 2021 analysis, but which were not described in the 1996 analysis. It is interesting to note the absence of these six mutation types described in the 1996 analysis, but absent in the 2021 analysis. It is unknown if these mutational types will reappear as CFTR types in the future, as this will be largely dependent on the frequency of prevalence of such mutation types in the population at any given time. Therefore, CFTR mutation types which are extremely rare in the population will experience large states of flux in their reporting. Furthermore, it is likely that the presence of additional CFTR mutation types in 2021 potentially reflect technological advances in DNA molecular analyses, particularly sequencing, and the formal establishment of agreed international mutation types, thereby enabling the reporting of rarer types locally.

In conclusion, characterisation of CFTR mutation alleles from people with cystic fibrosis provides essential information to help predict disease severity and effect of targeted CFTR modulator therapy. The arrival of CFTR modulator therapy has the potential to radically alter the current *status quo* due to significant improvements in lung function and quality of life, resulting in increased independent living and fertility.

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Transparency declarations/Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial, financial or other relationships that could be construed as a potential conflict of interest.

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Clinical Paper

Outcomes In Acute Kidney Injury Requiring Haemodialysis - A Retrospective Cohort Study

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ABSTRACT

Background

Acute kidney injury (AKI) requiring intermittent haemodialysis (AKI-IHD) is associated with significant morbidity and high mortality. There is limited data regarding clinical outcomes in individuals with AKI-IHD in Northern Ireland. The aim of this study was to explore clinical outcomes in a cohort of individuals with AKI-IHD, including rates of recovery to self-sustaining kidney function, mortality rates at 30 days and 2 years from start of haemodialysis, and to investigate potential predictors of these key outcomes.

Methods

The Acute Haemodialysis Unit in the Royal Victoria Hospital, Belfast, Northern Ireland, was established in 2011 to provide onsite inpatient intermittent haemodialysis (IHD) to individuals requiring this supportive treatment. A retrospective review of 188 incident IHD patients in the Royal Victoria Hospital from January 2018-December 2022 was undertaken. Demographic and clinical outcome information on 12th May 2023 was obtained from the nephrology electronic database eMed (Mediqal) and the Northern Ireland Electronic Care Record.

Results

188 individuals commenced IHD for the first time as a consequence of life-threatening complications of AKI during the 5-year period (January 2018-December 2022).

75% of these patients were not previously known to the nephrology service, (GROUP A, n=142, mean age 63 years, mean baseline serum creatinine 99 µmol/L) while 25% (GROUP B, n=46, mean age 67 years, mean baseline creatinine 278 µmol/L) had been attending a Nephrology Clinic for at least 12 months.

A significant proportion of AKI developed during the inpatient admission rather than at initial presentation (GROUP A 47%, GROUP B 50%).

92% of GROUP A recovered self-sustaining kidney function before discharge, compared to 59% of GROUP B. A lower baseline serum creatinine was the only predictor of kidney recovery in GROUP B, p value=0.02. No predictors for kidney recovery were identified in GROUP A.

The diagnosis of either AKI and/or dialysis was documented in 80% of electronic discharge letters for patients in GROUP A but only 54% of letters for patients in GROUP B.

The 30-day mortality (from IHD start) in GROUP A was 14% compared to 9% in GROUP B. Individuals with a diagnosis of heart failure were four times more likely to die before discharge (p value=0.02) and those aged ≥ 70 years twice as likely to die before discharge (p value=0.049). The two-year mortality rate in the two groups was similar (GROUP A 35% vs. GROUP B 37%) despite GROUP B being significantly older.

Conclusion

In this cohort of individuals with AKI-IHD, managed in the Royal Victoria Hospital, Belfast, the majority recovered self-sustaining kidney function.

The mortality rates at 30 days were lower than reported in the literature and may be due to careful patient selection. The poorer outcomes associated with AKI-IHD support and a concomitant diagnosis of heart failure or age ≥ 70 years (or both) are useful in guiding clinical and patient expectations and decision making.

Key words: acute kidney injury, haemodialysis

INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decline in kidney function occurring over days to weeks. AKI is associated with significant short-term and long-term sequelae including increased mortality (ranging from 20-60%), kidney failure requiring dialysis, prolonged hospitalisation, emergency readmission, the development of chronic kidney disease (CKD) and major adverse cardiovascular events[1, 2]. The annual cost of hospital acquired AKI to the National Health Service in the United Kingdom is estimated to be £434- £620 million pounds[3].

From a nephrology perspective, in a suitable candidate for haemodialysis support, key indicators for the initiation of intermittent haemodialysis (IHD) for AKI are the presence

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TABLE 1: DEMOGRAPHIC AND CLINICAL DATA

Variable	Group A N= 142	Group B N= 46	P-Value*
Mean age at intermittent haemodialysis start	63 years	67 years	0.035
Age ≥65 yrs	53.5%	67.4%	<0.01
Male gender	62%	71.7%	0.006
Mean baseline Creatinine (µmol/L)	99	278	<0.01
Mean admission Creatinine (µmol/L)	207	386	<0.01
Emergency versus elective admission	94%	89%	
Referred from medical specialties	63%	68%	
Acute kidney injury acquired during in-patient admission	47%	50%	
Sepsis	40%	44%	
Continuous renal replacement first dialysis modality	68.3%	18%	

Independent T test *

Group A = Not previously known to Nephrology

Group B = Established patient at Nephrology clinic

of a life-threatening complication particularly in the setting of minimal or no urine output. These include pulmonary oedema, refractory hyperkalaemia, severe metabolic acidosis or uraemic symptoms/complications.

The choice of haemodialysis treatment modality, IHD versus continuous renal replacement therapy (CRRT), and the setting for haemodialysis, are determined by circulatory stability, modality availability, the presence of multi-organ dysfunction and patient compliance.

AKI requiring intermittent haemodialysis (AKI-IHD) is rising in incidence due to increasing age in hospitalised patients and complex co-morbidities that are associated with significant morbidity and mortality[4].

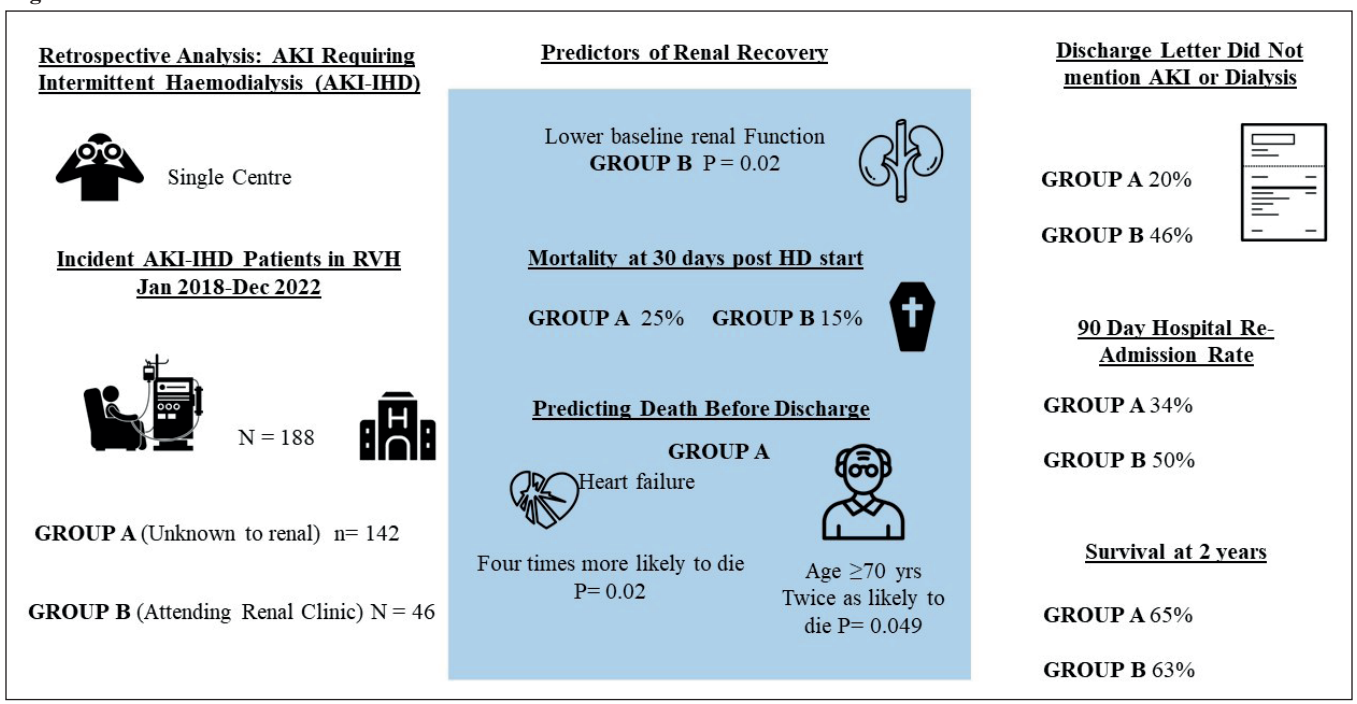
Data regarding the incidence of AKI that requires haemodialysis support, CRRT and/or IHD, (AKI-IHD) and the clinical outcomes in the United Kingdom, outside of the critical care setting, is sparse. This is partly due to the lack of robust real-time embedded data collection systems in acute care settings. There is limited published data on AKI-IHD incidence in Northern Ireland and most of that is from critical care settings[5].

The aim of this study was to review the incidence and outcomes of AKI treated with intermittent haemodialysis (AKI-IHD) by the nephrology service in the Royal Victoria Hospital, Belfast, Northern Ireland, between 2018-2022.

Table 2: Kidney Outcome Data

Variable	Group A	Group B
Mean number of intermittent haemodialysis sessions before recovery	9	8
Recovered renal function before discharge	92%	59%
Still on intermittent haemodialysis at 1 year	0.08%	49%
Renal function back at baseline at 1 year (if intermittent haemodialysis independent)	49%	25%

Figure 1



METHODS

The Royal Victoria Hospital Acute Dialysis Unit, is a three bed/station treatment centre that opened in December 2011 to facilitate inpatient IHD therapy for AKI-IHD and individuals with end-stage kidney failure, already established on chronic HD admitted for the management of other acute illnesses. A retrospective review was undertaken of 188 patients with AKI commencing IHD for the first time in the Royal Victoria Hospital Acute Dialysis Unit over a 5-year period, between January 2018 and December 2022.

The patients were identified using an Excel database that is completed on a daily basis by the dialysis nursing staff. Demographic and clinical outcome information were obtained from the Northern Ireland Electronic Care Record (NIECR) and the nephrology database eMed (Mediqal).

Data was analysed using SPSS version 26 for Windows (SPSS, Inc., Chicago, IL, USA). Values were considered statistically significant if $p < 0.05$. Binary logistic regression was used to investigate predictors of kidney recovery and survival at 30 days after start of dialysis.

RESULTS

Of the 188 incident dialysis patients identified, 142 were not known to the nephrology service (GROUP A) and 46 were established patients attending nephrology clinics for at least 12 months (GROUP B).

The demographic details of the patients are listed in Table 1. The GROUP B patients were older (mean age 67 vs. 63 years) with a higher incidence of heart failure (50% vs 23.2%) than those in GROUP A. The mean pre-admission baseline serum creatinine in GROUP A was 99 µmol/L compared to 278 µmol/L in GROUP B.

The majority of patients who developed AKI-IHD were emergency presentations. 63% were referred from other medical specialties in the hospital. Interestingly, almost half of the individuals developed AKI whilst an inpatient (47% GROUP A, 50% GROUP B).

The majority of AKI-IHD patients were referred from Cardiothoracic Surgery and from Cardiology.

68% of patients in GROUP A received CRRT in the Intensive Care Unit (ICU) as their first dialysis modality reflecting the burden of AKI in the setting of multi-organ failure requiring ICU support.

Kidney specific outcomes are listed in Table 2.

92% of individuals in GROUP A recovered self-sustaining kidney function before discharge compared to 59% in GROUP B. The mean number of IHD sessions undertaken in both groups for those who recovered was similar [9 in GROUP A (median 6) and 8 in GROUP B (median 3)].

Using logistic regression and adjusting for confounders, the only predictor of kidney recovery in GROUP B was a lower baseline serum creatinine (p value 0.02). No predictors of kidney recovery were identified in GROUP A.

At one year from initiation of IHD, 49% individuals in GROUP A had returned to their baseline kidney function compared to 25% in GROUP B. Discharge and survival details are as recorded in Table 3.

Table 3: Discharge and Survival Data

Clinical Outcomes	Group A	Group B
Mean Duration of admission (days) [Range, median]	68 [2-288,55]	32 [2-93,24]
Survived to Discharge	78%	91%
Discharged to own home	68%	78%
Alive at 30 days from intermittent HD start	75%	82%
Re-admitted within 90 days	34%	50%
Alive 2 years post 1st run of intermittent HD	65%	63%

The duration of hospital admission for patients in GROUP A was almost double that of patients in GROUP B (68 days vs. 32 days). The majority of individuals were well enough to be discharged back to their own home (68% GROUP A, 78% GROUP B).

The re-admission rate within 90 days was 34% in GROUP A vs. 50% in GROUP B.

The inpatient discharge letters varied in their quality with reference to documenting a diagnosis of either AKI and/or haemodialysis. 80% of the discharge letters for the patients in GROUP A mentioned either the occurrence of AKI or dialysis, compared to 54% of the discharge letters for patients in GROUP B.

With regard to mortality, 75% of patients in GROUP A were alive 30 days post initiation of IHD compared to 85% in GROUP B.

The mortality rate at 90 days was 24% for GROUP A (34/142) and 13% (6/46) for GROUP B.

78% survived to discharge in GROUP A and 91% in GROUP B.

With regards to predicting survival to discharge for patients in GROUP A using logistic regression, individuals with a diagnosis of heart failure were four times more likely to die before discharge (p value 0.02) while patients aged ≥ 70 years were twice as likely to die before discharge (p value 0.049).

Using logistic regression, no predictors of death before discharge were identified in GROUP B.

Of those who survived to discharge, 65% of individuals in GROUP A were alive 2 years from first initiation of IHD compared to 63% of individuals in GROUP B.

A pictograph summarising the study and key findings is illustrated in Figure 1.

DISCUSSION

This retrospective cohort review of 188 individuals who received AKI-IHD during hospital admission provides several interesting insights.

In many studies investigating AKI associated outcomes, individuals are treated as a heterogeneous group making interpretation or real-world application of that data difficult[1]. Individuals with pre-existing chronic kidney disease (CKD) who develop AKI-IHD are distinctively different than persons with previously normal kidney function who develop AKI-IHD. It could be postulated that in persons with normal kidney function, a more severe extra-kidney physiological insult is responsible for inducing AKI requiring dialysis. This is a key reason why in this study, the two populations were separated for analysis. As noted above, 68% of individuals in Group A (mean age of 63 years, average baseline serum creatinine of 99 μmol/L), required CRRT as the first dialysis modality in an ICU.

The requirement for CRRT reflects the presence of multi-organ dysfunction and need for multi-organ support. Individuals with multi-organ failure often have cardiovascular instability and continuous dialysis therapy is generally better tolerated haemodynamically than intermittent HD. Approximately 50% of critically ill patients with AKI requiring dialysis in the ICU setting die within one year[6].

The average length of overall hospital admission in Group A was more than double that of Group B (68 vs. 32 days) also reflecting the difference in severity of illness and recovery period.

Hospital-acquired AKI (HA-AKI) has been linked with increased length of hospital stay, health care costs, and risk of developing CKD, early and long-term mortality[7]. A recent UK Kidney Registry Report indicated that in England, of the 68.2% of AKI episodes that involved a hospital stay – 36.8% were admitted with community acquired AKI and 31.4% where already in hospital when their AKI developed.

The 30 days mortality rates of HA-AKI compared to

individuals with an AKI in the community that were never hospitalised was three-fold-24% compared to 8%[8].

In our study of selected individuals who were deemed suitable to be offered IHD, 50% of individuals acquired their AKI following admission.

A recent UK observational study of 93,196 episodes of HA-AKI reported that the highest incidence occurred in general medicine (21.9%), care of the elderly (18.9%) and general surgery (11.2%) [2].

In our combined cohort, a baseline creatinine was not available in 7/188 individuals. Of the 88/181 patients who developed AKI-IHD in the setting of HA-AKI, 47/88 (53%) occurred outside the critical care setting. 32% (15/47) of ward-based HA-AKI resulting in AKI-IHD occurred within surgical specialties and 68% (32/47) within medical specialties in the Royal Victoria Hospital.

The rates of kidney recovery following an episode of AKI-IHD are reported as ranging from 0%-40%[8]. Predictors of non-recovery reported in the literature include older age, diabetes, pre-existing CKD and hypertension[9].

In our combined cohort 82% (154/188) survived to discharge and of these individuals 80% (123/154) had recovered self-sustaining kidney function, 81% (100/123) in Group A and 19% (23/123) in Group B

At the end of the observation period, 92% individuals in GROUP A recovered self-sustaining kidney function compared to 59% in GROUP B.

The much higher recovery of self-supporting kidney function in patients within GROUP A likely reflects the impact of their normal kidney function prior to the pathophysiological insult that resulted in AKI-IHD i.e. they had a greater potential for kidney recovery because they had a much greater functional nephron (reserve) pre-insult[10]. The finding of the only predictor of kidney recovery in Group B being a lower serum creatinine prior to AKI-IHD would certainly support this.

The better kidney recovery rates than those reported in the literature may in part be associated with careful patient selection for IHD based on the likelihood of predicted overall survival in the context of severity of acute illness, pre-existing-comorbidities and functional status, by both the referring clinician and the nephrologist[11, 12].

The medical discharge letter is a vital communication between hospitals and general practitioners and an important legal document. Timely communication, clear documentation of key diagnoses and findings, an adequate assessment of the disease and understandable recommendations for follow-up care are essential aspects of the medical discharge letter[13].

It was interesting to find in our cohort of 188 patients, 5 had no discharge letter documented electronically at all. Of the 183 that had a discharge letter issued, the diagnosis of either AKI or dialysis was documented in discharge letters for 80% of patients in GROUP A but only 54% of patients in GROUP B.
Junior doctors have reported a lack of formal guidance and training on how to write medical discharge summaries with higher priority given to pressing clinical tasks[13]. In Northern Ireland, discharge summaries are typically completed by Foundation Year 1 doctors who may not be present on ward rounds or have a clear understanding of the complex clinical course of an individual patient with multiple charts following a prolonged admission. The absence of a diagnosis of AKI-IHD in a discharge letter can result in a number of adverse factors including delayed clinical follow-up and inappropriate drug prescribing (or a delay in re-initiation of drugs). This diagnosis is a key piece of information for the general practitioner and other specialist services in terms of understanding the risks for AKI recurrence and/or the future development of CKD.

AKI is associated with significant mortality. A systematic review of 47,017 individuals who had been discharged from hospital reported 8.9 deaths per 100 person-years in those who had AKI compared with 4.3 deaths per 100 patient-years in those without AKI, with the most common causes of death being cardiovascular disease (8%) and cancer (28%) [14].

In our combined cohort, the 90-day mortality rate for AKI-IHD was 21%. It is interesting that the two-year mortality rate of GROUP A was almost identical to GROUP B despite the excellent kidney recovery rate in GROUP A and younger age of individuals compared to GROUP B (almost 40%).

This review has a number of limitations.

It is a single centre retrospective study with relatively small numbers. The inability to determine a predictor of death before discharge in GROUP B, may be due to the small patient numbers. A regional study on AKI-IHD outcomes with a larger population would be highly informative. It would also be useful to compare outcomes in individuals with AKI stage 3 who did not require/were not suitable for dialysis to those with AKI who underwent dialysis.

Individual case notes were not used so more detailed information such as the specific causes of hospital acquired AKI-IHD across specialities or specific indications for HD initiation were not available as this data was rarely documented in the discharge letters or the kidney electronic database eMed. Also, the duration of CRRT, in an ICU setting, before IHD was commenced was not factored into clinical outcomes as this information is not readily available. However, the strengths of the study are that is provides local real-world data, outside the critical care environment, on outcomes in Northern Ireland for AKI requiring haemodialysis support, which is typically associated with significant short- and long-term adverse outcomes. It also has good follow up period of over 2 years.

There is limited data regarding outcomes in AKI-IHD outside the critical care setting in the UK. To our knowledge, this is the first published data exploring AKI-IHD related outcomes in a Northern Ireland population.
This study provides informative local outcome data for educating both clinicians and patients alike and highlights areas for service improvement in relation to prospective data collection for AKI-IHD and the need for accurate discharge information. It also highlights the high rates of HA-AKI in a regional treatment hospital and provides further impetus for further AKI prevention strategies in secondary care.

CONCLUSION

This study confirms that AKI-IHD is associated with significant short- and long-term mortality in individuals in Northern Ireland. The better outcomes for AKI in this retrospective cohort study, compared to published literature, are likely to reflect careful patient selection for IHD support. Our experience is that the majority of carefully selected individuals with AKI-IHD will survive and recover self-sustaining kidney function. However AKI-IHD in patients with previously normal kidney function who have an underlying diagnosis of heart failure or are older than 70 yrs, or both, is associated with poorer survival outcomes.

Hospital acquired AKI is a significant cause of morbidity and mortality. Clinical systems that allow for real time data collection and analysis may help identify factors associated with AKI that could aid meaningful changes in practice. The new digital health and care record, ENCOMPASS, that has been introduced across the region may prove useful in improving recognition and management of AKI.

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Clinical Paper

Paediatric Sinogenic Subdural and Extradural Empyema: A Review of Local Surgical Management Over 10 Years

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Abstract

Objective: To investigate timing and surgical approaches of multidisciplinary management of sinogenic subdural and extradural empyema in the paediatric population.

Methods: We performed a retrospective analysis of all cases of sinogenic subdural and extradural empyema at our tertiary referral centre over a 10-year study period from 1st May 2012 to 1st May 2022. Data on demographics, presenting features, surgical management, length of stay, radiological investigations, microbiology results and long-term morbidity was recorded in a spreadsheet for analysis.

Results: We identified 11 children (mean age 11.3 years ± 2.3). In this sample, 7 were male (63.6%) and 4 female (36.4%). There were 7 cases of subdural empyema (63.6%), 2 cases of extradural empyema (18.2%) and 2 cases with both subdural and extradural empyema (18.2%). There were significant underlying co-morbidities in 2 cases (18%). The frontal sinus was suspected source in 10 cases (91%). Endoscopic sinus surgery was performed in 10 cases (91%); with 9 of these cases (90%) as/with the initial operation or within 24 hours of initial operation. Craniotomy was required in 9 cases total (81%), with 5 cases (56%) as/with the initial operation or within 24 hours of initial operation. After initial craniotomy 4 cases (44%) required further neurosurgical evacuation of abscess. Additionally, 2 cases managed with initial burrhole later required craniotomy. All 3 cases of small volume subdural empyema without neurological deficit were initially managed with endoscopic sinus surgery only and all cases subsequently required craniotomy. All cases with subdural empyema required craniotomy (n=9) whereas all cases with isolated extradural empyema avoided craniotomy (n=2). There was a longer length of stay in those that presented with neurology or low GCS than those that did not (27 days ± 10 compared to 86 days ± 41, p= 0.009). Long term morbidity and repeated neurosurgical intervention were more common in those cases with subdural empyema than those without subdural empyema, (55% vs 0% and 67% vs 0% respectively) although only 2 patients did not have subdural empyema (no statistical analysis available given small numbers). A Streptococcus milleri group microbe was isolated in 82% of cases.

Conclusions: Endoscopic sinus surgery does not seem effective at preventing the need for craniotomy in cases of subdural empyema. It does have a role in aiding microbiological diagnosis. ESS may have a role in the treatment of extradural empyema and avoiding craniotomy. Subdural empyema has a higher morbidity and return to theatre rate than extradural empyema. Those that present with a neurological deficit or decreased GCS have a longer length of stay. Larger studies are required to assess the timing and extent of surgical interventions for subdural and extradural empyema.

Keywords: paediatric, sinusitis, subdural, extradural, empyema, surgery.

Introduction

Sinusitis complicates between 5-10% of all upper respiratory tract infections in the paediatric population[1], with intracranial complications reported in 10% of patients hospitalised, and approximately 30% of patients admitted with frontal sinus involvement[2]. Although rare, the intracranial complications of sinusitis are associated with high mortality (~3.3%) and morbidity (~27%), such as hemiparesis, aphasia, and epilepsy, so are regarded as a medical and surgical emergency[3]. The frontal sinus is postulated to have a more vulnerable skeletal framework due to its abundant network of valveless diploic veins, that drain the frontal sinus mucosa and interconnect with the dural venous sinuses, emissary veins and subdural veins. Retrograde propagation of thrombophlebitis through this venous system results in indirect or haematogenous spread. This method is believed to be more common than direct spread of infection, where bacteria directly enters the intracranial compartment through a necrotic defect in the posterior sinus wall secondary to osteomyelitis[3].

There can often be delayed diagnosis in the paediatric population with an already established intracranial collection at presentation and more fulminant clinical course. A recent meta-analysis on the management of intracranial complications of paediatric sinusitis suggests that a multidisciplinary team approach with aggressive treatment achieves favourable outcomes, but states that the most effective surgical method remains unclear given the wide variety of study designs, surgical techniques, and

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complications included[4]. Our aim was to investigate timing and surgical approaches of sinogenic subdural and extradural empyema in the Northern Irish paediatric population to help guide local management of these cases.

Methods and materials

We performed a retrospective analysis of all cases of sinogenic subdural and extradural empyema at our tertiary referral centre with onsite Ear, Nose and Throat, Neurosurgical, Paediatric, Infectious Diseases and Intensive Care specialties from 1st May 2012 to 1st May 2022. After obtaining institutional audit approval we analysed theatre management system records to identify all paediatric emergency cases that underwent endoscopic sinus surgery (ESS) or neurosurgical evacuation of abscess (including other relevant terms), and cross referenced this with discharge coding records for subdural and extradural empyema to obtain our patient population. We then examined patient records and imaging findings to exclude non-sinogenic causes and excluded other complications of sinusitis that did not have subdural or extradural empyema (e.g., orbital abscess, venous sinus thrombosis, meningitis etc). Data on demographics, presenting features, surgical management, length of stay, radiological investigations, microbiology results and long-term morbidity was recorded in a spreadsheet. Data was analysed via means and standard deviation, or median and interquartile range. The Mann Whitney U Test was used to compare means (SPSS version 26).

Results

3.1 Patients

We identified 11 patients with sinogenic subdural or extradural empyema. The mean age was 11.3 years (± 2.3), ranging from 7 to 14 years. In our data, 7 patients were male (63.6%) and 4 were female (36.4%). Two patients had significant underlying medical co-morbidities, 1 patient had a history of familial dystonic cerebral palsy with a deep brain stimulator in situ, and 1 patient had trisomy 21 and factor V Leidin deficiency. The remaining patients had no significant medical co-morbidities with no previous documentation of chronic rhinosinusitis. The clinical features documented to warrant imaging investigation were headaches (n=7, 63.6%), peri-orbital or facial swelling (n=5, 45%), persistent pyrexia (n=4, 36%), reduced Glasgow Coma Scale [GCS] (n=3, 27%), seizures (n=2, 18%) and hemiplegia (n=1, 9%).

3.2 Imaging

All 11 patients were investigated with a contrast enhanced CT scan, with 3 patients (27.3%) having both CT and MRI scan. In 1 case, an extra dural abscess was not identified on initial contrast enhanced CT scan but seen on MRI. In another case, a contrast enhanced CT scan was performed and initially reported no intracranial empyema. This patient had a sinus washout and was managed with intravenous antibiotics. They later developed seizure activity and had repeat imaging demonstrating a subdural empyema. A very small subtle subdural empyema was reported in retrospect on the initial CT scan. For the purpose of this study, we treated this as a subdural empyema initially managed conservatively with ESS. In the other 9 cases the empyemas were identified on the initial imaging modality (with 2 other cases having additional MRI scan for further evaluation of abscess). Of the 11 patients, 7 cases (63.6%) had only subdural emypemas, 2 cases (18.2%) had only extradural empyemas and 2 cases (18.2%) had both subdural and extradural empyemas. The frontal sinus was the suspected index sinus in 10 (90.9%) cases with the sphenoethmoidal sinuses the source for 1 case (9.1%). A bony defect in the index sinus was reported in 2 cases (18.1%) with indirect haematogenous spread suspected in 9 cases (81.8%).

3.3 Surgical Management Summary

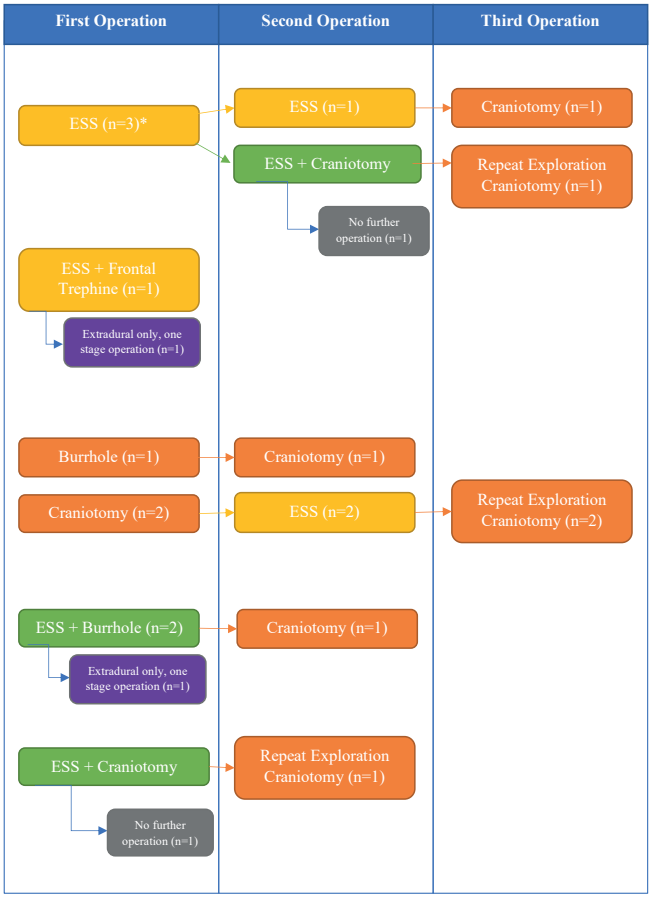
Figure 1 displays the surgical management of all 11 cases. In total, 10 cases (90.1%) required a neurosurgical procedure (craniotomy or burrhole), of which 9 patients (81.8%) required craniotomy. Of those 9 patients, 4 patients (44%) had a craniotomy as part of their initial surgery, one patient had craniotomy (11%) within 24 hours after burrhole and ESS and 1 patient (11%) had craniotomy within 72 hours of initial burrhole. 3 patients (33%) had a craniotomy after failed conservative measures with ESS only. These were 3 cases of small volume empyema and no neurological deficit, all of which later went on to develop seizure activity. All cases with subdural empyema (n=9, 100%) required craniotomy. All cases of isolated extradural empyema (n=2, 100%) avoided craniotomy (1 managed with combined burrhole/ESS and 1 managed with ESS and frontal trephine) and were managed as single stage operations. From the 9 cases that required craniotomy, 4 cases (44.4%) required further neurosurgical evacuation, with 5 cases (55.6%) not requiring any further operative intervention.

From the total 11 cases, 8 cases (72%) required multiple operations, with 6 cases (54%) requiring repeated neurosurgical intervention (4 cases required repeat evacuation of craniotomy and 2 cases required craniotomy after initial burrhole). No cases of isolated extradural empyema required multiple operations. ESS was performed in 91% of all cases in our study. Only 2 cases of the total 11 (19%) reported a bony defect in the frontal sinus wall (direct spread) and both these cases were managed as single stage operations. Indirect spread was demonstrated in 9 cases (82%), with 8 of those 9 cases (89%) requiring multiple operations. Timings for the first ESS and Craniotomy procedures are illustrated in Figure 2.

3.4 Surgical management of those cases with altered GCS or neurology prior to initial operation

In total, 6 patients (55%) had reduced GCS or neurological findings prior to initial surgery (1 case with hemiplegia, 2 cases with seizures and 3 cases with decreased GCS). All these cases had a neurosurgical procedure as their initial

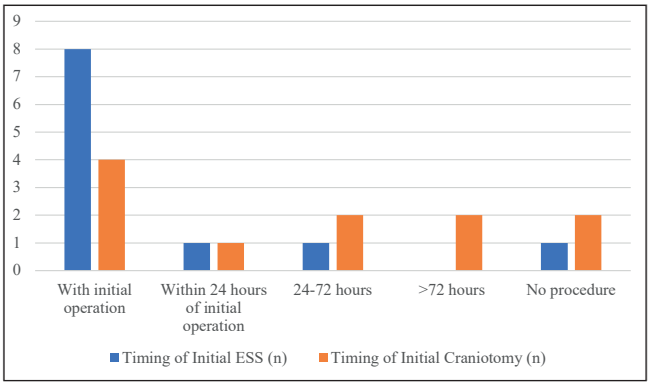
Figure 1. Surgical intervention pathway



Yellow box- ENT operation only; Orange box- Neurosurgical operation only; Green box- Combined ENT and Neurosurgical operation; Purple box: extradural empyema only; n- number of patients

*All 3 cases of small volume subdural empyema managed with ESS required craniotomy

Figure 2. Timing of Surgical Intervention



operation with or without a combined ENT procedure. Of these 6 cases, 1 case (17%) was managed as a single stage operation (combined craniotomy and ESS), 3 cases (50%) were managed as a 2 stage operation (1 combined burrhole/ESS with subsequent craniotomy within 24 hours; 1 burrhole with subsequent craniotomy and removal of deep brain stimulator within 72 hours; 1 combined craniotomy/ESS with subsequent re-exploration of craniotomy 12 days later), and the remaining 2 cases (33%) were managed as a 3 stage operation (1 craniotomy with subsequent ESS within 24 hours and further neuronavigated craniotomy washout 14 days later; 1 craniotomy with subsequent sinus washout within 72 hours and further neuronavigated aspiration 28 days later).

3.5 Surgical management of cases without neurology and small volume empyema

Of the total 11 cases, 5 cases (45%) had no neurological findings and small volume empyemas. From these 5 cases, as their initial operation 4 cases (80%) had ENT procedures only and 1 case (20%) had an initial combined burrhole/ESS. Of these 5 cases, 2 cases (40%) were managed as a single stage operation (1 combined ESS/burrhole evacuation; 1 ESS with frontal trephine) and both these cases were isolated extradural empyema; 1 case (20%) was managed as a 2 stage operation (ESS with subsequent combined craniotomy/ESS within 48 hours); and 2 cases (40%) were managed as a 3 stage operation (1 ESS with subsequent revision ESS at day 5 and further combined ESS/craniotomy 6 days later; 1 ESS with subsequent combined craniotomy/ESS at day 4 and further re-evacuation via craniotomy 18 days later).

3.6 Microbiology cultures

From our 11 cases, a Streptococcus milleri group microbe was grown from intranasal or intracranial pus in 7 cases (64%) cases and additionally from 2 other patients' blood cultures, so in total isolated in 9 cases (81.8%). Further intranasal and intracranial microbes were isolated as demonstrated in Table 1, of which some patients had more

Table 1. Surgical Microbiology Cultures

Cultures Obtained	n
Streptococcus Milleri:	7
Streptococcus intermedius	4
Streptococcus constellatus	1
Streptococcus anginosus	2
Streptococcus gordonii	1
Streptococcus group C	1
Staphylococcus capitis	1
Staphylococcus epidermidis	1
Denticola	1
Fusobacterium nucleatum	1
Mixture of bacteria (not specified)	1
No culture obtained	3

n = number of patients with organism

than one organism. Patients were often on antibiotics in the community or in hospital prior to cultures so it is expected some commensal pathogens may be isolated that are likely not responsible for the acute infection. Type strains of 16S rRNA gene sequences were not available.

3.7 Outcomes

The mean length of stay for our patients was 59 days with ranges from 18 to 150 days. Those that presented without any neurological deficit or reduced GCS before initial operation had a statistically shorter inpatient admission stay of 27 days (± 10) compared to 86 days (± 41) in those that presented with a neurological deficit or reduced GCS (p= 0.009).

From our 11 cases total, we had 5 cases (45%) that have long term morbidity (greater 1 year post surgery), 2 cases (18%) that are on prophylactic antiepileptic medications but within a year of follow-up which may or may not be required long-term, and 4 cases (36%) that have no long-term complications (with potential to increase to 6 cases (55%) if cases are successfully weaned off prophylactic antiepileptic medications). There were 4 cases (36%) with a residual hemiparesis; all 4 of which are also on long-term anti-epileptic medication and 1 with a hemianopia, and additionally 1 one other patient is on long term antiepileptic medication.

Of those 4 cases that have a long-term hemiparesis, 3 cases (75%) presented with low GCS or hemiparesis prior to surgery of which all had emergent craniotomy immediately after initial imaging, and 1 case (25%) had failed initial conservative measures with antibiotics and sinus surgery and later developed neurology. Follow-up time for this patient is just outside the first year and is continuing to improve with only minimal residual weakness. Of those with treated extra-dural empyema only (n=2), there were no long-term complications.

Discussion

ESS as an adjunct to intravenous antibiotics, can be a challenging operation in the paediatric population during an acute infective episode. Children have a smaller nasal passage and underaeration of paranasal sinuses compared to the adult population, and access will be further impeded with oedematous intra-nasal mucosa and a higher propensity to bleed. There are a wide range of potential sinus operations to consider, ranging from a simple sinus washout, middle meatal antrostomy, limited ethmoidectomy or frontal trephine, up to more advanced full house endoscopic sinus procedures with navigation guidance, frontal sinus drillout and direct drainage of intracranial empyema. There are a range of options to treat the subdural or extradural empyema including parenteral antibiotics, burrhole evacuations, craniotomy or cranialisation of the frontal sinus.

There is ongoing debate regarding the best management for subdural and extradural empyema secondary to sinusitis. A recent 2021 meta-analysis has shown that in the past 45 years there has been no significant change in pooled estimates in paediatric outcomes for 90 day mortality (2.3% [95% CI, 1.1%-3.6%; I^2 = 0, p>0.99]), permanent neurological disability (21.3% [95% CI, 15.3%-27.3%; I^2 = 75.2%, p <0.001]), or return to theatre (37.3% [95% CI, 29.5%-45%; I^2 = 71.2%, p<0.001]) despite a statistical increase in the use of ESS over the study time period[4]. This suggests that the increasing prevalence on ESS is not associated with better outcomes. The study also compares the same outcomes for combined ENT and neurosurgical procedure versus sinus intervention only versus neurosurgery only. It again did not demonstrate any significant difference in the outcomes between the groups but highlights the large degree of selection bias and the need for further robust studies[4].

Some centres advocate an early aggressive combined ENT and neurosurgical operation. Farah et al. 2008 published their retrospective series of 20 paediatric patients over a 7-year study period[5]. After identification of subdural empyema all patients proceeded to have a wide craniotomy with pus washout and deloculation if septae were present, with concurrent sinus washout: they had 1 mortality in their series. They report 10 patients (50%) having seizure activity (4 patients pre-operatively and 6 patients post-operatively), all of which had good seizure control and discontinuation of anti-epileptics after 1 year. They reported 3 patients with a transient neurological deficit, with all surviving patients in their study having a Glasgow Outcome Scale of 5 (indicating good recovery with resumption of normal life but there may be minor neurological or psychological disability) at 1 year. In their study 20% of cases had recollection of subdural empyema requiring further surgical intervention, which is better than the reported meta-analysis rate of 37%[4], and indeed better than our rate of repeated neurosurgical intervention of 54%. They suggest the role for conservative measures with intravenous antibiotics is only appropriate in the early phase before any collection of pus[5]. It is worth noting however that with such small numbers, data can be skewed e.g. if patients present late in the course of their disease with more extensive abscess they are more likely to require multiple operations.

Patel et al. 2015 also recommend early combined ENT and neurosurgical procedure[6]. Their 5-year study identified 27 paediatric cases of sinogenic intracranial abscess, of which 17 cases (63%) were managed as a joint ENT/neurosurgical procedure and again showed rate of revision neurosurgical procedures rates at 22%. They managed 6 cases (22%) with an ENT procedure only (in cases with small abscesses and no focal neurological deficit), with 50% of these later requiring a neurosurgical operation. Of the cases that were successfully managed without a neurosurgical operation there were 2 were extradural abscesses and 1 was a parenchymal abscess[6]. In our study, we had 4 cases with small abscess and no focal neurological deficit which were initially managed with an ENT only operation, 75% of which required a

neurosurgical operation. Also in our study, the 1 case that was successfully managed without a neurosurgical operation was an extradural abscess, with the 3 subdural empyemas all requiring craniotomy.

Patel et al. demonstrated that subdural abscesses are associated with a significantly poorer clinical course and outcome than extradural abscess[6]. In their study they had 14 cases of extradural abscess and 9 cases of subdural abscess. They found morbidity at 6 months significantly higher in the subdural group at 67% compared to the extradural group at 14% (p=0.0166). Our study showed long-term morbidity of 55% in subdural empyemas (with a further 22% on prophylactic anti-epileptic medications within the first year of surgery) compared to 0% of extradural empyemas. Patel et al. found no cases of extradural abscesses presented with a neurological deficit versus 78% of subdural empyema (p=0.0001), and 7% had reduced GCS on admission in extradural empyema versus 56% in subdural empyema (p=0.0183) [6]. Similarly, in our study, 0% of isolated extradural empyema had any neurological deficit or reduced GCS, and 66% of our subdural empyemas presented with low GCS or neurological deficit. In both studies, no cases of only extradural empyema had any seizure activity. In their study, no extradural empyema required multiple neurosurgical operations versus 67% of subdural empyemas[6]. Our study shows identical results of no extradural operations requiring repeat neurosurgical operations and 67% of subdural empyema requiring repeat neurosurgical intervention. All our cases of subdural empyemas that were initially managed with burrhole later required craniotomy.

Other studies have however demonstrated benefits from a more conservative approach. Del Gaudio et al. performed a 5-year retrospective analysis of 23 patients with intracranial complications of sinusitis[7]. The median age of cases in their study was 14 years, with 3 cases over the age of 21. In their study, 20 cases had intracranial abscesses. There was 1 death, 9 cases had emergent craniotomy, and 10 cases were trialled with initial conservative measures in patients with an abscess <1cm with no neurological deficit. Of the 10 cases managed conservatively, 4 cases (40%) were managed conservatively with antibiotics alone and 6 cases (60%) were managed with antibiotics and endoscopic sinus surgery. Of those cases managed with antibiotics alone, 50% later required operative intervention with craniotomy, whereas 83% of those managed with antibiotics and ESS required craniotomy. These results would suggest that the use of ESS does not appear to alter the need for neurosurgical intervention, and they question its role in the acute setting. They reported no increase in morbidity associated with initial conservative management and avoided a craniotomy in 3 cases[7].

Del Guadio et al. go on to discuss the aetiology of intracranial abscesses secondary to sinusitis and the 2 proposed routes of spread of infection: direct and indirect. They report that intracranial complications of sinusitis are most commonly a result of indirect spread through the frontal sinus[7]. In our study, the frontal sinus was the index sinus in 91% of cases and the sphenoethmoidal sinuses responsible for 9% of cases. There was direct communication, or a bony defect reported in 18% of cases with indirect spread responsible for 82% of cases. Of note in our study, both cases that had a direct method of spread were managed as a single stage operation. Del Guadio et al. reported only 4% of their cases as having a direct method of spread and suggest ESS is indicated in these cases in the acute setting. They do not advise ESS in the acute setting in the management of intracranial complications of sinusitis when secondary to indirect spread. They also advise reserving ESS for recurrent intracranial abscess despite neurosurgical drainage with persistent acute or subacute rhinosinusitis, or to treat persistent rhinosinusitis after the intracranial abscess has been treated[7]. In our study, both cases that had direct spread were managed as a single stage operation, with one case not requiring any neurosurgical intervention.

Garin et al. performed a study assessing the role of ESS in sinogenic epidural and subdural empyema. In their 2-year retrospective paediatric study they identified 9 subdural empyemas and 8 extradural empyemas[8]. In their subdural empyema population 2 cases (22%) had initial craniotomy of which 100% were managed in a single operation and none of which had any long-term morbidity. They had 6 cases (67%) that were initially managed with only endoscopic transnasal approaches (ETA): 83% later required craniotomy, which is comparable to 100% in our study; 17% did not require craniotomy. They had 1 case with subdural empyema that had an initial burrhole but later required craniotomy, which again is similar to our study in that all our cases (n=2) of subdural empyema that trialled initial burrhole later required craniotomy. They concluded that the best surgical approach for subdural empyema is a large craniotomy, and that the role of ESS is potentially limited to aiding microbiological diagnosis[8].

They however, did suggest that endoscopic transnasal approaches could be used as an alternative to open neurosurgical approaches when managing extradural empyema if direct drainage of the empyema can be accessed transnasally[8]. When frontal sinuses are involved, they advise using a Draf III procedure with direct opening of the posterior sinus wall. Of 4 patients where the empyema could be drained directly transnasally they successfully managed 3 of these cases (75%) without craniotomy. Performing a Draf III procedure with direct drainage of abscess may not however be feasible in all units, as an emergency procedure out of hours in an unwell paediatric patient.

Cranialisation has been demonstrated as an alternative to a combined ENT and neurosurgical procedure when the offending sinus is the frontal sinus, particularly when there is evidence of infection or osteitis on the posterior table of the frontal sinus[9]. During this procedure the empyema is evacuated, the posterior wall of the frontal sinus is removed, the nasal sinus mucosa is removed and the nasofrontal

duct is plugged off. Patel et al. performed cranialisation in 3 cases and avoided the need for ESS, with 33% required a further neurosurgical procedure[6]. The disadvantages of cranialisation over FESS sinusotomy is the lack of preservation of normal bony and mucosal anatomy, frontal neuralgia, technical difficulties in obliterating the tract and need for repeat imaging to assess for mucocele formation[6]. Graft remodelling, in the graft used to plug the nasofrontal duct, may also mimic recurrent disease on follow-up imaging modalities. We did not use cranialisation in any of our cases.

Limitations

One of the biggest limitations of our study is that it is a single centred retrospective study and its small number of patients. We are the regional centre covering Northern Ireland with a general population of approximately 1.9 million[10], yet the average cases of sub-or-extradural empyema are approximately 1 case per year (11 cases in 10 years). It is difficult to compare our sample to other studies given our small cohort size, different types of procedures used, and the fact patients often had multiple procedures within 24 hours. Those patients that are more unwell with a neurological deficit on presentation were more likely to have craniotomy and ESS whereas those with smaller volume abscess with no neurological deficit had wider range of management strategies (ranging from conservative management to ESS only, to neurological procedure only or combined operation). Larger or multicentre studies must be done to identify best management strategies for these patients. There are few robust studies in the literature and no randomised controlled trials. Our study only had 2 cases of isolated extradural abscesses, and these seemed to have better prognosis. Once again, more studies are needed to draw firm conclusions. In our study, 2 patients had significant medical co-morbidities, which is likely a confounding factor when assessing any outcomes. It is also possible that there may be underreporting of subtle subdural and extradural abscesses on initial CT imaging that may successfully be managed conservatively.

Conclusions: Sinogenic subdural and extradural empyemas are associated with high morbidity. Multi-disciplinary team management between surgeons, Neurosurgeons, Paediatricians, Radiologists, and Infectious Diseases leads to a diverse array of timings and types of interventions. Children with neurological deficit prior to initial operation had a statistically longer length of stay (p=0.009). Subdural empyema had a poorer clinical outcome compared to extradural empyema, with higher morbidity and more frequently requiring repeated neurosurgical interventions. Aggressive medical and surgical management is advised. The use of ESS in subdural empyema does not seem to avoid the need for craniotomy, although it can aid in microbiological diagnosis. In cases of subdural empyema secondary to sinusitis we would therefore recommend a joint neurosurgical craniotomy with ENT middle meatal antrostomy for microbiology sampling as the initial operation, avoiding more complex ENT procedures out of hours. The use of ESS in extradural empyema, particularly with direct spread of infection, may be of more benefit, although larger more robust studies must be undertaken.

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Clinical Paper

Perceptions of Obesity and Bariatric Surgery Among Newly Qualified Doctors: A UK-based Multi-Hospital Survey Study

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ABSTRACT

Background

Obesity is a major public health challenge, yet formal education on bariatric and metabolic surgery (BMS) remains limited in undergraduate and early postgraduate medical training. Foundation Year 1 (FY1) doctors are often responsible for managing post-operative bariatric patients, but their confidence and preparedness in this area are unclear. This study aimed to assess FY1 doctors' confidence, knowledge, and perceptions of BMS, identifying educational gaps to guide future training.

Methods

A cross-sectional survey was distributed to FY1 doctors across seven hospitals in South-East London (August–December 2024). The questionnaire assessed demographics, confidence in managing BMS patients, prior training, knowledge, and perceptions of obesity and BMS.

Results

Seventy-seven FY1 doctors participated. The majority (77.9%, n=60) had no formal BMS training, and fewer than half (42.9%, n=33) had clinical exposure to BMS patients. Only 20.8% (n=16) felt comfortable managing these patients, with confidence levels higher among those with prior clinical exposure but without statistical significance ($p = 0.0682$). Misconceptions were present, with 41.6% (n=32) believing obesity is self-inflicted and 7.8% (n=6) viewing BMS as cosmetic. A majority (84.4%, n=65) supported integrating BMS education into medical training.

Conclusion

FY1 doctors demonstrated low confidence in managing bariatric patients, possibly due to limited training and exposure. Findings highlight the need for structured BMS education, focusing on peri-operative care rather than procedural details, to better equip future doctors in managing obesity and post-bariatric surgery patients.

Keywords: Obesity, Bariatric Surgery, Medical Education, Attitude of Health Personnel

Introduction

Obesity is a major global health challenge with significant individual and societal costs. It is associated with an increased risk of type 2 diabetes, cardiovascular disease, liver disease, osteoarthritis, psychological disorders, and certain cancers, leading to premature disability and mortality[1–4]. Bariatric and metabolic surgery (BMS) is one of the most effective long-term interventions for sustained weight loss and reducing obesity-related comorbidities in patients with severe obesity[5]. Recognising its benefits, the UK National Health Service (NHS) considers BMS a cost-effective strategy to reduce the health and economic burden of obesity[4,6,7].

Despite rising obesity rates, formal obesity education remains limited at all levels of medical training worldwide[8]. Foundation Year 1 (FY1) doctors, as the front line NHS practitioners, play a key role in managing obesity and related conditions. However, to the best of our knowledge, no published research has specifically examined FY1 doctors' understanding, confidence, and preparedness in managing patients undergoing BMS.

This study aims to assess FY1 doctors' confidence in managing patients undergoing BMS. Additionally, it evaluates their knowledge, perceptions and familiarity with NHS-recommended obesity interventions to identify educational gaps that could guide future medical training.

METHODS

Study design

This was a cross-sectional observational survey study assessing FY1 doctors' confidence in managing patients undergoing BMS, as well as their knowledge and perceptions of obesity and BMS.

Population and data collection

An anonymous survey was distributed to all FY1 doctors starting in August 2024 across seven hospitals in South-East London. Responses were collected over four months (7th August - 4th December 2024), with 77 complete responses received.

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Survey

The self-completed questionnaire consisted of the following sections:

Demographics - Gender (Male, Female, Prefer not to say) and age group (Under 25, 25-30, 31-35, Over 35).

Confidence in managing BMS patients – Participants rated their comfort levels using a five-point Likert scale.

Awareness, perceptions, and understanding of obesity and BMS.

Knowledge and prior training in obesity and BMS.

Free-text comments – Participants provided suggestions on BMS training and education.

A copy of the survey is available from the corresponding author.

Ethical considerations

The UK National Research Ethics Service decision tool (http://www.hra-decisiontools.org.uk) confirmed that formal ethical approval was not required. Participation was voluntary, and all responses remained anonymous. Participants provided informed consent before survey completion and could withdraw at any stage without consequence.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 10.4.1 (627). The Shapiro-Wilk test assessed normality, revealing that all variables significantly deviated from a normal distribution. As a result, non-parametric tests were used throughout. A p-value < 0.05 was considered statistically significant.

RESULTS

Participant demographics

The survey yielded 77 complete responses. Among respondents, 53.2% (n=41) were female, and most (49.4%, n=38) were aged 25-30 years. The demographic characteristics, age and gender distribution, are summarised in Table 1.

Table 1. Demographic characteristics of respondents.

Total number of respondents	77	
Gender, n, (%)		
Female	41 (53.2)	
Male	35 (45.5)	
Prefer not to say	1 (1.3)	
Age in years, n (%)		
Under 25		33 (42.9)
25-30		38 (49.4)
31-35		4 (5.2)
Over 35		2 (2.6)

Knowledge and Perceptions of Obesity

Most respondents (93.5%, n=72) recognised that obesity is classified as a disease. However, only 57.1% (n=44) correctly identified the BMI threshold for obesity (≥30). A majority (84.4%, n=65) perceived obesity as a "burden on society", while 41.6% (n=32) viewed it as a "self-inflicted disease".

Exposure and Knowledge of Bariatric and Metabolic Surgery

A significant proportion of respondents (77.9%, n=60) reported no formal training in BMS during medical school, and fewer than half (42.9%, n=33) had exposure to real-life BMS patients during their medical school placements.

Despite this, nearly all respondents (90.9%, n=70) were aware that surgery is an NHS-approved obesity management option. Only one respondent (1.3%) was unfamiliar with any bariatric procedure. Figure 1 illustrates respondents' familiarity with:

- Obesity management options provided by the NHS (Figure 1a)
- Bariatric procedures (Figure 1b).

The median number of bariatric procedures recognised was three (IQR = 2-4). The most well-recognised procedure was sleeve gastrectomy (83.1%, n=64), while One Anastomosis Gastric Bypass (OAGB) was the least recognised (36.4%, n=28).

Attitudes Towards Bariatric and Metabolic Surgery

Most respondents (66.2%, n=51) considered BMS to be effective or very effective in treating obesity, and 61% (n=47) believed it to be cost-effective for long-term obesity management. However, 7.8% (n=6) regarded BMS as primarily cosmetic, and 20.8% (n=16) did not believe it should be funded by the NHS. Attitudes toward BMS are illustrated in Figure 2.

Only 20.8% (n=16) identified surgery as the "most effective" method for achieving sustained weight loss, whereas lifestyle modifications (42.9%, n=33) and dietary changes (27.3%, n=21) were more frequently selected. Pharmacotherapy (7.8%, n=6) was the least preferred option.

Confidence in Managing Bariatric Patients

Confidence levels in managing patients undergoing bariatric surgery varied among respondents, as demonstrated in Figure 3.

Figure 1. Bar charts illustrating the proportion of respondents familiar with different obesity management options provided by the NHS (Figure 1a) and different bariatric procedures (Figure 1b).

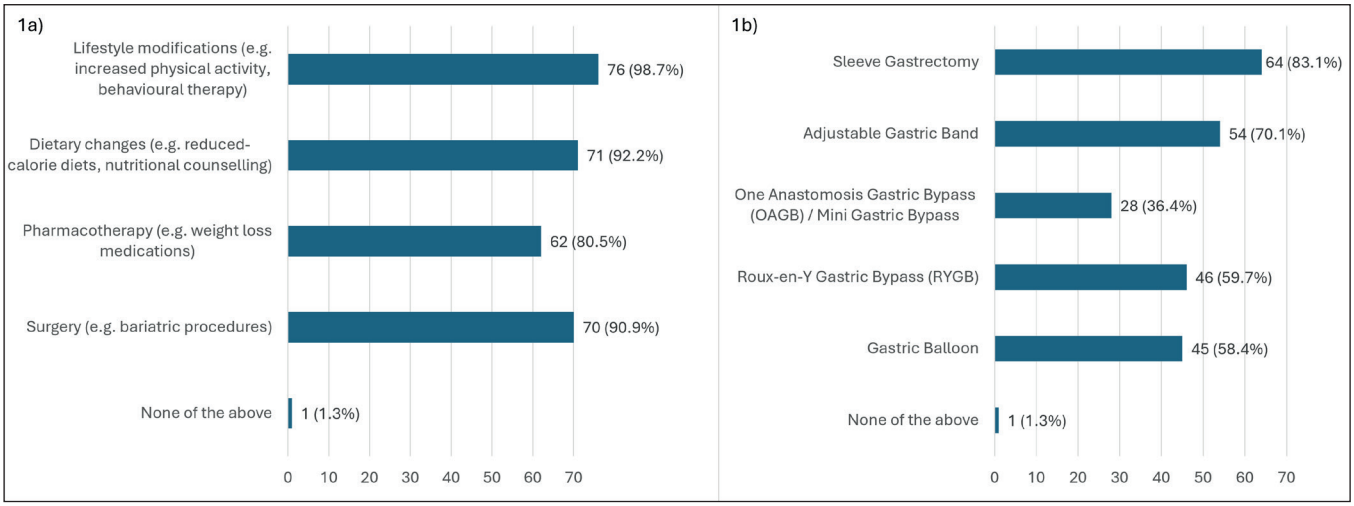


Figure 2. Stacked bar chart showing proportion of responses to questions assessing attitudes towards Bariatric and Metabolic Surgery.

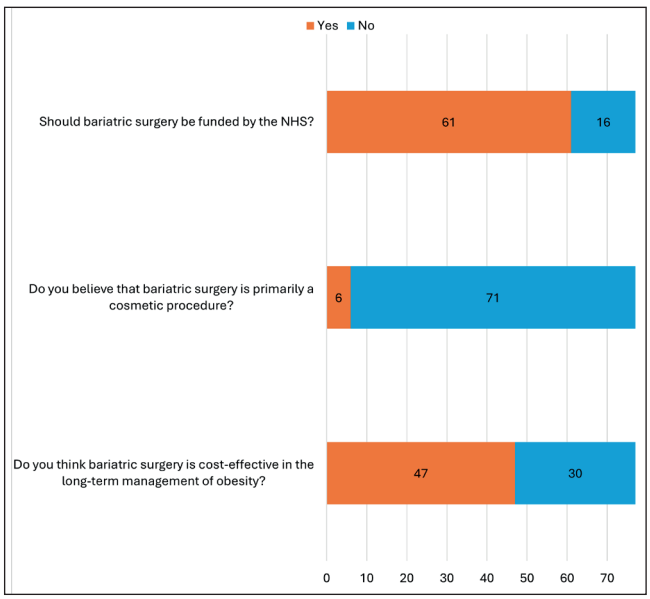
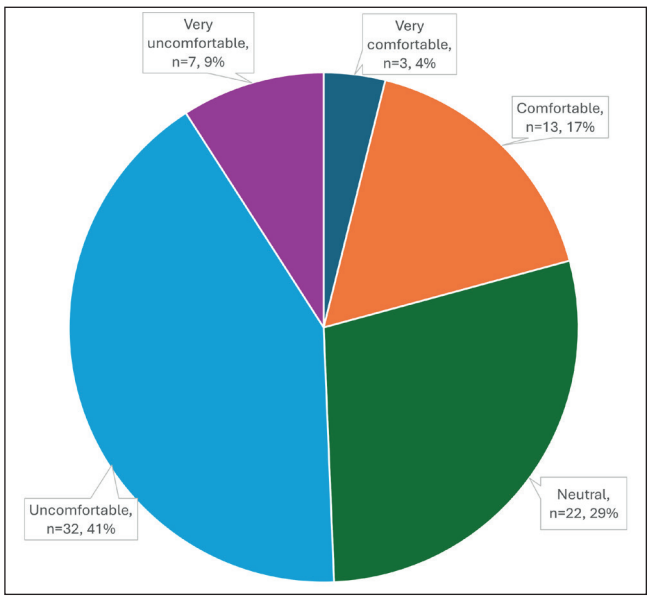


Figure 3. Pie chart illustrating proportions of responses to question "How comfortable do you feel managing patients undergoing bariatric surgery?"



Only 20.8% (n=16) reported feeling "comfortable" or "very comfortable" managing BMS patients. Those without prior clinical exposure to BMS reported lower confidence levels (median = 2 ["uncomfortable"]) compared to those with exposure (median = 3 ["neutral"]), though this difference was not statistically significant (Mann-Whitney U = 558.5, P = 0.0682). There was no association between prior formal training and confidence levels (Mann-Whitney U = 440.5, P = 0.3769), nor was there a significant correlation between familiarity with bariatric procedures and confidence in managing BMS patients (Spearman's rank-order correlation: r(75) = 0.03968, P = 0.7319).

Educational Needs and Interest in Training

Most respondents (84.4%, n=65) supported incorporating additional training on obesity and BMS into the medical curriculum, and 71.4% (n=55) expressed interest in attending workshops or additional sessions on BMS.

There was no significant association between prior formal training and interest in further BMS training (Fischer's Exact Test, P = 0.7645).

Analysis of free-text responses revealed that respondents' comments on BMS training and education primarily focused on peri-operative care (pre- and post-surgical management) rather than the procedures themselves.

Discussion

This study highlights a significant lack of training and exposure to bariatric and metabolic surgery (BMS) among FY1 doctors, reflected in their low confidence in managing patients undergoing BMS. A large proportion (77.9%, n=60)

had no formal BMS training, and less than half (42.9%, n=33) had clinical exposure to real-life BMS patients during medical school placements. There was strong interest in additional training, reinforcing the need to integrate BMS education into undergraduate and/or early postgraduate medical training in the UK.

From the 2024–25 academic year onwards, all UK medical students must pass the United Kingdom Medical Licensing Assessment (UKMLA) before obtaining medical registration[9]. A review of the UKMLA content map confirms that obesity is included as an examinable condition[10]. However, BMS is not explicitly mentioned[10], perhaps due to its relatively recent emergence as a mainstream surgical intervention. Traditional surgical education remains heavily focused on acute conditions (e.g. appendicitis, pancreatitis, intestinal obstruction) and cancer-related surgery[10]. This raises questions about variability in BMS teaching across UK medical schools, as formal curriculum inclusion is not yet standardised. Future studies could explore these discrepancies across institutions and compare UK undergraduate BMS education with that of other countries. Findings could then inform recommendations for integrating BMS into future UK medical curricula, ensuring FY1 doctors feel more confident managing BMS patients.

Knowledge Gaps and Misconceptions

Our study identified specific knowledge gaps, most notably a lack of awareness regarding obesity classification. Only 57.1% (n=44) correctly identified the BMI threshold for obesity (≥30), which may impact the early recognition and management of obesity-related complications. Early identification is crucial for preventing comorbidities by initiating obesity management strategies or initiating appropriate referrals as early as possible.

Furthermore, misconceptions persist regarding the causes of obesity and the role of BMS. A substantial proportion (41.6%, n=32) of respondents believed obesity is self-inflicted, reflecting a limited understanding of its complex, multifactorial nature. Obesity is driven by a combination of genetic, metabolic, psychological, socio-economic and environmental factors[3]. Misconceptions like these can influence patient interactions, potentially leading to stigma, biases in clinical decision-making, and inadequate advice (e.g. advising "eat less, move more," which is neither evidence-based nor effective for many patients).

Additionally, 7.8% (n=6) of respondents viewed BMS as primarily cosmetic, and 20.8% (n=16) opposed NHS funding for BMS. While lifestyle and dietary modifications were the most commonly endorsed long-term interventions from respondents, evidence shows that BMS is the most effective treatment for sustained weight loss and remission of obesity-related diseases[5,11–13]. These findings suggest potential barriers to appropriate referrals for BMS, as doctors who lack understanding of its benefits may delay escalation to specialist obesity services. This underscores the urgent need for enhanced education on obesity as a disease and the evidence supporting BMS as an effective intervention.

Demand for More Training and Preferred Learning Approaches

Encouragingly, most respondents (84.4%, n=65) recognised the gaps in their BMS education and supported its formal integration into medical training. Additionally, 71.4% (n=55) expressed interest in attending additional BMS workshops, reinforcing the need for structured learning opportunities. Interestingly, this demand was not limited to those who had never received prior training, suggesting that even those with some exposure felt their training was insufficient.

While FY1 doctors demonstrated good overall recognition of bariatric procedures, this did not correlate with confidence in managing BMS patients. Only 20.8% (n=16) felt comfortable managing these patients, despite the majority being familiar with at least some of the surgical techniques. Clinical exposure appeared to play a more significant role than formal training in determining confidence (though the relationship did not reach statistical significance). This suggests that BMS education initiatives should emphasise clinical exposure, rather than didactic learning alone.

Only a small proportion of respondents had real-life experience with BMS patients, highlighting the need for increased clinical exposure during medical school. Opportunities to engage with BMS rotations and interact with post-operative patients should be actively promoted. The free-text responses further emphasise the importance of peri-operative care (e.g. nutritional support, post-operative monitoring, and complication management) over procedural knowledge. Given that FY1 doctors are more likely to manage BMS patients peri-operatively rather than performing surgery, training should focus on these aspects, aligning with their future responsibilities.

Limitations

This study has several limitations. Firstly, as participation was voluntary, there is a risk of self-selection bias, whereby respondents may have had greater pre-existing interest in BMS or medical education, potentially inflating the proportion of FY1 doctors desiring additional training.

Additionally, we did not collect data on participants' medical school of origin, introducing potential sampling bias. If a significant portion of respondents trained at institutions with limited BMS education, this could have exaggerated the perceived gap in formal teaching and clinical exposure. Future studies should include a broader representation of medical school backgrounds to determine whether gaps in education are widespread or institution-specific.

The questionnaire was brief and did not assess depth of understanding regarding bariatric procedures or peri-operative management. While familiarity with procedures was evaluated, no formal assessment of clinical competence or decision-making was performed, limiting our ability to

determine whether knowledge gaps translate into suboptimal clinical practice.

Lastly, this study was conducted within a single UK region (South-East London) and limited to seven hospitals within the London Foundation School, restricting generalisability to a national level. A larger, multi-deanery or nationwide study would provide a more representative sample and better inform educational policy. While free-text responses suggested a preference for BMS education to focus on peri-operative care, rather than the procedural knowledge, these insights could be more rigorously evaluated through focus groups or the implementation of BMS training followed by prospective assessments of confidence and competency levels.

Conclusions

This study highlights significant gaps in knowledge, clinical exposure, and confidence among FY1 doctors regarding BMS. A lack of formal training, persistent misconceptions, and low confidence levels indicate a need for curriculum revisions and targeted educational interventions.

We recommend the integration of BMS education into undergraduate curricula, ensuring standardised core teaching across UK medical schools. Educational interventions should prioritise clinical exposure and emphasise peri-operative management rather than procedural details, aligning with FY1 doctors' clinical responsibilities. Increased exposure and structured teaching may also help address obesity-related stigma and misconceptions. By implementing these changes, medical education can better equip future doctors to manage the increasing burden of obesity and deliver appropriate, evidence-based, and unbiased care for patients undergoing BMS.

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Ethics statement: As mentioned in the manuscript above, The UK National Research Ethics Service decision tool (http://www.hra-decisiontools.org.uk) confirmed that this study did not require formal ethical approval.

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Ulster Med J 2025;**94(2):**94-95

Opinion

Self-directed learning and clinical decision support

Kieran Walsh[1], Lynsey Morton[2]

Self-directed learning and clinical decision support both have a role to play in improving medical education and clinical care. Self-directed learning can enable healthcare professionals to identify and fulfill learning needs and evaluate learning outcomes.[1] Clinical decision support can help healthcare professionals learn new knowledge and put that new knowledge into practice for the benefit of patients.[2] But what about putting the two concepts together? When used in synergy, could they result in outcomes that are more than the sum of their parts? This short article looks at these concepts in combination and explores ways in which we could use them together to improve outcomes for healthcare professionals and for patients.

The first instance of synergy between the two concepts is at the point of care. Self-directed learning usually involves identification of a learning need. In clinical medicine, this might come from a patient interaction where the clinician might not know the next best steps in diagnosis, management, or follow-up. The clinician would then find an answer and ideally put their learning into practice for the benefit of the patient. The process is effective and can also be efficient - the entire process could take minutes and yet this grounded form of learning can then stay with the clinician for years to come. What could make the process even more efficient is a clinical decision support system that enables the clinician to find an answer within seconds.[3] A system that is accessible and built with the user in mind and that will work on any device online or offline via an app or even integrated into the electronic healthcare record. This is self-directed learning and clinical decision support working in unison to enable effective and efficient learning.

Another instance of synergy is in the credit that learners might receive from this form of learning and knowledge acquisition. Clinicians need to be lifelong learners, and indeed modern regulatory bodies insist that they continually learn to keep their knowledge and skills updated but also that they can show evidence that they are continually learning. Partly as a result of this, clinicians often seek continuous professional development or continuing medical education credits for their learning. They often receive such credits as a result of attendance at internal or external meetings or by completing formal e-learning courses. It is difficult to formally accredit self-directed learning in and of itself - however clinical decision support or knowledge resources that enable self-directed learning can be accredited. These same clinical decision support resources can also encompass a tracker that enables the clinician to keep a record of what they have learned or the time that they spent on a site. This is reasonable evidence of activity and can be strengthened by a clinical decision support system that enables learners to add reflections on their learning and/or notes about the impact that their learning has had on their practice. All this can enable healthcare professionals to direct their own learning using clinical decision support and get learning credits for it at the same time.[4] Thus day to day activities on a clinical decision support resource could contribute to lifelong learning. The link between decision support tools in practice and their educational benefits is based on the idea that deep learning will result from the usage of decision support. However, clicks on a website do not automatically result in learning. Nonetheless there are reasons to believe that decision support does help with deep learning. The reason why healthcare professionals use decision support is because they have a learning need that they need to put into action. This should result in learning that is in context and that therefore should last. One final note is that learning from clinical decision support is based on the assumption that this support helps and does not replace the decision-making capacity of the clinician. If it were to replace the clinician, it could have an adverse effect on learning. At present most clinical decision support is built to *support* the clinician.

The best form of clinical learning is that which is based on the patient, and self-directed learning can involve the patient. For example, the patient might pose a question to a clinician who might then search for an answer – sometimes in partnership with the patient. They can then discuss the answer with the patient and come to a shared decision about the next best course of action - for example in deciding between investigations or management options. This is self-directed learning at its most practical and best - but it is also something that clinical decision support can also help with. For example, clinical decision support resources often contain knowledge for clinicians and for patients. The patient information can parallel the professional information even though the language used will be more accessible. Thus, clinical decision support can enable self-directed learning and shared decision-making at the same time.[5]

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The domains of clinical reasoning and problem-solving also demonstrate where self-directed learning and clinical decision support overlap. Clinical reasoning and problem-solving are naturally based on self-directed learning - however clinical decision support can complement self-directed learning activities by providing clinical guidelines, decision-making frameworks, treatment algorithms, differential diagnosis tables, and a range of other actionable and practical knowledge assets. In combining self-directed learning with clinical decision support, healthcare professionals can enhance their learning, acquire demonstratable continuous professional development credits and can at the same time enhance their clinical care in diagnosis and management. Clinical decision support can also improve the quality of clinical documentation.[6]

Of course, bringing self-directed learning and clinical decision support together is not a panacea for medical education and clinical care - there are some potential downsides. Self-directed learning could involve the use of any knowledge resources - however, using clinical decision support would mean that the learner would be looking at knowledge resources that have been curated. This might limit the freedom of exploration of the self-directed learner. However, it might equally ensure that knowledge resources that were searched had been checked and curated for their quality. How such resources are curated is important. If clinical decision support resources are to truly counter bias and unforced errors, they need to be tailored precisely to the needs of the user. Some might provide too much information – some of which may only be relevant to the superspecialist – whereas others might provide too little for more experienced users. Another issue is that self-directed learning is often based on the needs of individual patients, whereas clinical decision support is based on population-based recommendations. Part of the skill of practicing medicine is marrying the two. This perhaps points to the need for the education of clinicians in both self-directed learning and in the use of clinical decision support.

Another consideration is that using digital clinical decision support may be a low-cost form of continuous professional development. Digital clinical decision support as a form of education means that there are none of the costs associated with traditional CPD – such as the costs of travel to face-to-face events or accommodation at such events.[7]

The role of AI in clinical decision support will be increasingly important in the future. Generative AI can support clinical decisions by synthesising large volumes of medical literature to suggest diagnoses, investigations and treatments. Agentic AI can autonomously perform certain tasks, such as ordering tests or recording decisions. However, at present all forms of AI are subject to potential hallucinations and so could result in clinical errors or problems in education.

Despite these potential problems, bringing self-directed learning and clinical decision support together can enable effective and efficient learning; it can provide evidence of continuous professional development; it can facilitate shared decision-making; and it can also help with the development of clinical reasoning and problem-solving skills.[8 9] For them to truly work in unison, clinical decision support must be provided to clinicians and clinicians must also receive education in self-directed learning.

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KW works for BMJ Best Practice which is a clinical decision support resource.
LM has no competing interests.

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Ulster Med J 2025;**94(2):**96-103

Medical History

Hugh Percy, 10th Duke of Northumberland: Chairmanship of the Agricultural and Medical Research Councils

John Hedley-Whyte[1], Debra R. Milamed[2]

Introduction

Hugh Algernon Percy, KG, FRS, born 6 April 1914, became 10th Duke of Northumberland in 1940 after confirmation of the Death in Action of his older brother the 9th Duke in Belgium before Dunkirk[1]. Hugh Percy was educated at Eton, followed by Christ Church, Oxford which he entered in October 1932 with the intention of studying Law. During the winter holidays that year, Northumberland was injured falling off his horse and did not immediately return to his studies. The "House" Archivist reports, "He was sent down in March 1935 after failing to sit for an examination. Christ Church was happy for him to return for the summer term and take the missed exam then, but he decided not to return[2]." He later told me[1] on more than one occasion that if a student missed lectures he could simply read books and thereby learn more.

Upon his return from World War II, Northumberland began his service on the Northumberland County Council. From 1964 he served as Chancellor of the University of Newcastle. He was appointed Chief Steward at Buckingham Palace in 1973 and remained in that post for the remainder of his life. The 10th Duke's distinguished career included chairmanship of the Agricultural Research Council (1958-1968), where he oversaw the response to the 1967-68 epidemic of foot-and-mouth disease, and chairmanship of the Medical Research Council 1969-1977[1,3].

Percy Famly History

Hugh Smithson (1714/5-1786) adopted the name and arms of Percy by an Act of Parliament in 1750[3,4]. As Hugh Smithson Percy he served as Lord Lieutenant of Ireland from 1763 to 1765. He was created Earl Percy and Duke of Northumberland on 22 October 1766 (Fig.1)[4]. His grandson, Hugh Percy, the third Duke of Northumberland (1785-1847) also served as Lord Lieutenant of Ireland from 1829-1830[5].

Two notable members of the Percy family, both Fellows of the Royal Society, played roles in the history of the United States. Lieutenant General Hugh Earl Percy, son of the 1st Duke who had served as Lord Lieutenant of Ireland[4], fought in the running Battle of Lexington and Concord and the Battle of Long Island during the American Revolution[3,6]. He later became the 2nd Duke of Northumberland, FRS (1742-1817) (Fig.2)[3]. The 2nd Duke's half-brother, James Smithson, FRS (1765-1829) endowed the eponymous Smithsonian Institution of Washington, DC[3,7].

Figure 1
Hugh (Smithson) Percy (1714/5-1786), Earl of Northumberland, later Lord Lieutenant of Ireland 1763-5, and 1st Duke of Northumberland, in peer's coronation robes and garter chain. Oil on canvas, 238.8 cm x 147.3 cm, by Joshua Reynolds (1723-1792). From the Supreme Court, Middlesex Guildhall Art Collection, No. 747 and reproduced with permission.

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Figure 2
Hugh Earl Percy (1742-1817). Engraving on abalone, 29.5" x 23", by V. Green, January 1, 1777. Catalogue no. PI1768.1n. Lieutenant General serving in America, 1777. Print mounted on cream color mat board, under glass, with a black, wood frame embellished with gold along the inner and outer edge (frame not shown). From the Prichard Bequest, courtesy of the Concord Museum, Concord, Massachusetts, and reproduced with permission.

The 10th Duke in World War II

After serving in Greece, Italy and Sicily during World War II as an officer of the Northumberland Hussars, the 10th Duke returned to his Castles, including Alnwick in the fall of 1943[3]. The Northumberland Hussars had joined the British 1st Armoured Division, and in October 1942 the 50th (Northumbrian) Infantry Division. They had served in Egypt, Sicily and at El Alamein with Montgomery, and had extensive experience with amphibious landings. This regiment returned to England in October 1943 and played a major role in the training and preparation for Operation OVERLORD and in June 1944, the D-Day landings at Normandy[8].

My father, Brigadier Angus Hedley-Whyte, D.S.O., F.R.C.S. had been the Commanding Officer of what became, post Pearl Harbor, the U.S. Army's Fifth General Hospital (Harvard) at Musgrave Park, just outside Belfast[9,10,11,12]. In 1943 we returned, after a posting to Hatfield House, to our home in Newcastle-upon-Tyne. My father was then based in York. For the remainder of the War, my father served as Consultant Surgeon to Northern Command associated with Field Marshal Montgomery, since 1942 Commander of the British Eighth Army[12,13]. Field Marshal Bernard Law Montgomery, later Viscount Montgomery of Alamein, was one of nine children of Cambridge-educated Bishop Henry Hutchinson Montgomery (1847-1932) of Tasmania, whose family was from Inishowen in the north of County Donegal[14,15,16] (Fig.3).

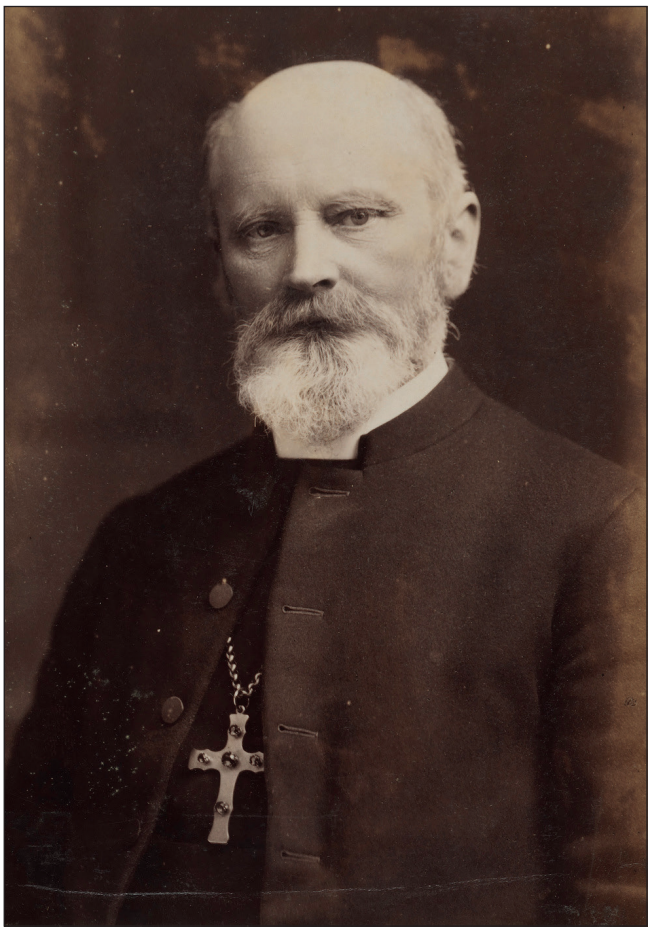

Figure 3
Henry Hutchinson Montgomery, KCMG (1847-1932), Bishop of Tasmania 1889-1901, by an unknown photographer. NPG No. P1700(89b) © National Portrait Gallery, London and reproduced with permission.

My father communicated frequently with the 10th Duke regarding the medical needs of the Northern regiments including the Northumberland Hussars. The nearby Fenham Barracks, adjacent to Moorfield, the estate of my maternal grandfather, provided accommodation and training grounds for both officers and enlisted soldiers. My father, called to consult at Fenham Barracks, often visited along with the 10th Duke and Montgomery and attended strategic planning meetings almost daily during the latter part of the War.

A radar station had been built at Ottercops Moss, near Otterburn, only a few miles west of Alnwick Castle and Hulne Park, as part of the Chain Home defense network[17,18,19]. German aircraft flying toward England from Denmark and Norway could be spotted and intercepted over the

North Sea. Rudolph Hess's plane flying toward Scotland was first detected from this station on 10 May 1941. The Messerschmitt 110 plane crashed near Glasgow and Hitler's deputy was taken to hospital[20]. The 10th Duke encouraged and facilitated support of this important component of the local war effort adjacent to his estates.

Monitoring the Health of Troops

Prior to D-Day Montgomery had the use of a special train called "Rapier", in which he traveled through England, Wales and Scotland to "visit every formation which was to take part in OVERLORD....I [Montgomery] must have inspected, and been inspected by, well over a million men" [15].

In the winter of 1943-1944, my father travelled with Montgomery via special train, or my father's unescorted Rolls Royce to assess the health of Allied troops in the North of England in preparation for the invasion of France. The physical and mental well-being of troops was of great concern to Montgomery[13,15]. Those requiring specialized treatment were referred to appropriate hospitals in London, Leeds, Newcastle and Edinburgh for care. Troops were monitored for vaccination status and for signs of infectious disease, particularly those of viral etiology, such as measles[21], as well as tuberculosis[22]. I accompanied them during their inspection tours of several convents used as nursing facilities during the War.

The incidence of measles in Allied Troops during World War II was much lower than in World War I. Socio-geographic changes in the intervening years had rendered more recruits immune[21]. Montgomery was aware that there had been measles outbreaks among the Highland Light Infantry before D-day. Serum specimens and environmental samples were sent to laboratories at Newcastle-upon-Tyne, Mill Hill, Middlesex, London, Leeds, Edinburgh and Glasgow for testing. My father served as courier, personally delivering the samples.

During the War, Montgomery suggested to the 10th Duke that he contract with my father to stable our horses in the Peth Stables on the Duke's Alnwick estate[23]. This arrangement proved satisfactory for many years (Fig. 4).

Post World War II: Career of the 10th Duke of Northumberland

Post World War II, the 10th Duke served in both civilian and military leadership roles. He was Councilor and later Alderman on the Northumberland County Council. He was a Reserve Officer in the Territorial Army until the age

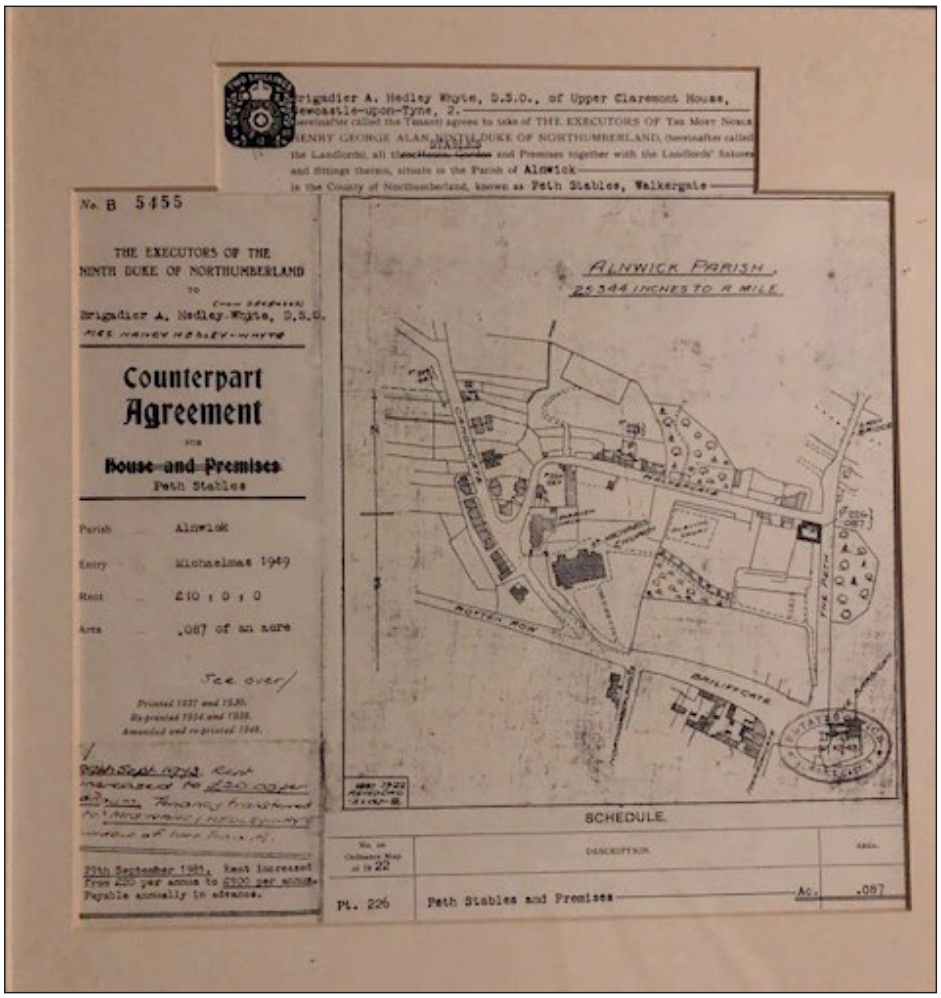

Figure 4
Lease agreement for Peth Stables, 1949, between 10th Duke of Northumberland and Brigadier Angus Hedley-Whyte, DSO.
The rent per annum was initially £10; later as agreed, £20 for the following twenty years.

of 50, and Honorary Colonel of the 7th Battalion, Royal Northumberland Fusiliers. The Duke held the post of Lord Lieutenant of Northumberland from 1956 until his statutory retirement at age 70 in 1984. From 1956 to 1968 he served as President of the Northumberland Territorial Army and Auxiliary Forces Association, and until 1971, of the North of England Territorial Army and Volunteers Reserve Association. From 1963 he served as the first Chancellor of the University of Newcastle, after its separation from Durham University, founded 1832[1,3]. He was appointed Chief Steward at Buckingham Palace in 1973 and remained in that post for the remainder of his life. In 1946 Northumberland married Lady Elizabeth Diana Montagu-Douglas-Scott (1922-2012), daughter of the 8th Duke of Buccleuch and Queensberry. The Buccleuch lands were near Northumberland's estates[1,3].

The health and welfare of both domestic and wild animals was of great interest to the 10th Duke who regularly consulted with experts in veterinary medicine and science. The animals on his estates, including hounds, horses, cattle, deer and others, were regularly sampled for viral and bacterial pathogens. Members of my family often served as veterinary couriers when the samples were sent to laboratories in London, Newcastle, Glasgow and Edinburgh for testing.

The 10th Duke's Chairmanship of the Agricultural Research Council, 1958-68

Hugh, the 10th Duke, advanced the work of the British Agricultural Research Council (ARC) which he chaired from 1958 to 1968. The ARC had expanded its activities and influence during the post-World War II years with the establishment of additional specialized laboratories and research facilities[24]. This trend continued during the 10th Duke's chairmanship[24,25]. The membership of the Agricultural Research Council was expanded to include members with legal, as well as agricultural expertise, and prominent veterinary scientists. Council members visited Denmark, France, the Federal Republic of Germany, The Netherlands, Argentina, Brazil, Uruguay and the United States.[1,24] The 10th Duke chaired the UK's Committee of Inquiry into the 1967 outbreak of foot-and-mouth disease. This Committee was appointed in February 1968, and published its report in November 1969[26,27].

The Pirbright Institute

The Pirbright Institute, in Surrey, was established in 1914 as a tuberculosis testing station for cattle[28]. In 1924 this facility was designated the Pirbright Experimental Station for the Foot-and-Mouth Disease Research Committee. By 1933 the Pirbright was the sole British Centre for research on foot-and-mouth disease, and in 1939 a full-time Director of Research, Dr. Ian A. Galloway was appointed and the Institute renamed the Foot-and-Mouth Disease Research Institute[28,29]. Director Galloway was assisted in his research programme by John Burns Brooksby[30], and W.M. Henderson[31] both later awarded CBE and FRS. Foot-and-mouth disease is a virus of the genus *Aphthovirus* (Family *Piconaviridae)*. Under Galloway's directorship four additional strains of foot-and-mouth disease virus were elucidated, in addition to the original three serotypes[32,33,34,35]. Vaccines were developed, underscoring the importance of viral subtype differences in vaccine development and deployment[36]. Later findings have revealed genetic differences of 30-50 percent in the *VP1* gene among serotypes, and multiple subtypes[37].

In 1958 the Pirbright was designated the World Reference Laboratory for Foot-and-Mouth Disease by the United Nations Food and Agricultural Organization. This designation remains in force[28].

Foot-and-Mouth Disease Outbreaks

Great Britain's *Contagious Diseases (Animals) Act of 1869* had designated foot-and-mouth as a notifiable disease and empowered local authorities to regulate the movement of infected livestock and appoint inspectors[27,38]. An epidemic of foot-and-mouth disease due to 32 outbreaks of viral type O_1 in 289 cattle and 73 sheep took place in Northumberland in July through September 1966. Eradication required slaughter of 5,753 cattle, 38,448 sheep and 714 pigs[38]. The origin was never conclusively determined, but the most likely source was infected meat or offal from foreign sources[38].

This epidemic was followed by several outbreaks the following year, culminating in the 1967-68 foot-and-mouth disease epidemic which began in October 1967, with an outbreak at Bryn Farm, Oswestry, Shropshire, traced to pig swill containing infected Argentinian lamb[27]. From October 1967 to early June 1968 there were 2,364 reported cases of foot-and-mouth disease in Great Britain resulting in the slaughter of approximately a half-million animals. Initial confirmations of diagnosis were made by laboratory analysis with clinical symptoms evaluated for subsequent cases. Samples were sent to the Pirbright Institute to identify viral strains. Pirbright Director Ian Galloway had elucidated subtype differences between foot-and-mouth disease viral strains which impacted the development of effective vaccination programs[36]. The Ministry of Agriculture, Fisheries and Food did not have vaccines available for administration at that time, although they were available from manufacturers[26,27]. Seropositivity of vaccinated animals rendered them unacceptable for international trade[27,32].

In February 1968, Frederick Peart, Minister of Agriculture, Fisheries and Food, appointed the Committee chaired by the 10th Duke of Northumberland to report on the epidemic. Members included Anthony Cripps, QC, Professor David Evans, C. Henry Plumb, Eric Thomas, Sir Edward Thompson, Professor David Walker and Sir William Weipers. John Jotcham served as Secretary with Melba White as Assistant Secretary[26,27].

During the 1967-68 foot-and-mouth disease epidemic,

Hugh, the 10th Duke, chaired numerous meetings. My mother, Nancy Hedley-Whyte, was deputized to chair the local meetings at Alnwick Castle. There she met with young people who were enrolled in a three-month training course for control of foot-and-mouth disease in their local districts.

During the 1967-68 foot-and-mouth disease outbreak, our family riding routes were revised. Riding out of Peth Stables, we entered directly into Hulne Park and farmland owned by the Percys, and we were ordered to ride only on a set route, with no entry to certain fields. Double oxers barriers were deployed.

Foot and Mouth Disease in Northern Ireland and Beyond

In 1939 Chief Veterinary Officer of Northern Ireland's Ministry of Agriculture, James McAllan, reported in this journal on diseases of animals that affect humans. He described foot-and-mouth disease as of great importance to the community, even though it was then thought to be rarely transmissible to man[39]. Foot-and-mouth disease as defined by the Pirbright Institute[28] is distinguished from the hand, foot and mouth disease caused by enteroviruses, Cocksackievirus A16, Cocksackievirus A6 and enterovirus 71 (EV-A71) most commonly transmitted among children[40].

The Ministry of Agriculture in Northern Ireland reported in 1967 that there had been no foot-and-mouth disease since 1949 due to strict controls on imports of animals and their products, poultry products, hay, straw and vegetables[41]. During the 1967-1968 epidemic in Britain and the years immediately following, the foot-and-mouth disease virus remained undetected despite active surveillance[42].

In Northern Ireland, foot-and-mouth and other veterinary diseases are monitored and reported by the Department of Agriculture, Environment and Rural Affairs (DAERA)[43,44]. As a separate epidemiological unit from other regions of the UK, Northern Ireland would cooperate with the Republic of Ireland during an outbreak in either or both jurisdictions. Both DAERA and the Republic of Ireland's Department of Agriculture, Food and Marine (DAFM) recognize the necessity of such joint efforts[45,46].

The 2001 outbreak in England spread across the Irish Sea, but vigilance by Northern Ireland authorities quickly thwarted a major outbreak[46]. The immediate response by the Republic of Ireland contributed in no small way to its control[45]. The published Foot-and-mouth disease regulations of Northern Ireland[44] and continued vigilance have been successful in recent years. DAERA published its most recent edition of the Foot-and-Mouth Disease Control Strategy in 2016[47].

The United States reports that there has been no foot-and-mouth disease since 1929, due to constant surveillance and controls of imports[48]. British and other outbreaks into the 21st century have underscored the importance of prevention to avoid disastrous economic consequences[49].

The 10th Duke's 1966 Visit: Boston, MA, Massachusetts General Hospital and Plum Island

During his chairmanship of the Agricultural Research Council, the 10th Duke made unpublicized visits to research scientists at Harvard University and the Massachusetts Institute of Technology. He visited the Harvard Fatigue Laboratory and the Massachusetts General Hospital. In 1966 I was asked to help organize a visit of the 10th Duke and representatives of the Agricultural Research Council to Boston. The subjects of clinical trial design and research ethics were of great interest to both the Duke and to my Massachusetts General Hospital Department Head, Henry K. Beecher, who that year published a key paper on this important topic[50].

The 10th Duke's Agricultural Research Council Representatives visited the U.S. Army and Department of Agriculture's Plum Island Animal Disease Research Center. This specialized, secure research center had been opened in 1954 on an island off the coast of New York, to address prevention of foot-and-mouth disease and other livestock pathogens. It continues its mission to the present, now under the auspices of the U.S. Department of Homeland Security[51].

TABLE 1. KEY ADVANCES OF THE BRITISH MEDICAL RESEARCH COUNCIL UNDER CHAIRMANSHIP OF 10TH DUKE OF NORTHUMBERLAND, 1969-1977[52]

YEAR/S	ADVANCES	SCIENTISTS CITED
1970-	Recognition of role of hypertension in treatment of cardiovascular disease and stroke	Medical Research Council Working Party on Mild to Moderate Hypertension[53,54]
1970-79	Clinical trials of chemotherapy for leukaemia	Medical Research Council Working Party[59,60,61,62]
1973	Invention of MRI	Sir Peter Mansfield, 2003 Nobel Prize in Physiology or Medicine[55,56]
1975	Development of monoclonal antibodies	Dr. Cesar Milstein and Dr. Georges Kohler, MRC Laboratory of Molecular Biology, Nobel Prize in Physiology or Medicine, 1984 (shared with Niels K. Jerne)[57,58]
1977	Invention of DNA sequencing; determination of the base sequence of nucleic acids	Dr. Frederick Sanger, MRC Laboratory of Molecular Biology, Nobel Prize in Chemistry, 1980 (shared with Paul Berg and Walter Gilbert)[63,64,65]

10th Duke's Chairmanship of the Medical Research Council, 1969-1977

The 10th Duke's contributions as chairman of the Agricultural Research Council were recognized by his appointment to chair the British Medical Research Council (MRC) in 1969[1,3]. Notable advances made during the Duke's chairmanship of the MRC included early clinical trials of treatment of hypertension in relation to cardiovascular disease[52,53,54], first use of MRI[52,55,56], development of monoclonal antibodies[52,57,58], advances in chemotherapy treatment for childhood[52,59,60,61] and adult leukemia[62], and invention of DNA sequencing, including determination of the base sequence of nucleic acids[52,63,64,65] (Table 1).

In 1985, The MRC Working Party published its long-term study of the relationship between treatment of hypertension and heart disease begun during the 10th Duke's chairmanship. Both stroke rate and incidence of cardiovascular events were reduced with active treatment in the study population of 17,534 patients, or 85,572 patient years, recruited largely from general practices[53]. This MRC Working Party also demonstrated that diuretic or beta-blocker treatment of older adults aged 65-74 with hypertension reduced risk of stroke, coronary heart disease and death[54].

Sir Peter Mansfield, FRS (1933-2017) and his team at Nottingham University received MRC grants that enabled them to develop magnetic resonance imaging (MRI) equipment[52,55]. Decades later Mansfield shared the 2003 Nobel Prize in Physiology or Medicine with Prof. Paul C. Lauterbur of the University of Illinois[56].

The 1984 Nobel Prize in Physiology or Medicine was awarded to Professors Cesar Milstein of the MRC Laboratory of Molecular Biology, Cambridge, England[57], along with Georges J.F. Köhler and Niels K. Jerne for "theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"[58]. This has increased treatment modalities for cancer and other conditions, including infectious diseases such Covid-19[66].

Advances in the treatment of childhood and adult leukaemias have changed the prognosis and treatment plans for patients worldwide[59,60,61,62]. The MRC Childhood Lymphoblastic Leukaemia (ALL) trial was designed to explore whether results similar to those of the successful U.S. Children's Cancer Study Group would result from an identical trial protocol. Findings demonstrated similar results and pointed out possible deficiencies in earlier MRC trials[60]. The record of these clinical trials provides historical perspective on key developments in the structure and operation of post-World War II British science and the increasing importance of statisticians in medical research[60,61]. Since the 1970s the MRC Adult Leukaemia Trials have shown "stepwise" improvement in outcome. At the same time adult survival rates were found to be less favorable than those for children. A smaller proportion of adults with acute lymphocytic leukaemia were enrolled in the earlier clinical trials[62].

Frederick Sanger (FRS 1954, CBE 1963, OM 1986), winner of the 1958 Nobel Prize in Chemistry for "his work on the structure of proteins, especially that of insulin[63,64], was funded by the MRC within Cambridge University's Department of Biochemistry. In 1962 Sanger was appointed Head of the Protein Unit at the newly opened MRC Laboratory of Molecular Biology at Cambridge[63]. Here he continued his work by developing sequencing methods for RNA molecules, and determining sequencing of nucleic acids in DNA. This resulted in the innovative "dideoxy" technique for DNA sequencing, which enabled simultaneous reading of 500-800 base pairs[63,64]. Sanger, with Professor Walter Gilbert of Harvard University, was awarded a shared half of the 1980 Nobel Prize in Chemistry "for their contributions concerning the determination of base sequences in nucleic acids" [65]. The remaining half was awarded to Paul Berg of Stanford University "for his fundamental studies of the biochemistry of nucleic acids with particular regard to recombinant DNA"[65].

The 10th Duke described to me at length the determination of the ranking, cost factors and relevance of grant applications submitted to the Medical Research Council. The review process was intended to "Develop and implement scientific research policy aimed at improving the prevention, diagnosis, management and therapy of disease, rehabilitation, and the general well-being of the community"[67]. The optimal use of allocated government funds would achieve parity in support of university research and the Medical Research Council's own facilities. The 10th Duke's chairmanship was facilitated by the offices he maintained on his Northumberland estates.

Hedley-Whytes' Sabbatical, 1984-1985

During the 1984-1985 Academic Year my wife and I were in Newcastle-upon-Tyne on sabbatical from Harvard. I spoke regularly with the 10th Duke. He expressed great interest in all aspects of Epidemiology, clinical trials, Statistics and other subjects such as the welfare of members of the National Union of Mine Workers. As chancellor of the University of Newcastle he used his influence to assure the medical care of miners injured in the major 1984-85 Miners Strike[68,69].

Epilogue

The Tenth Duke of Northumberland died on 11 October 1988. My wife and I heard this news in our Concord, Massachusetts home not far from the site where the 2nd Duke had fought against the American colonists[70].

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Key words:
Foot-and-mouth disease, Education, World War II.

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Obituary

Professor Barry E Kelly MD FRCSEd FRCR FFRRCSI 1961-2025

Patrick J Morrison CBE MD DSc

Barry Eoin Kelly was born on Wednesday 14 June 1961, around the same time that a custom-built Lincoln convertible was arriving at the White House for the use of President John F Kennedy. Kennedy would later be assassinated in that car on 22nd November 1963. My first meeting with Barry was in February 1987 when he was a senior house officer in cardiac surgery in the Royal Victoria Hospital Belfast. We'd drive our cars (not convertibles at that time, but Barry had plans….) into the car park at about 7am. His two tasks for the day were to strip the saphenous vein for grafting and to select the correct classical music for the cardiac surgeon – both jobs required meticulous preparation. My job as houseman was greeting the senior cardiac surgeon at 7.32am, (two minutes after he parked his Rolls Royce at the hospital entrance), taking and holding his leather briefcase and handing him my stethoscope for his use for the duration of the ward round. After that he'd head up to theatre where Barry would have the chest open and music ready to go. I'd go back to telling the unfortunate occasional patient they were being sent home after being found smoking in the toilets the previous day. Surgical post-op mortality was low and it was kept that way. We recognised later on that this was valuable 'resilience and audit training'. Barry took those meticulous skills further with his encyclopaedic knowledge of anatomy and with a surgical fellowship under his belt, breezed the radiology fellowship exams and lit the fuse on a stellar career in radiology, being appointed consultant radiologist to the Royal Victoria Hospital in 1995. He lectured at Queens University Belfast as a reader, and at Ulster University as a professor.

He held every major radiological measure of esteem in this island and beyond; presidency of the Ulster Radiological Society, Dean of the Faculty of Radiologists at the Royal College of Surgeons of Ireland in Dublin (2012-2014), and was a major player in the European Society of Radiology. He examined at multiple levels in both UK and Irish radiology colleges and in the European Diploma in Radiology which he helped set up. For the Ulster Medical Society, as well as editor, he served on council for several years and regularly appeared on the annual lecture programme under various guises, giving the Desmond Whyte lecture[1] on at least two occasions when most lecturers had just about enough material in their career for one.

When I became editor of the journal in 2005, it was trundling along carefully like a monochrome hatchback out for a safe and regular Sunday run on a quiet country road at under 30mph, stopping in the corner shop for safe journalistic fare of case reports and papers. I traded that vehicle up for a large estate car in brightly coloured paint with a V8 engine and

Barry Kelly, Editor, Ulster Medical Journal 2010-2014.

PubMed livery down the sides. I drove it on motorways at a full 70mph and started the process of stocking the ample boot space with editorials and reviews, stopping at literary service stations for the best review articles with commentaries that I could get. Barry watched me from the front passenger seat in 2009 as deputy editor, and assumed the editorship in 2010[2]. On taking over, he stepped in, flicked the lights on to full beam, floored the accelerator, without stopping to fasten his seatbelt, and drove it round the nearest publishing racetrack in a manner characteristic of his early childhood love of new toys where he once launched his new bicycle downstairs on Christmas day, propelling it – unscathed - through a plate glass door at the bottom. He stopped regularly at the best journalistic delicatessens for top quality articles with variety and had a profusion of ideas - the estate car boot now brimming with reviews and articles covering a very wide range of specialties from eminent authors in their field. Every editorial added another section to the journal – sections familiar to readers today – Gamechangers[3], Curiositas[4], Bookcase[4], pictorial reviews[5], and of course, old fashioned paper submission not being fast enough, he added in the fuel injection of a fully electronic submission process[6].

His meticulous skills shone through and with his literary flair the journal went from strength to strength. In my tenure I'd introduced full colour imaging and for a radiologist this was a great gift. The journal had the best quality and annotated figures in a PubMed journal anywhere. Sometimes if an author failed to contribute their promised piece approaching the publication deadline, he would just write the piece himself on the topic that same evening[7]. He was ahead of his time in so many areas, introducing anonymous peer review, continuing medical educational credits for reviewers[8], QR codes for readers to scan[3] and installed a new twin air horn to blow for the Journal in the form of Twitter[7] and Facebook so that journal impact and awareness was maximised. Sometimes his prophetic announcements – such as his editorial on swine flu where he said 'the question now being asked is whether the official response was overzealous' – were like déjà vu in the recent Covid pandemic[9]. He covered a vast range of themes in his editorials from ancient civilisation[10] right through musings on death[11] and cosmology[12]. As he screeched into the pit stop with a handbrake turn flourish for the final time[13] to hand over to his successor, it was fortunate he was doing so to a cardiologist, a specialty used to dealing with much wear and tear of internal pumps and electrics, as a much larger battery or even pacing assistance was now needed. He was made an Honorary Fellow of the Ulster Medical Society after his editorial term in recognition of his work.

After giving the Royal Victoria Hospital Oration[14] in 2019 which the journal published in full in 2021, 'retirement' freed up time for him to fit in his interests of philosophy, writing, and lecturing which until then, the day job had kept getting in the way. We would regularly correspond with interesting articles for each other. He was fascinated by the development of artificial intelligence in radiology having again picked up on it before others, during his editorship. When I sent him a note of the latest scanner's ability to virtually unwrap and decode ancient scrolls, he was instantly off making more slides for another talk.

Last year he sent me a podcast on consciousness and succinctly summarised theories on it at the time into three categories – 1. It's a mysterious unknowable fundamental force in the universe; 2. No it isn't, its chemicals and electricity in your brain; 3. It's panpsychism. Pure Barry, distilling down the arguments and evidence into simple language. My own feeling is that choice 1 is correct so I'm expecting his huge brain energy (physics dictates that the energy has to go somewhere), whatever project it's working meticulously on now, freed of the constraints of his physical body, is creating wonderful images whilst travelling in another dimension somewhere in the cosmos, and likely travelling at the speed of light (or faster…).

Barry died peacefully at home on 22nd June 2025. He is survived by his wife Susan and daughters Katie and Rosie.

The author has no conflict of interest to declare.

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Letters

'More than Skin Deep: Listening, Learning and Living with Hailey'

Editor,

A 56-year-old female patient presented with a history of right elbow pain precipitated by lifting her left leg with her right arm. The patient had long-standing left-sided weakness secondary to multiple sclerosis. A bicep rupture was presumed and she was admitted for an MRI biceps and multidisciplinary input.

Admission documentation noted a history of Hailey-Hailey disease (HHD). She had brought her skin maintenance regime from home and initially declined assistance with personal care. On Day 3, the patient recounted being unable to apply maintenance lotions whilst in hospital due to ongoing arm pain. Her mobility had significantly declined affecting air circulation and she had developed new vesicular skin lesions in the groin and vulval areas. The ward team had been unaware of her HHD diagnosis as it was not entered formally into the medical history and did not therefore transfer to the daily ward round pro-forma. Inflammatory markers were normal. A skin swab showed no significant growth. As per advice from the dermatology team, the patient was treated with a reducing regime of Lotriderm (betamethasone dipropionate & clotrimazole) and Daktacort (hydrocortisone acetate & miconazole nitrate), as required, with good effect.

Hailey-Hailey Disease, also known as benign familial pemphigus, is a rare autosomal dominant disorder affecting adhesion of epidermal keratinocytes. It is a chronic condition, commonly presenting during the second to fourth decade. The genetic defect occurs on *ATP2C1* which codes for protein SPCA1, a calcium and manganese pump which maintains normal intracellular concentrations of calcium[1]. Disruption in calcium homeostasis affects cell-to-cell adhesion, barrier repair and epidermal differentiation[1,2].

HHD typically presents with symmetrical, erosive vesicles in intertriginous regions, most commonly the groin or axillae. These can progress to larger crusted plaques with exudates. Fissures may develop if left untreated. White nail bands are a diagnostic clue seen in approximately 70% of patients[3]. Lesions are non-scarring and transient, often precipitated by sweat or friction. The disease course is chronic, characterised by relapsing and remitting episodes with secondary bacterial or viral infection a common complication[2,4]. Herpetic infections should be specifically excluded given the risk of rapid dissemination with potentially life-threatening consequences.

Management involves maintaining the skin barrier. Topical antimicrobials or topical steroids are considered in mild flares whilst botulinum toxin injections may be used to reduce sweating in more extensive disease. HHD does not impact life expectancy however it can significantly impact life quality[1].

This interesting case raises several learning points relevant to encountering uncommon conditions. Firstly, the importance of maintaining potentially relevant co-morbidities within the daily review note. This is of particular importance in acute medicine where different consultants are often assigned daily. Though individually uncommon, rare diseases collectively affect 3.5 million people in the UK[5]. Patients often become experts in their own condition and can inform healthcare professionals to update electronic care records accordingly. Clinicians should critically reconcile home medications at admission and enquire about unfamiliar topical treatments with patients. Finally, and perhaps most crucially, healthcare workers should consider a patient's ability to manage skin maintenance regimes while in hospital and enquire regarding this. Potential skin barrier issues can be spotlighted to nursing colleagues, decreasing the risk of flares/infections.

Arguably, our patient's flare could have been mitigated with increased awareness of the condition by ward staff, prompting simple interventions including regular changing of bedsheets, provision of cotton sheets to cover plastic hospital chairs and greater assistance with the patient's personal care.

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Ulster Med J 2025;**94(2):**107-108

Curiositas - Psychiatric Puzzles

QUIZ 1

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1. **Who is this man?**
2. **What neuropsychiatric condition does he have?**
3. **What psychiatric triad is associated with this condition?**

Cedar Andress (General Adult Psychiatry Specialist Registrar, South Eastern Health and Social Care Trust).

QUIZ 2

This image is licensed under :CC-BY-SA-3.0-DE

1. **Who is this man?**
2. **What was his cause of death?**
3. **What Class A drugs were commonly given to soldiers he commanded during this period?**
4. **What Class A substances were administered to this man by his doctor?**

Cedar Andress (General Adult Psychiatry Specialist Registrar, South Eastern Health and Social Care Trust).

QUIZ 3

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1. **What is the structure above?**
2. **Tobar na nGealt is a famous one, found in County Kerry. What is it famous for?**
3. **What surprising commonly used element for the treatment of mental illness has been found in higher levels here?**

Bronagh McCarragher (General Adult Psychiatry Specialist Registrar, South Eastern Health and Social Care Trust)

QUIZ 4

This image is licensed under CC BY-SA 2.0

1. **This is one of the most photographed individuals of the 20th Century. Who is she?**
2. **Which eating disorder did she suffer from?**
3. **What are the key clinical signs/symptoms of this condition?**

Bronagh McCarragher (General Adult Psychiatry Specialist Registrar, South Eastern Health and Social Care Trust)

CONSIDER CONTRIBUTING TO CURIOSITAS?

Please refer to *'Curiositas: Guidelines for contributors'* http://www.ums.ac.uk/curiositas.html and email curiositas@ums.ac.uk with your ideas and submissions.

Curiositas: Answers

QUIZ 1

1. Lewis Capaldi is a 28-year-old sing-songwriter from Glasgow.

2. He has been open about his diagnosis of Tourette's syndrome[1], a neuropsychiatric condition that is characterised by involuntary motor and vocal tics. This was very prevalent during his performance in 2023 at Glastonbury festival[2] and led to him taking time off his career in music to focus on his mental health and to improve his management of this condition. Tics are sudden, repetitive and involuntary movements or sounds, known to occur with a wax-and-wane type presentation which can be exacerbated by factors such as stress, anxiety or excitement. They present in childhood and are more common in males than females. Some children's symptoms diminish or disappear by adulthood. Understandably, tics can be distressing for the individual, impacting on their quality of life and confidence in public. The cause of this disorder is unknown, however current research points to gene mutations and abnormalities in the basal ganglia, frontal lobes and cortex, as well as these circuits and neurotransmitters. There is no cure for the condition but treatments to manage the tics include medication (dopamine antagonists or alpha- adrenergic agonists) and behavioural therapies.

3. Obsessive-compulsive disorder (OCD) and/or attention deficit hyperactivity disorder (ADHD) are common in the majority of those with Tourette Syndrome, a known clinical triad[3]. It is important for clinicians to be aware of this, especially as treating one condition can often impact the other – for example first line stimulant medications for ADHD can exacerbate tics.

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QUIZ 2

1. Adolf Hitler (born 20th April 1889) was the dictator of Nazi Germany from 1933 to 1945.

2. Hitler committed suicide by shooting himself in the head with his own pistol on 30th April 1945 in a bunker, alongside his wife of less than two days, Eva Braun, who it is speculated took a cyanide capsule to end her life.

3. During World War II, the German military widely used Pervitin, a methamphetamine developed to enhance soldier performance. It was designed to increase energy, reduce the need for sleep, and suppress inhibitions, making combat feel easier and more manageable[1]. This pharmacological approach to warfare extended all the way to Adolf Hitler himself, whose dependence on drugs became increasingly severe as the war progressed.

Hitler had long suffered from chronic abdominal pain, and when conventional treatments failed, his personal physician, Dr. Theodor Morell, began administering a cocktail of powerful medications. Among them was Eukodal (oxycodone), a potent opiate known for its euphoric effects[2]. Because Hitler had a weak stomach and disliked taking pills, he preferred injections, receiving Eukodal up to several times a day. Over time, his use escalated, with Morell eventually combining Eukodal with high-grade cocaine, which had originally been prescribed to treat ear damage following an explosion at Hitler's Eastern Front command bunker. As the war turned against Germany, bombs destroyed the factories producing both Pervitin and Eukodal, leading to a critical shortage of these drugs. By February 1945, in the final months of the war, it is believed that Hitler was suffering not only from the pressures of impending defeat but also from drug withdrawal, compounding his physical and mental decline.

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QUIZ 3

1. This structure is a water well.

2. "Tobar na nGealt" (translation "Well of the Mad") is a Well, situated at the bottom of the valley of Gleann na nGealt, located in County Kerry, Ireland. It is famous for being known to provide "The Cure" for a range of physical and mental illness. Holy wells in Ireland are steeped in traditions and rich in folklore. People have travelled from near and far to find "The Cure" from these waters, not only for mental illness, but for many conditions including arthritis, headaches, sore throats and eye infections.

3. Research has found higher levels of certain minerals within the water of some of these wells[1], which may be implicated in providing symptomatic relief in a variety of ailments. Of particular interest to psychiatrists, unusually higher levels of lithium have been found in some of these wells.

The levels of lithium found were not at levels equal to prescribed doses of lithium, however it is thought they may have contributed to a mood stabilising effect, with repeated exposure[2].

Lithium is a naturally occurring mineral which has been used in psychiatry from as far back as the mid-19th century. It was reintroduced in 1949 for the treatment of mania and is now a well-established psychiatric treatment. It reduces the frequency and severity of manic and depressive episodes.

In practice, lithium is a very effective drug, however must be prescribed and monitored carefully[3]. It has a narrow therapeutic level window of 0.4- 0.8 mmol/L for most indications. Lithium toxicity can occur at levels above 1.5 mmol/L, but can also been seen at lower levels.

In summary: sometimes "The Cure" is in the Chemistry!!

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QUIZ 4

1. This is Princess Diana, the Princess of Wales. Alongside her world-renowned humanitarian work, she also played a vital role in reducing the stigma around mental illness by openly discussing her own struggle[1].

2. Princess Diana suffered from bulimia nervosa. She famously talked about her struggles with bulimia in her interview with the BBC's current affairs programme[2], Panorama in 1995, which was watched by 23 million people.

3. Bulimia nervosa is characterized by recurrent episodes of binge eating, followed by compensatory behaviours - for example, self-induced vomiting, excessive exercise and misuse of laxatives or diuretics. These behaviours are often driven by a distorted body image and an intense fear of weight gain. In contrast to anorexia nervosa, many people with bulimia nervosa are of normal weight or are even overweight.

Physical symptoms can include: dental erosion from stomach acid, Russell's sign (knuckle calluses which develop on the dorsal aspect of the dominant hand due to friction against teeth), electrolyte imbalances, gastrointestinal disturbance and parotid gland swelling[3].

Bulimia is frequently associated with comorbid anxiety disorders, depressive illnesses and substance misuse.

The main treatments for bulimia nervosa include psychological therapies, dietician input and in some cases pharmacotherapy (often SSRIs which can be particularly helpful if there is a comorbid anxiety or depressive illness).

Treatment for bulimia nervosa requires holistic, compassionate care that addresses both physical and mental health.

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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*.

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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.

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.

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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.

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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.

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