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Editorial

In defence of the lecture(d)

Michael Trimble

In my previous editorial, I had reflected on the effects of our 'technological society' and its slavish devotion to ever-increasing efficiency. I had not, however, considered the loss of efficiency that occurs when such technology fails. Producing this issue has been hindered by an email blockade between the university and the Trusts. This was put in place following a cyber-attack on the university's computer systems earlier in the year. Nevertheless, we have made it to press, albeit possibly a little later than scheduled. Perhaps unsurprisingly, as society slowly emerges from the shadow of Covid-19 and lockdown, we have a number of papers describing the effects of the pandemic on various specialties. We also have papers pertinent to undergraduate and postgraduate education and contributions on medical history. A guest editorial commemorates the bicentenary of The Belfast Natural History and Philosophical Society, a body that has some shared history with the development of the medical school in Belfast in the person of James Drummond.

Last time I had written about the growing use of e-learning and online meetings and their effects on staff and teacher. I had promised to follow this up with some thoughts on how this affects students. Clearly, they have not had the university experience they had hoped (and paid) for. They have experienced, online lectures and seminars, virtual tutorials, and the wonders of flipped-classrooms. What many of them have not experienced is personal contact. I want to focus my thoughts on that much-maligned teaching medium – the lecture. An article in the Atlantic notes

> Commentators frequently single out the lecture as the prototypically old school, obsolete learning technology, in comparison to which newer educational techniques offer interactive, customized, and self-paced learning alternatives.[1]

Another wag has described the lecture as

> as a process whereby the content of the professor's notebook are transferred by means of a fountain pen to the student's notebook without having passed the mind of either.[2]

But, to quote 20th century philosopher Joni Mitchell,

> Don't it always seem to go
>
> That you don't know what you've got
>
> Till it's gone[3]

I would like to consider some positive aspects of the lecture. But, rather than focusing on the purely educational points, I want to think about the lecture as a social event. The gathering together of the year for a lecture promotes group identity and bonding. Where else will you see who is in your year group? Many of this year's first year medical students have only 'met' the other members of their case-based learning tutorial group – and that has been online. The lecture also brings the lecturer before their audience: They are more easily questioned and held to account about their material. They can sense the mood and atmosphere of the room and the auditors. Such immediate feedback is important – as anyone who has attempted humour in an online lecture will recognise! They can judge whether the students are receptive or looking puzzled over an inadequately explained point. The lecturer being present also allows for those quiet questions at the end of the talk, the ones that you might not want to voice in front of the whole group on Zoom, in case you feel foolish. A lecture can also be performance art. I imagine whatever medical school you attended, in whatever time period, you and your peers will remember certain lecturers; the larger than life personalities whose lectures were eagerly anticipated rather than endured. When we look back at our time in medical school, these are some of the nostalgic memories that spring to mind. Will the present generation hark back to that amazing Zoom tutorial in the same way? I somehow doubt it. Finally, online teaching can certainly impart information, perhaps it may even be better than a lecture for this, but I doubt that it can convey enthusiasm. A lecture can be inspirational.

I hope that the enthusiasm that has been shown for online learning will be tempered with acknowledgement that it is not the be-all and end-all. The traditional lecture can aid group identity and bonding, help hold the lecturer to account, provide some joy in learning and – if well done- provide inspiration to our students.

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Ulster Med J 2021;**90(2):**58 - 60

Guest Editorial

The Bicentenary of The Belfast Natural History and Philosophical Society

Alun Evans

Elsewhere in the Journal (112-116), I describe the establishment and objectives of The Belfast Natural History and Philosophical Society in 1821, and its Bicentenary on 5th June this year. From what did this interest in Natural History stem? According to David Allen in his masterful Social History of 'The Naturalist in Britain', "It was the Enlightenment, with its ultimate power of dispassion and objectivity… By dispelling superstitions and accustoming people to see themselves and their surroundings with detachment…[thus]...Stripped by science of its ultimate mysteries, nature gradually assumed a fresh and entirely different mysteriousness…"[1] A wave of literary and philosophical societies, gradually spread across the "new industrial areas" of the north of England, especially textile towns (like Belfast), in the late eighteenth century, and these were followed by natural history societies.[2] Some of this was driven by 'Dissenting (from Anglicanism) Academies,' and Warrington Academy, a prime example based on Unitarianism, was founded in 1857.[3] The great Chemist, Joseph Priestly, taught there and his "innovation of the teaching of history was … that sciences and natural history" became part of the regular curriculum. Jean-Paul Marat, who was stabbed to death in his bath by Charlotte Corday, may have taught French at the Academy.[4] Its first pupil, Thomas Percival, the great Physician, established the Manchester Literary and Philosophical Society in 1781,[2] and in 1802 was the main author of the 'Health and Morals of Apprentices Act', designed to curb the exploitation of pauper children. Percival also published the first book on Medical Ethics in 1804.[3]

The impetus for The Belfast Natural History Society stemmed from the Belfast Academical Institution which had opened in 1814.[5] To understand the ethos that pervaded the school in its early days, it is necessary to examine the motivations of one of its chief protagonists, William Drennan, who was born in Belfast in 1754. His father, the Reverend Thomas Drennan, was Minister of the First Presbyterian Church in Rosemary Street. Drennan studied Medicine in Edinburgh, graduating MD in 1778.[6] He was a major driver of the chain of events, which culminated in the 1798 Rebellion, although, by then, he had lost interest in the cause.[7] He was also a considerable poet, coining the phrase '*The Emerald Isle*' and 'lazy root,' for 'potatoes'.[8] In 1783 William wrote to his sister, Martha McTier, recommending a Warrington-style Academy in Belfast as "…a truly desirable and patriotic scheme."[9] Warrington Academy dissolved in 1786, and although Drennan had no direct exposure to it, several of its ex-pupils were Irish,[10] and two of these, Edward Corry and The Reverend Boyle Moody, were Drennan's friends in Newry from where he was writing.

Soon after his return to Belfast in 1807, William became deeply interested in the foundation of the Belfast Academical Institution which became simply 'Inst' and only acquired the prefix 'Royal' in 1831.[11] In this, Drennan was ably assisted by another 'United Irishman', the eminent Naturalist, John Templeton (1766-1825),[12] who contributed his 'Naturalist's Report,' and notes on 'Meteorology' to the Belfast Monthly Magazine, which he co-founded with Drennan, from 1808-14. Drennan delivered the Address at Inst's opening on the 1st February, 1814.[13] It is rousing stuff, containing this line to commend the school's setting: "… backed by a sublime and thought-inspiring mountain: for it is these grand features of nature, rather than the machinery of art, which ought to enlarge the soul and dilate the affections in its earliest and sweetest and most lasting associations." Drennan and Templeton became School Visitors, providing direction to the course the school was steering.[14] Drennan died in 1820; over a century later, Inst's Historian, John Jamieson, concluded that, "He was an indefatigable supporter of Inst, with an uncompromising sense of purpose and duty."[15]

It is, therefore, unsurprising that seven years later the Belfast Natural History Society was founded, and under one month later, the Society elected John Templeton, by then in failing health, as its first Honorary Member.[16] The Society was founded by one of Inst's Professors and by at least four of its former pupils. The professor was James Lawson Drummond

James Lawson Drummond (From a Water-colour Drawing by W. C. Day of London. Presented to the Society by a few members in 1843.)

Source: Deane A (Ed). Belfast Natural and Philosophical Society (Centenary Volume, 1821 – 1921). BNH&PS 1924: Frontispiece

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(see Figure), who, the year before, had galvanised matters by anonymously publishing his 'Thoughts on the Study of Natural History.'[17] Drummond was born in Larne in 1783. His father was a naval surgeon who died when James was three, so his mother moved to Belfast along with James' brother and sister.[18] He was educated at Belfast Academy, became an assistant naval surgeon in 1806, sailed under the command of Admiral Collingwood,[19] who succeeded Nelson at Trafalgar.[20] Drummond then qualified in Medicine from Edinburgh in 1814, became Physician to the Belfast Dispensary, and then joined the staff of Inst in 1818 as Professor of Anatomy and Physiology. His main role was to help students preparing for the Presbyterian ministry acquire a little medical knowledge,[21] and "taught a very wide field of natural history."[22] His remuneration was small, but for two years from 1823, when funds were tight, he drew no pay at all.[23] Drummond's next major contribution to Belfast life was organising the fund-raising to build the Museum in College Square North. It opened in 1831, and a sketch of Inst from a window of the Museum in 1842 testifies to the intimate relationship the two buildings enjoyed. This intimacy was destroyed by the construction of the 'Tech' early in the 20th Century. It was built there to be close to Inst's Art Department but proved to be a severe case of the child overlying the mother.[24]

The Museum met the prerequisites for a Natural History Society listed by Allen,[2] including a forum for discussion, a library to store collections of books and the Society's Proceedings, and 'Cabinets of Curiosities,' which the Society assembled and filled with great vigour. Meanwhile, Drummond was constantly publishing, and his 'Letters to a Young Naturalist' was his most popular book, which included a tirade against cruelty to animals,[25] a view he shared with his Unitarian Minister brother.[26] His 'First Steps in Botany' ran to four editions.[23] He also had the honour of having a Sea Cucumber named after him.[27] The Society also helped to establish a Botanic Garden for Belfast in 1827,[28] initiating the publication of the First Series of The Ulster Journal of Archaeology in 1853, and the Belfast Naturalists' Field Club in 1863.[29] This introduced the element of 'Field Trips' which, according to Allen, was the usual progression for Natural History Societies, but it came rather later in Belfast than in Great Britain. This time it was largely Belfast Royal Academy old boys who were involved.[29]

Drummond's most resounding achievement, however, was the establishing of the Faculty of Medicine at Inst in 1835. He had promoted the idea of a joint surgical and medical school for the province as early as 1826. Drummond supervised construction of the accommodation of the new Faculty and even contributed £200 (at least £20,000 today) from his own pocket.[23] It was therefore fitting that when the Faculty opened, Drummond became its first President, and again in 1844. Drummond resigned his chair owing to ill health after 31 years when the Medical Faculty moved to the recently opened Queen's College. Drummond was a serial monogamist but had no children: his first two wives predeceased him. His third marriage, in 1850, was to Eliza O'Rorke, of Ballybollan House, near Ahoghill, County Antrim. She was 20 years his junior, from an ancient Catholic family, but the couple had a Church of Ireland Ceremony. Drummond died at his house, beside the Museum, on 17th May 1853. He is buried in the Old Graveyard in Ahoghill. Eliza was laid to rest in the same plot, 43 years later. Their grave is in urgent need of refurbishment and it is the Society's plan to undertake this work in Drummond's honour to mark its Bicentenary. A small pilgrimage to the grave is planned.

Drummond attracted many epithets, but my favourite from the Dublin Penny Journal in 1833,[30] concerns the Society he was so instrumental in founding:

> *Such a modest, yet manly gravity of deportment, such an orderly regularity, and such sound intelligence we could not have anticipated to have found pervading such a youthful assembly, and left an impression on our minds which will not be speedily forgotten.*

Two centuries ago, William Lawson Drummond became the Society's first President; I have the great honour of being its President during its Bicentennial year.

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Review

Rhabdomyolysis: Revisited

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RHABDOMYOLYSIS: REVISITED

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ABSTRACT

Rhabdomyolysis (RML) is a pathological entity characterized by symptoms of myalgia, weakness and dark urine (which is often not present) resulting in respiratory failure and altered mental status. Laboratory testing for myoglobinuria is pathognomonic but so often not present during the time of testing that serum creatine kinase should always be sent when the diagnosis is suspected. Kidney injury from RML progresses through multiform pathways resulting in acute tubular necrosis. Early treatment (ideally<6 hours from onset) is needed with volume expansion of all non-overloaded patients along with avoidance of nephrotoxins. There is insufficient data to recommend any specific fluid. The mortality rate ranges from 10% to up to 50% with severe AKI, so high index of suspicion and screening should be in care plan of seriously ill patients at risk for RML.

INTRODUCTION

Rhabdomyolysis (RML, lysis of skeletal muscle cells) is a pathological syndrome of acute or subacute onset in which a patient develops localized or generalized myalgia and weakness, associated with a rapid rise in the serum creatine kinase (CK) level, the extent of which will depend upon the timing of analysis with respect to the acute event.[1] A systematic review on the definition of RML recommends these clinical symptoms combined with a CK cut-off value of >1000 IU/L or CK > 5 times upper limit of normal (ULN) as mild RML.[1] Additionally, measured myoglobinuria and acute kidney injury (AKI) indicate a severe RML[1]. The above definition holds true after exclusion of elevated CK due to other aetiologies like myocardial infarction,[2] status epilepticus,[3] or a chronic neuromuscular disease.[4] The coexistence of RML in these aetiologies is also a possibility with acute elevation of CK.[1]

RML has been documented in historic times. The Old Testament refers to a plague suffered by Israelites after consumption of quails during their exodus from Egypt.[5] AKI characterized by dark red urine and oliguria from quail poisoning (and resultant *Coturnism*) has been reported from Greece in the past.[6,7] In contemporary era, the first cases of traumatic RML with renal failure were reported during Messina earthquake in 1908 and then, subsequently in the World War I.[8] However, the first detailed report of RML and AKI was by Bywaters et al. who described four war victims from the Battle of Britain in 1940.[9] The same author identified myoglobin in the urine of air-raid traumatic crush injuries.[10] Non-traumatic myoglobinuria was initially reported by Koenigsberg Haff in erstwhile province of East Prussia and then later from Sweden.[11] It was, however, until the 1960's when other causes like heat injury,[12] and a metabolic myopathy predisposing to acute renal failure were recognized.[13,14]

The true incidence of RML is unknown since it is frequently oligo-symptomatic or asymptomatic. Approximately 26,000 cases of rhabdomyolysis are reported annually in the United States.[15] African Americans, males, obese patients, patients younger than ten years of age, and patients older than 60 years old all have a higher incidence of RML.[16] The percentage of patients developing AKI varies from 13% to approximately 50%, depending on clinical and organizational setting.[17] In those with severe RML, the incidence of AKI goes up to 81% with 26% needing kidney replacement therapies.[18] Mortality from RML is 10%, which increases in the setting of AKI and reaches 50% in AKI stage 3.[19,20]

AETIOLOGY

The etiology of RML varies according to the age group, geographical variation and the timing in relation to the analysis. Traumatic causes are more common in the developing countries, while drug abuse is the most frequent cause in the Western world.[21] Infections and congenital diseases are largely responsible for pediatric RML, while drugs and trauma are the most common causes in adults (up to 80% of cases).[22] The list of causes of RML is exhaustive and is beyond the scope of this article, however, broad categories have been covered in figure 1.

Recently, RML has been reported in cases of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory

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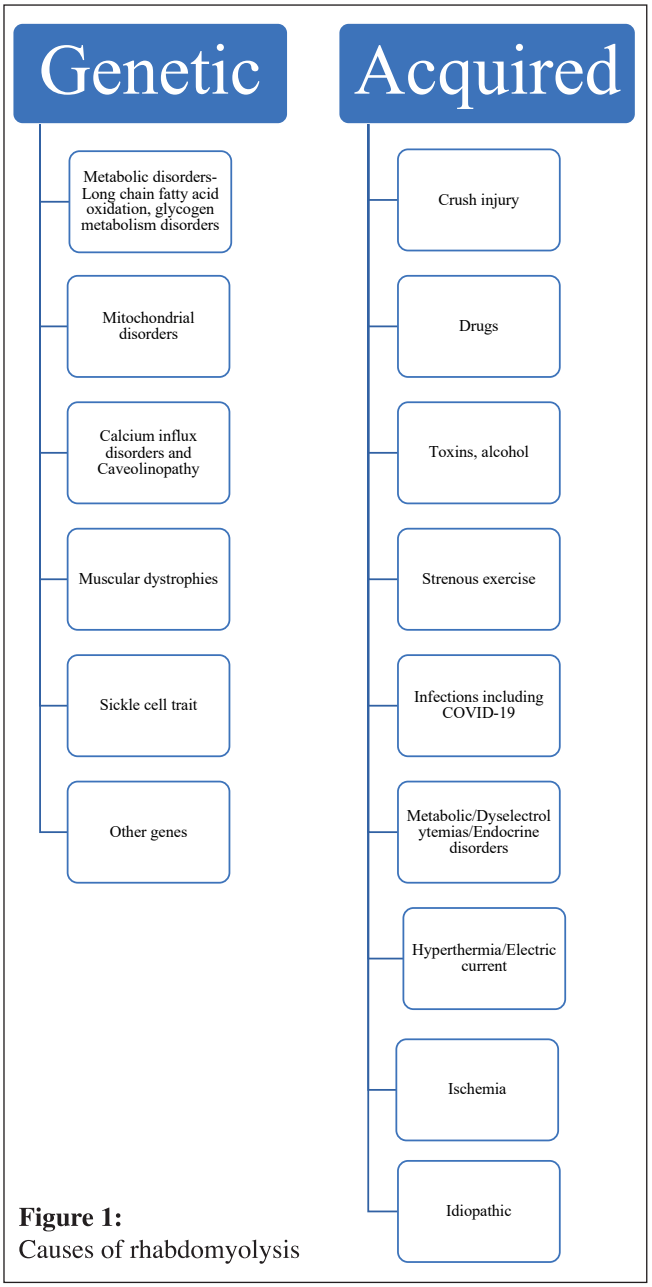

Figure 1:
Causes of rhabdomyolysis

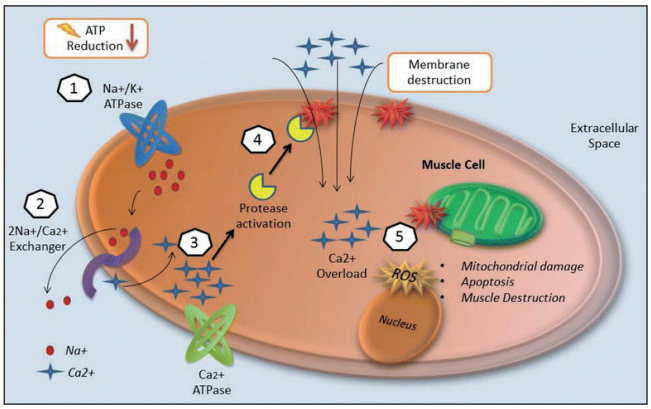

Figure 2: Injury mechanisms of rhabdomyolysis.[1] Energy (ATP) depletion inhibits Na^+/K^+ ATPase function, thus increasing intracellular sodium.[2] The $2Na^+/Ca^{2+}$ exchanger increases intracellular calcium.[3] Ca^{2+} ATPase is not able to pump out intracellular calcium due to energy depletion.[4] Intracellular calcium activates proteases such as phospholipase 2 (PLA2), which destroy structural components of the cell membrane, allowing the entrance of more calcium.[5] Calcium overload disrupts mitochondrial integrity and induces apoptosis leading to muscle cell necrosis. (Adapted from Chavez et al: Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care Lond Engl. 2016 Jun 15;20(1):135. Open access article distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).[27]

syndrome coronavirus 2 (SARS-CoV-2). The first case was a report of a COVID-19 patient from Wuhan, China, who developed RML during hospitalization.[23] Second patient was an octogenarian who initially presented with RML and was subsequently diagnosed as COVID-19.[24] A recent review reported nine patients (all adult males) with COVID-19 related myositis/RML, of which three passed red cells in urine and one had cola colored urine.[25] The postulated mechanisms include excessive immune response and cytokine storm, direct viral invasion and circulating viral muscle toxins.[26]

PATHOPHYSIOLOGY

The disorders causing RML result in mechanical stress on the cell, which in turn leads to cellular membrane injury, hypoxia and the release of degradative enzymes, ATP depletion and the generation of oxidative free radicals.[27] This results in persistent contraction of the myofibers and an inflammatory cascade causing cell death. Injured muscles sequester up to 10-12 liters of fluid in a few days culminating in a compartment syndrome.[28,29] (figure 2)

The destruction of approximately 100 g of muscle tissue is capable of inducing RML.[30,31] The intracellular metabolites (potassium, phosphates and urate) and intracellular proteins (myoglobin, CK, aldolase, lactate dehydrogenase, aspartate aminotransferase, and nucleic acids) are released in the extracellular space and circulation. The release of excessive myoglobin into the plasma overwhelms the capacity of the binding proteins (mainly haptoglobin). Myoglobin then gets filtered across the glomerulus, causing tubular damage. The pathophysiology of AKI in rhabdomyolysis is likely to be multifactorial, including vasoconstriction, hypovolemia, direct myoglobin toxicity and intraluminal cast formation.[21,29] Myoglobin can exert a direct cytotoxic effect through the enhancement of local oxidative stress in the tubular cells.[30,32] The high rates of generation and urinary excretion of uric acid further contribute to tubular obstruction by uric acid casts. The precipitation of these casts is amplified in acidic urine. The free iron released from degradation of intratubular myoglobin catalyzes free radical production and further enhances ischemic damage.[29,33,34] A recent study showed that heme-activated platelets released from necrotic muscle cells during RML promoted AKI.[35] Alkaline conditions prevent this effect by stabilizing the reactive ferryl-myoglobin complex.[36]

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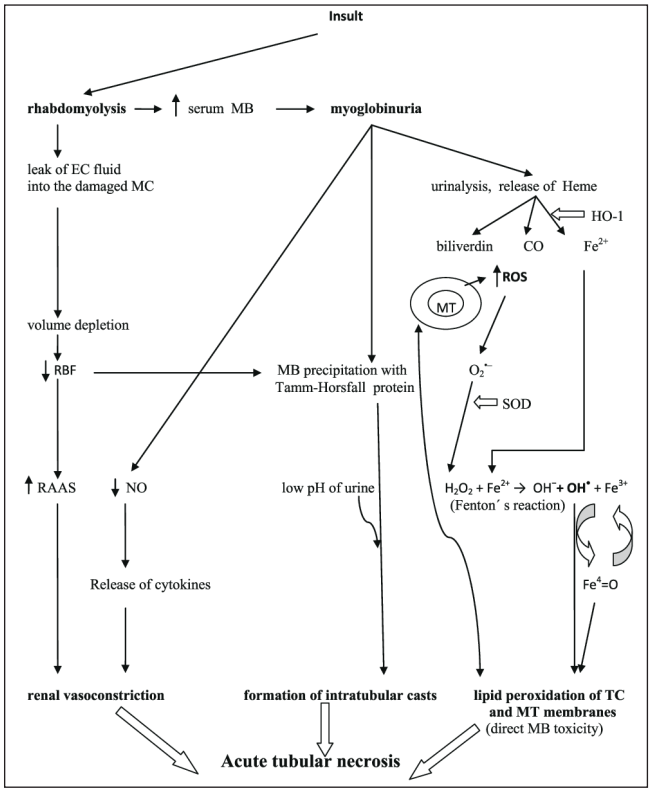

Figure 3: Pathophysiology of rhabdomyolysis-induced acute kidney injury. CO, carbon monoxide; EC, extracellular; Fe 2+ , ferrous iron; Fe 3+, ferric iron; Fe4 = O, ferryl iron; HO-1, heme oxygenase-1; H2O2, hydrogen peroxide; MB, myoglobin; MC, muscle cell; MT, mitochondria; NO, nitric oxide; OH-, hydroxyl anion; O2-, superoxide radical; OH*, hydroxyl radical, RAAS, renin–angiotensin–aldosterone system; RBF, renal blood flow; ROS, reactive oxygen species; SOD, superoxide dismutase; TC, tubular cell. (Adapted from: Petejova et al : Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review. Crit Care Lond Engl. 2014 May 28;18(3):224. Open access article distributed under the terms of the Creative Commons Attribution License. (http://creativecommons.org/licenses/by/2.0)32

Disseminated intravascular coagulation (DIC) and renal arteriolar constriction also occurs.[17,22] The transient prerenal phase, if not treated early progresses to persistent AKI, which is almost always, due to acute tubular necrosis.[21] (figure 3)

CLINICAL FEATURES

There is a wide variation in the clinical presentation of RML.[37] The 'classic' triad of symptoms includes muscle pain (23% of patients), weakness (12% of patients) and dark urine (Coca-cola colored or tea-colored, 10% of patients).[1,19,38] Because of the relatively quick renal clearance of myoglobin, this dark urine often lasts for a short duration, and may be overlooked by both patients and clinicians.

The clinical manifestations can be classified as musculoskeletal signs, general manifestations and complications. The muscle pain, weakness, swelling, tenderness and contracture may involve specific groups of muscles or may be generalized. The most frequently involved muscle groups are the calves and the lower back. The muscles can be tender and swollen, and there can be skin changes indicating pressure necrosis. However, these classic features are seen in less than 10% of the patients.[39] Systemic circulation of intracellular muscle components can yield additional non-specific symptoms like malaise, fever, tachycardia, nausea or vomiting.[37]

Cardiovascular symptoms may stem from the associated electrolyte abnormalities (i.e., potassium, calcium, phosphate) and may range from arrhythmias to cardiac arrest.[40] Patients may be hypoventilating if RML was drug-induced or due to trauma or hyperventilating due to pain if they are awake and agitated.[27] Respiratory failure and acute respiratory distress syndrome may occur in some patients.[21] Hepatic dysfunction secondary to proteases released from muscle injury is seen in 25% of patients with RML.[41] AKI and DIC (thought to be due to activation of clotting cascade thromboplastin released during muscle injury) are late complications, developing 12–72 hours after the acute insult.[42] AKI as a complication of RML is quite common, representing about 7 to 10% of all cases of acute kidney injury in the United States.[43] The course of AKI is typically initial oliguria followed by polyuria in 1-3 weeks after the primary insult, however, some cases may non-oilguric from the beginning.[31] Another complication is metabolic acidosis as a result of uremia and lactic acidosis from ischemia. A non-anion gap acidosis may also occur from release of sulfur-containing proteins in large amounts overwhelming kidney excretion.[44]

LABORATORY WORK UP

Serum creatine kinase

Serum CK concentration, mainly the CK-MM subtype, is the most sensitive indicator of damage to muscles. The normal plasma CK level varies between 45 to 260 U/L.[45] Serum CK begins to rise approximately 2 to 12 hours after the onset of muscle injury, peaks within 24 to 72 hours, and then declines at the relatively constant rate of 39% of the previous day's value.[46] (figure 4) A CK cut-off value of >1000 IU/L or CK > 5 times upper limit of normal (ULN) in correct clinical context could diagnose mild RML.[1] An exception to these criteria is statin-related RML where it is defined as CK elevation >10 times ULN with evidence of renal impairment and muscle symptoms or CK > 50 times ULN.[47] The concentration of CK is directly proportional to the extent of muscle injury. A persistently elevated CK level suggests continuing muscle injury or development of a compartment syndrome.[48] Whether increased levels of CK point to an increased risk of subsequent AKI, and/or need of kidney replacement therapy is unclear as CK is only a surrogate marker of myoglobin nephrotoxicity.[49,50,51] Rarely, total CK may be factitiously low in RML. Running the sample in dilution should be considered if the low values do not correlate with the diagnosis.[52]

Serum and urine myoglobin

Myoglobin is normally bound to plasma globulins, and has a rapid renal clearance with a half-life of 2-3 hours. A

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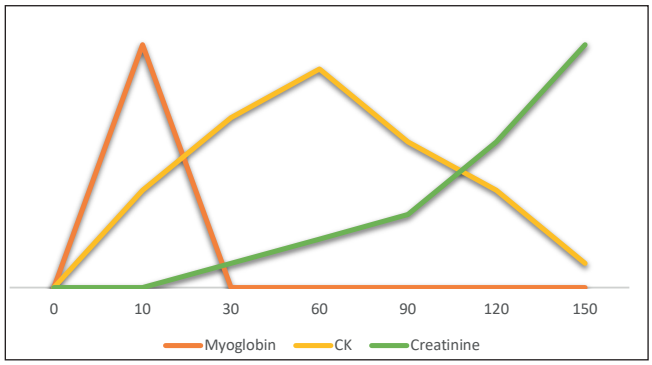

Figure 4: Time course (in hours; y-axis) of serum myoglobin, CK, and creatinine with respect to the insult. CK, creatine kinase.

small quantity of filtered myoglobin (0.01–5%) is normally excreted with urine. The normal concentration of myoglobin in the serum is below 5.7nmol/L (100 µg/L) and in urine below 0.57nmol/L (10 µg/L). After the occurrence of muscle damage, the circulating myoglobin levels exceed the plasma protein binding capacity, reach the glomeruli and are eventually excreted in the urine. Before the urine becomes discoloured (dirty-brown) by myoglobin, the level of myoglobin in the urine must exceed 57000 nmol/L (100 mg/dl). In RML, the level of myoglobin in the serum increases within 1–3 h, reaches its peak in 8–12 h, and then returns to normal within 24 h after the onset of the injury. (figure 4) Thus, the detection of myoglobin in the blood or urine is pathognomonic for the diagnosis of RML, provided that it is made in the initial phases of the syndrome (i.e., within the first 24 h).[42] A systematic review showed that myoglobinuria is detected in 17% of the patients with RML.[1]

The practical applicability of serum and urine myoglobin in the diagnosis of RML has several caveats.[42] Firstly, serum myoglobin usually increases before a rise in CK and drops more rapidly than does the decline in CK. Moreover, myoglobinuria may not be visible or may resolve early in the course of RML. These facts make this parameter less sensitive and therefore should not be relied upon to rule out the diagnosis of RML. Secondly, myoglobinuria is detected by urine dipstick tests (orthotolidine), which also react with the globin fragment of haemoglobin. Thus, in the presence of red blood cells or haemolysis, the specificity of this test is limited. False negative (heme-negative dipstick) results may occur in the presence of high specific gravity, ascorbic acid, or high nitrite concentration.[53] Radioimmunoassay is more sensitive and specific than dipstick.[54] However, this test is often not readily available, and it may take more than 24 hours to obtain results.

Urine myoglobin analysis is also affected by sample timing, glomerular filtration rate (GFR), and urine flow rate.[55] Urine myoglobin concentration may be falsely low if the collection represents a mixture of urine filtered after the injury with preinjury urine from the bladder or if filtered myoglobin excretion is limited because of kidney dysfunction.[21] Alternatively, the presence of urine myoglobin may indicate good renal function in that the kidneys are still able to excrete the high plasma myoglobin load.[55]

Other relevant laboratory findings

In 45% of the cases of RML, the urine dipstick can be found to be positive for the presence of protein. Proteinuria is due to the release of myoglobin and other proteins by the disrupted muscle cells. In the microscopic examination of urine, red blood cells are relatively few (<5 per high-power field).[46] There could be detection of coarse granular red-brown myoglobin casts. The fractional excretion of sodium may remain low even in the later course of the disease, reflecting primarily tubular obstruction rather than tubular necrosis.[21]

Creatine released in large quantities from the muscles gets converted into creatinine in the circulation. Some of the studies have suggested a higher ratio of serum creatinine/blood urea nitrogen in RML.[56] At the later stages of RML, the proteins released by the dead muscle cells are catabolized, thereby increasing the production of urea and thus the urea/creatinine ratio returns to normal.[57] Hyperkalemia is the most life-threatening electrolyte abnormality in RML. Its mechanisms include efflux from intracellular to extracellular compartment, hyper-catabolism, inadequate excretion in AKI and iatrogenic (blood transfusions).[58] Hypocalcaemia is also common in RML from influx of plasma calcium into injured muscles, calcium-phosphate precipitation in muscles, calcitriol suppression from hyperphosphatemia and parathyroid hormone resistance.[21,36] Upon complete cellular necrosis, the calcium initially entrapped in the cytoplasm of muscle cells is released back into the plasma. This, in combination with the secondary hyperparathyroidism that develops due to early hypocalcaemia and high levels of vitamin D (produced in great quantities by the glomerular cells), leads to the late manifestation of hypercalcemia.[46] Furthermore, inorganic and organic phosphoric components are dissolved and large amounts of inorganic phosphorus are released into the plasma, leading to hyperphosphatemia.[46] Hyperuricemia is seen as a result of purines derived from nucleic acids of damaged myocytes.[46] The elevation in aspartate transaminase and lactate dehydrogenase is quite common in RML.[59] Rarely, features of DIC including thrombocytopenia, increased fibrinogen degradation products (FDP), and extended prothrombin time (PT) are present.[46]

Muscle biopsy

A muscle biopsy is usually not required. For a diagnostic evaluation of muscle structure in select cases, biopsy is best deferred until at least 3 months after symptom resolution.[60] The histopathological findings include loss of cross striations and nuclei (necrosis and fragmentation of muscle fibers) with the absence of inflammatory cells.[61,62]

Kidney biopsy

Similarly, renal biopsy is not required to make the diagnosis of RML. The characteristic biopsy feature is acute tubular injury with globular red-brown casts which are positive for myoglobin by immunohistochemistry.[63,64] (figure 5)

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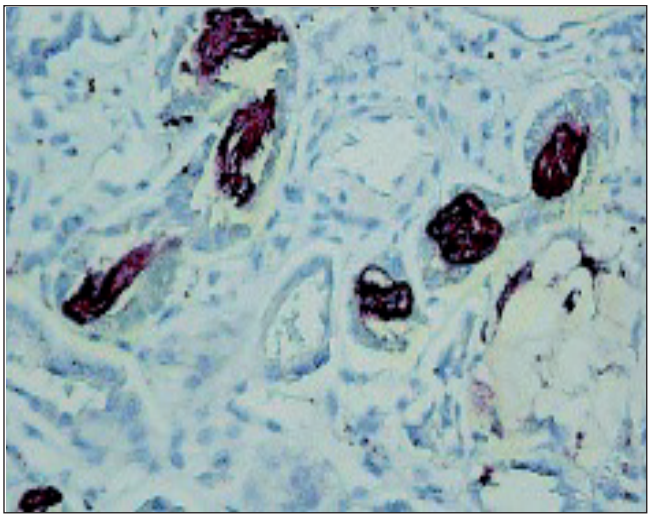

Figure 5: Kidney biopsy showing positive immunoperoxidase staining for myoglobin pigmented casts in a young female with heavy cocaine use and acute kidney injury. (Modified from Mansoor et al : Systematic review of nephrotoxicity of drugs of abuse, 2005–2016. BMC Nephrol [Internet]. 2017 Dec 29 [cited 2020 Apr 30];18. Open access article distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).64

Imaging

RML is a clinical diagnosis with supporting serum/urine tests. However, in cases of uncertainness, ultrasound, computerized tomography, magnetic resonance imaging and skeletal-scintigraphy provide supporting clues in diagnosing RML.[65] MRI seems to be more sensitive than CT or US (sensitivity 100%, 62%, 42% respectively).[66] Though these imaging modalities are non-specific; their help in localization is found useful when fasciotomy is being contemplated.

Investigating exertional RML

The risk of exertional RML is increased up to 11-fold in those with prior heat injuries and more than 50% of patients with exertional RML have a history of heat cramps or heat exhaustion.[67] Risk factors for greater increase in CK post-exercise include low premorbid physical fitness, males, African ethnicity, dehydration and high intensity prolonged weight bearing exercises.[68] A higher pre-disease CK and lower coenzyme CoQ10, specifically CK:CoQ10 ratio, is associated with risk of exertional RML in African Americans.[69] Further work up should be considered in patients with no history of heat exposure, or who have exertional RML. The acronym "RHABDO" has been suggested as an aide-memoire. (table 1)[70] Identifying genetic disorders presenting as RML is a diagnostic dilemma due to their rarity and marked heterogeneity, needing a high degree of clinical suspicion. Even presence of an identifiable trigger does not necessarily exclude an underlying genetic cause. Whole exome/genome sequencing and next generation sequencing may identify new genetic aetiologies of RML.[71,72]

R	Recurrent episodes of exertional rhabdomyolysis
H	HyperCKaemia persists 8 weeks after the event
A	Accustomed physical exercise
B	Blood CK >50 x ULN (>10 000 ULN in female Caucasian patients)
D	Drugs/medications/supplements and other exogenous and endogenous factors cannot sufficiently explain the rhabdomyolysis severity
O	Other family members affected/Other exertional symptoms (cramps, myalgia)

Table 1: Selection of patients for screening of a genetic disorder as a cause of exertional rhabdomyolysis. CK, creatine kinase; ULN, upper limit of normal. (Adapted from Scalo et al: Exertional rhabdomyolysis: physiological response or manifestation of an underlying myopathy? BMJ Open Sport Exerc Med. 2016;2(1):e000151. Open access article distributed under the terms of the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) License. (http://creativecommons.org/licenses/by-nc/4.0/)[70]

In episodic RML in children and young adults, apart from detailed history (including a family history of consanguinity), a thorough search for muscle-energy correlation is mandated.[22] The major fuel source (glycogen/fatty acids/amino acids) depends on intensity and duration of activity. A metabolic myopathy from a defect in any one fuel source is likely to present during or immediately post activity most dependent on that fuel source.[73] For example, long chain fatty acids are metabolized to acyl-CoA during fasting or prolonged low intensity exercise. Symptoms in lipidoses typically occur after 24-48 hours of exercise, when glycogen stores are exhausted. On the contrary, glycogenoses manifests as premature fatigue/myalgia within minutes of moderate to high intensity exercise, when defective anaerobic glycolysis results in failure of energy production. A reduction in exercise intensity resolves myalgia and the ability to begin exercising again after 6-10 minutes, without recurrence of symptoms (second wind phenomenon) is classical of McArdle disease, an autosomal recessive glycogen storage disorder.[73,74] These investigations are likely unnecessary in patients with COVID-19 as this is a described provoking factor.

TREATMENT

The management of RML is targeted towards prevention of AKI. Any nephrotoxic medication should be discontinued. British guidelines recommend that adult and paediatric patients identified as being at risk of developing AKI due to RML, and who are not volume overloaded, should receive prompt intravenous volume expansion in order to achieve a high urinary flow rate.[75] Recent Danish guidelines for prevention of RML induced AKI also suggest using early rather than late fluid resuscitation.[76] The underlying principle is maintenance of a satisfactory urine output with fluid administration.

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Other agents like mannitol were thought to be useful. It increases renal blood flow and GFR, acts like osmotic diuretic preventing obstructive myoglobin casts and scavenges free radicals. In addition, loop diuretics increase tubular flow and decrease precipitation of myoglobin. The evidence of benefit with these agents is not convincing in studies reported.[77,78] The guidelines suggest against the use of loop (or any other) diuretics or mannitol to prevent AKI.[76]

The evidence for specific type of fluid which confers the greatest benefit is of low quality. There is a weak recommendation to suggest using crystalloids rather than colloids. A recent meta-analysis of twenty-seven studies demonstrated no evidence which supported a preferred fluid type.[79] Historically, alkalinisation of the urine aiming for a urinary pH > 6.5 to mitigate intra-tubular precipitation of myoglobin has been the practice.[36] However, the guidelines suggest against the routine use of alkalinisation with sodium bicarbonate (low quality of evidence).[76] The primary role for sodium bicarbonate is simply to treat metabolic acidemia if present. Intravenous fluids should be initiated as soon as possible, preferably within the first 6 hours after muscle injury, at a rate that maintains a urine output in adults of 300 mL/h.[79] Clinical judgment should be exercised in deciding when to stop fluid. If oliguric AKI develops and patient is a positive fluid balance, then administering additional fluids would be harmful.

The guidelines also suggest against the use of antioxidants or routine use of kidney replacement therapy as compared to none in prevention of RML induced AKI.[76] However, no recommendations/suggestions could be provided on continuous kidney replacement therapy (CKRT) vs intermittent hemodialysis (IHD), filtration vs diffusion or low vs high cut-off membranes for AKI prevention.[76]

Prediction for Kidney failure or mortality

An admission prognostic score by McMahon et al. is likely to be useful in emergency room for risk stratification in RML.[80] It includes age, sex, type of injury, and clinical laboratory parameters. In a retrospective observational study, a score of at least 6 was more sensitive (86% vs 83%) and specific (68% vs 55%) than peak CK of 5000U/L in predicting AKI requiring dialysis.[81] Another risk score formula predicting AKI in patients with severe RML applied laboratory values related to the extent of muscle injury (CK levels, metabolic acidosis) and the general condition prior to the index event (hypoalbuminemia and decreased PT).[82] A retrospective analysis of patients who were hospitalized for RML with admission CK > 1000U/L and serum creatinine of < 115 umol/L (1.3 mg/dL) were found not to be at risk for developing AKI if treated promptly with fluids, regardless of their initial CK levels.[83] Another recent large, multicenter, retrospective study of 387 patients reported that invasive ventilation and severity of RML, including myoglobin level, are associated with the risk of stage 2–3 AKI. The long-term fall in estimated glomerular filtration rate (eGFR) correlated to serum phosphate and myoglobin (>8000U/L) at admission.[18] These scoring assessments assist clinicians to identify patients who are at high risk of developing AKI so that they could be triaged for aggressive medical management. Furthermore, the transition from AKI to CKD in such patients would have future prognostic considerations.

Treatment of Myoglobinuric AKI

The basic principles of treatment of such patients remain same: adequate nutrition, management of metabolic complications and kidney replacement therapy (KRT) if overt renal failure develops. Dialysis is indicated when uremic encephalopathy, deteriorating kidney function, uncontrolled hyperkalemia, metabolic acidosis, and fluid overload occur due to RML and AKI. KRT modes include CKRT and intermittent KRT. Conventional IHD does not remove myoglobin effectively owing to the size of the protein and is therefore usually mandated by renal indications.

Myoglobin which is compatible with convective removal, can be transported to the filtrate by continuous hemofiltration and hemodiafiltration.[84,85,86] Compared with IHD and peritoneal dialysis, CKRT is better able to maintain stable haemodynamic and homeostasis status, and remove myoglobin and inflammatory mediators.[87] CKRT may therefore, theoretically, be a better choice for blood purification than intermittent KRT in the management of RML. Selected case reports have shown promising results in both pediatric and adult population.[88,89] In a Cochrane systematic review, the authors were unable to conclude whether or not CKRT is a safe and effective option to treat people with RML.[90]

High cut-off and medium cut-off dialyzers have also been found to be useful in myoglobin elimination, though, the clinical benefits of such treatment strategies have yet to be established.[91,92,93] Other extracorporeal therapies like plasmapheresis has been shown to have no favorable effect on outcomes or on the myoglobin burden of the kidneys.[94,95]

CONCLUSION

The clinical features of RML are highly varied and the timing of testing is important. While the classic triad of myalgias, weakness and dark urine still holds it is rarely present and the ephemeral nature of urine myoglobin and the multiple possibilities for false negatives (especially in the current era of using ascorbic acid supplementation in critical illness) make this an insensitive test as well. It requires a high index of suspicion and careful history taking to suggest RML and serum CK is the most sensitive laboratory test likely to result in the crucial early window for volume expansion to ensure dilution of the urine the reduce the risk of renal impairment. The mechanisms of renal injury are as varied as the causes of RML but the essential elements are oxidative stress (and myoglobin toxicity), mechanical injury from cast formation and vasoconstriction/ hypoperfusion.

While the classic approach has been avoiding nephrotoxins and early alkaline fluids (sodium bicarbonate) to achieve alkalization of the urine to decrease precipitation, there is no good quality evidence to support this or any specific fluid

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to achieve expansion in non-overloaded patients. Multiple predictive models are available but if a patient does progress to renal injury this should be managed as with acute tubular necrosis of any cause.

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Clinical Paper

Treatment outcomes of patients with Atopic Dermatitis (AD) treated with dupilumab through the Early Access to Medicines Scheme (EAMS) in the UK

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SUMMARY

BACKGROUND

Dupilumab, a monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling is indicated in dermatology for the treatment of moderate-to-severe atopic dermatitis (AD) in adult and adolescent patients 12 years and older and severe AD in children 6-11 years, who are candidates for systemic therapy. Dupilumab received Early Access to Medicines Scheme (EAMS) approval for adults in March 2017.

OBJECTIVES

The purpose of this study was to assess the efficacy outcomes of treatment with dupilumab in EAMS.

METHODS

A retrospective analysis of adult patients enrolled in the dupilumab EAMS in the UK. Scores were assessed at baseline and follow up, including the Eczema Area and Severity Index (EASI), Investigator's Global Assessment Score (IGA) and Dermatology Life Quality Index (DLQI).

RESULTS

Data were available for 57 adult patients treated with dupilumab for at least 12 weeks; 73.6% of patients had received prior treatment with 3 or 4 immunosuppressants. Baseline scores for the EASI and DLQI were 27.93 (standard deviation, SD 13.09) and 18.26 (SD 6.18) respectively. AD severity scores showed statistically significant improvement at week 16±4 weeks ($p < 0.001$ for all). The mean change in EASI was 14.13 points with 66.7% and 36.7% achieving a 50% (EASI-50) and 75% (EASI-75) improvement in EASI, respectively at $16^{+/-}$ 4 weeks. IGA scores improved by at least two categories for 75% patients. DLQI scores decreased by a mean of 9.0 points, with 80% patients demonstrating a MCID 4-point improvement. For 85% patients, clinicians rated the treatment response as being either 'better' (19%) or 'much better' (65%).

CONCLUSIONS

Dupilumab is associated with a significant and clinically relevant improvements in AD as measured by patient- and physician-reported outcome measures. Importantly, the clinical efficacy, despite the refractory disease of this EAMS cohort, is comparable to that previously reported in clinical trials.

INTRODUCTION

Systemic therapy is typically considered in atopic dermatitis (AD) resistant to topical therapy and where phototherapy is ineffective or contraindicated[1,2]. Traditionally used systemic agents include azathioprine, methotrexate and ciclosporin. Of these, only ciclosporin is licensed in AD and the EMA licence limits use up to 12 months.

Dupilumab, a monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling is indicated in dermatology for the treatment of moderate-to-severe atopic dermatitis (AD) in adult and adolescent patients 12 years and older and severe AD in children 6-11 years, who are candidates for systemic therapy.

In the United Kingdom (UK) the Early Access to Medicines Scheme (EAMS) aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Promising Innovative Medicine (PIM) status was granted to dupilumab in December 2015 and EAMS positive scientific opinion in March 2017. Dupilumab was made available to adult patients with severe AD who had failed to respond, or who are intolerant of, or ineligible for all approved therapies with or without corticosteroids.

The efficacy and safety of dupilumab has been evaluated in pivotal randomised, double-blind, placebo-controlled studies (SOLO 1, SOLO 2, CAFÉ and CHRONOS)[4,7]. It is

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hypothesised that treatment of AD via EAMS would match that shown previously in large RCTs. Therefore, the aim of this analysis was to assess the efficacy in EAMS a pre-license access scheme in the UK.

PATIENTS AND METHODS

Patients

Patient inclusion and exclusion criteria have been listed in Table 1.

Inclusion criteria:

-Signed written informed consent
-Adult patients >18 years with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all approved therapies (ciclosporin)
-Patient has received treatment with dupilumab for ≥3 months before the date of data collection as part of the Early Access to Medicines Scheme
-Patient has returned for at least one follow-up visit since initiation of treatment

Exclusion criteria:

-Patient has been on dupilumab <3 months before the date of data collection
-Patient has not attended any follow-up visits
-Patient has received treatment with dupilumab prior to EAMS e.g. previous enrolment in a dupilumab clinical trial
-The patient has active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 1 week before the first anticipated date for dupilumab administration
-The patient has known or suspected immunodeficiency, including a history of invasive opportunistic infections (e.g. tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the treating physician
-The patient has used any of the following treatments within 5 half-lives (if known) or 12 weeks before the first anticipated date for dupilumab administration (if half-life is not known or not applicable)
-Immunosuppressive/immunomodulating drugs [e.g., systemic corticosteroids (more than physiological replacement doses), ciclosporin, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.]
-Investigational drugs
-The patient has severe or recent (within 12 weeks) endoparasitic (e.g. helminth) infections, suspected infection, or is at high risk for such infections
-The patient has severe concomitant illness(es), new conditions, or insufficiency understood conditions that, in the treating physician's judgment, might result in unreasonable risk to the patient
-The patient is a pregnant or breastfeeding woman, or is planning to become pregnant or breastfeed
-The patient is female and of childbearing potential and is unwilling to use adequate methods of contraception to avoid pregnancy
-The patient has a potential allergy or hypersensitivity to the excipients of the dupilumab product (L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, water for injection, acetic acid

*Italicised text are criteria that were part of EAMS enrolment

Table 1. In-/exclusion criteria

Dupilumab was made available to adult patients in the UK with severe atopic dermatitis who had failed to respond, or who were intolerant of or ineligible for all approved therapies. Dupilumab could be used with or without topical corticosteroids.

The study was a retrospective review of the hospital medical notes, databases and electronic systems of eligible patients (those who had received treatment with dupilumab through the EAMS for more than 3 months) with AD recruited to EAMS at 8 dermatology sites throughout the UK. All data was collected by the clinical teams and overseen by the lead dermatologist for EAMS at each site.

Baseline patient data was available from EAMS entry forms held by the sponsor (Sanofi Genzyme). Patients were independently selected by their hospital physician in line with the EAMS indication; applications were reviewed and accepted by the sponsor's medical lead (RR). Applications were received electronically from sites in a pseudo-anonymised format (initials and date of birth collected), once accepted, patients were assigned an EAMS reference number and applications were held by the medical team.

Follow-up data collection and analysis was conducted by an independent healthcare research consultancy (York Health Economics Consortium, YHEC). Sites were contacted directly and provided with paper/electronic clinical report forms (CRF). Data were collected in an anonymised format by members of the direct care team. Data were only collected for patients who had consented at the start of EAMS. The collected data were sent in an anonymised format (EAMS reference number) to YHEC for data management, analysis and report generation.

All data were entered onto data collection forms from electronic health records by study site contacts at each site.

Instruments, clinician rating and data collection

Severity of atopic dermatitis (AD) was rated by the clinician using the Eczema Area and Severity Index (EASI) [5] which ranges from 0 to 72, as well as the Investigator's Global Assessment Score (IGA) with scores ranging from 0 to 4[1].

EASI scores were categorised as follows: 0 =clear; 0.1 to 1 = almost clear; 1.1 to 7 = mild disease; 7.1 to 21 = moderate disease; 21.1 to 50 = severe disease; ≥51 = very severe disease[6].

Patients completed the Dermatology Life Quality Index (DLQI)[7] with scores ranging from 0 to 30.

The DLQI scores were categorised as follows: 0 to 1 = no effect on patient's life; 2 to 5 = small effect; 6 to 10 = moderate effect; 11 to 20 = very large effect; 21 to 30 = extremely large effect[8].

Absolute and percentage change were recorded for both the EASI and DLQI scores. Also reported was EASI-50 and EASI-75 (50% and 75% improvement in EASI score, respectively). An EASI reduction of 6.6 points indicates a minimally clinically important difference (MCID)[9]; a 4-point reduction is the MCID for the DLQI scores[10].

Clinicians also recorded a response to treatment rated on a 5-point Likert scale: "Much worse", "Worse", "About the same", "Somewhat better" and "Much better".

The timing of follow-up visits varied between patients, therefore time since the previous clinic visit was categorised as follows: 2 to 4 weeks (14 to 27 days); 4 to 8 weeks (28 to 55 days); 8 to 12 weeks (56 to 83 days); 12 to 20 weeks (84 to 139 days; also referred to as 16±4 weeks) and 20 weeks or more (≥140 days).

Data management and Statistical analysis

A total of 8 EAMS sites based in England and Northern Ireland provided data for inclusion in this study. The analysis mainly comprised descriptive statistics. Continuous variables were summarised using mean and standard deviation, with minimum and maximum values reported to provide the

1 http://www.eczemacouncil.org/research/investigator-global-assessment-scale/

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range. Categorical variables were summarised as frequency and proportion.

Inferential statistics were used to assess the statistical significance of observed differences for the 16±4 weeks' timeframe. For continuous scale variables a paired samples *t*-test was performed. For ordinal variables a Wilcoxon Signed Rank test was performed.

Pearson's correlations were performed to assess the relationships between different measures of severity.

No imputation was performed for missing data. Missing values were excluded from relevant analyses. Precise sample sizes are reported for each analysis. Quality control was undertaken on the data as follows: each clinical site was contacted and the anonymised data for 10% of the total patients held at the clinical site were checked against the data recorded in the study database.

The analysis was conducted using IBM SPSS Statistics software (version 24).

Ethics

This was a retrospective analysis of data. Patient consent was obtained prior to enrolment on the EAMS. Anonymised data were obtained directly from the patients' care team. This study was approved by the NHS Health Research Authority (Reference: 19/HRA/0017, 10th April 2018) and all necessary local NHS Trust approvals were obtained.

RESULTS

Patients

The quality control checks revealed no differences between data recorded at clinical sites and within the study database. Figure 1 depicts the number of patients for whom data were available, exclusions and reasons for exclusions. Of the 65 patients treated with dupilumab via the EAMS scheme, 8 were excluded due to insufficient data. The remaining 57 patients comprised 20 (35.1%) females and 36 males (63.2 %) with a mean age of 41.2 years (SD: 14.21 years; range: 20 to 76 years); Gender and age were not available in one and two patients, respectively.

Past immunosuppressant use was reported for 91.2% (52 patients), the majority of which (73.6%; 42 patients) had been prescribed three or four different immunosuppressants. The most common immunosuppressants prescribed were ciclosporin (86.2%; 50 patients), azathioprine (81.0%; 47 patients) and methotrexate (70.7%; 41 patients).

Thirty patients (52.6%) were on one immunosuppressant at time of enrolment and one patient (1.8%) was on two. In these patients, ciclosporin was most common (19.0%; 11 patients), followed by methotrexate (15.5%; 9 patients).

EASI Scores

Baseline EASI scores were available in 55 of 57 patients and ranged from 4.3 (mild disease) to 72.0 (very severe disease)[6] with the most common category being severe disease, and

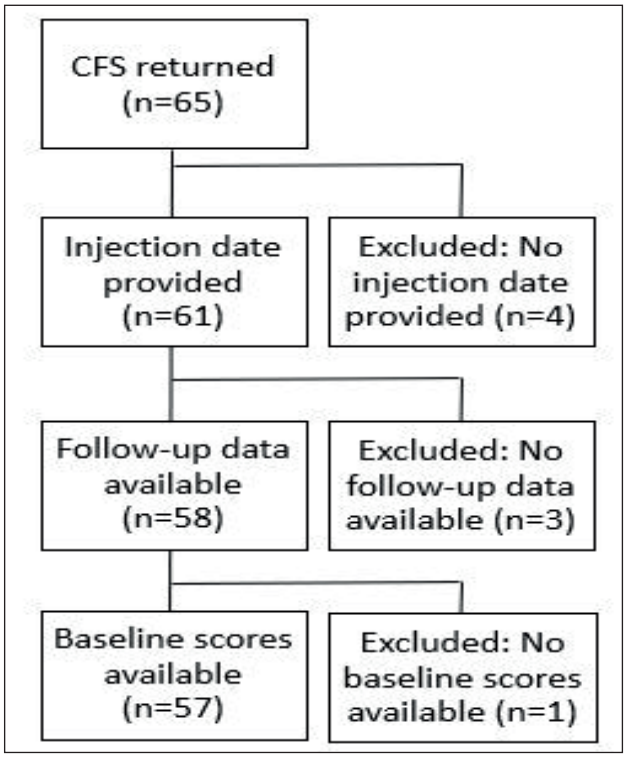

Figure 1.
Diagram demonstrating flow of excluded and included patient data.

Statistic	Measure	All (*n*=55)	Immunosuppressant use at enrolment		Gender	
			No (*n*=26)	Yes (*n*=29)	Female (*n*=19)	Male (*n*=36)
Mean (SD)	EASI score at baseline	27.93 (13.09)	29.99 (14.62)	26.09 (11.50)	24.41 (12.65)	29.79 (13.11)
Frequency (n, % within stratification group)	EASI scores 'clear' at baseline	0	0	0	0	0
	EASI scores 'almost clear' at baseline	0	0	0	0	0
	EASI scores 'mild' at baseline (<7)	2 (3.7%)	0	2 (6.9%)	0	2 (5.6%)
	EASI scores 'moderate' at baseline (7.1-21)	13 (24.1%)	7 (26.9%)	6 (20.7%)	7 (36.8%)	6 (16.7%)
	EASI scores 'severe' at baseline (21.1-50)	38 (69.1%)	17 (65.4%)	21 (72.4%)	11 (57.9%)	27 (75.0%)
	EASI scores 'very severe' at baseline (>50.1)	2 (3.7%)	2 (7.7%)	0	1 (5.3%)	1 (2.8%)

Table 2. EASI Scores at baseline

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			Stratification			
		All (*n*=32)	Immunosuppressant use at enrolment		Gender	
			No (*n*=11)	Yes (*n*=21)	Female (*n*=13)	Male (*n*=18)
	EASI rating at the 16+/-4 week follow-up					
Mean (SD)	EASI score	7.62 (6.26)	6.09 (6.73)	8.42 (6.02)	7.59 (6.16)	7.59 (6.69)
Frequency (n, % within stratification group)	Clear	5 (15.6%)	3 (27.3%)	2 (9.5%)	3 (23.1%)	2 (11.1%)
	Almost clear	1 (3.1%)	1 (9.1%)	0	0	1 (5.6%)
	Mild (<7)	9 (28.1%)	3 (27.3%)	6 (28.6%)	3 (23.1%)	6 (33.3%)
	Moderate (7.1-21)	16 (50.0%)	4 (36.4%)	12 (57.1%)	7 (53.8%)	4 (44.4%)
	Severe (21.1-50)	1 (3.1%)	0	1 (4.8%)	0	1 (5.6%)
	Very severe (>50.1)	0	0	0	0	0
	Change in EASI severity between baseline and the 16+/-4 week follow-up					
		All (*n*=30)	No (*n*=11)	Yes (*n*=19)	Female (*n*=12)	Male (*n*=18)
Mean (SD)	Absolute change in EASI score	14.13 (10.71)	16.04 (12.08)	13.03 (10.01)	11.36 (9.90)	15.98 (11.10)
	Percentage change in EASI score	55.84% (43.01%)	62.46% (53.16%)	52.00% (36.98%)	51.69% (40.63%)	58.60% (45.46%)
Frequency (n, % within stratification group)	MCID reduction	22 (73.3%)	8 (72.7%)	14 (73.7%)	8 (66.7%)	14 (77.8%)
	50% reduction or greater	20 (66.7%)	9 (81.8%)	11 (57.9%)	8 (66.7%)	12 (66.7%)
	75% reduction or greater	11 (36.7%)	6 (54.5%)	5 (26.3%)	3 (25.0%)	8 (44.4%)

Table 3. EASI scores at follow-up

the sample mean values for the full cohort (27.93, SD = 13.09) corresponding to a rating of severe disease (Table 2).

Follow-up EASI scores were available for 32 patients at 16+/-4 weeks (Table 3) with a mean score of 7.62 (SD = 6.26; range = 0.0 to 21.6). No patients had 'very severe' disease at follow-up and only one had 'severe disease' based on EASI score (Figure 2).

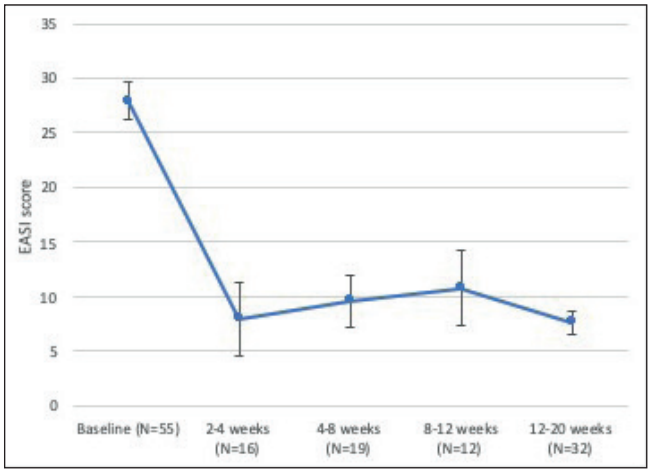

Figure 2. Mean EASI scores at baseline and 16+/-4 weeks

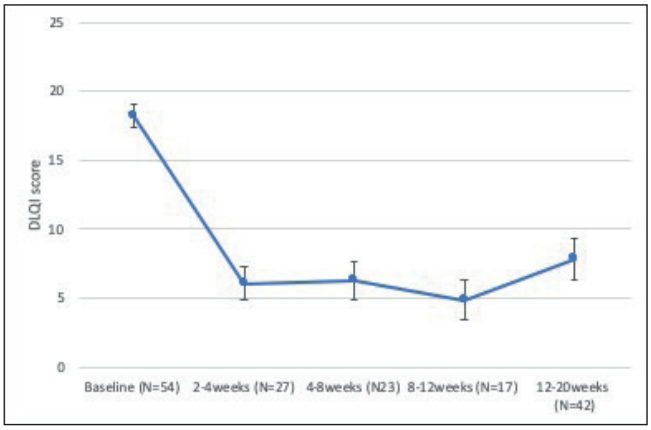

Figure 3. Mean DLQI scores at baseline and 16+/-4 weeks

In 30 patients a baseline and 16+/-4 week follow-up EASI score was available. The mean change in EASI score was an improvement of 14.13 points (SD= 10.71; range of +9 to -33). Mean percentage improvement was 55.84% (SD= 43.01%) between baseline and follow-up at 16+/-4 weeks. EASI-50 was observed in 20 patients (66.7%) and EASI-75 in 11 (36.7%); 22 patients (73.3%) reported a reduction of at least 6.6 points, indicative of a MCID.

A paired-samples t-test indicated that the EASI scores at the 16+/-4 week follow-up were significantly lower than at baseline (p<0.001).

IGA Scores

			Immunosuppressant use at enrolment		Gender	
Statistic	Measure	All (*n*=51)	No (*n*=25)	Yes (*n*=26)	Female (*n*=17)	Male (*n*=34)
Frequency (n, % within stratification group)	IGA scores 'clear' at baseline	0	0	0	0	0
	IGA scores 'almost clear' at baseline	0	0	0	0	0
	IGA scores 'mild' at baseline	2 (3.9%)	1 (4.0%)	1 (3.8%)	1 (5.9%)	1 (2.9%)
	IGA scores 'moderate' at baseline	13 (25.5%)	6 (24.0%)	7 (26.9%)	5 (29.4%)	8 (23.5%)
	IGA scores 'severe' at baseline	36 (70.6%)	18 (72.0%)	18 (69.2%)	11 (64.7%)	25 (73.5%)

Table 4. IGA scores at baseline

Baseline IGA scores were available in 51 of 57 patients. IGA scores ranged from 2 (mild) - 4 (severe) with a median score of 4 (70.8%, see Table 4). Both baseline and 16+/-4 week follow-up IGA scores were available for a total of 28 patients (Table 5). In 21 (75%) patients the IGA ratings improved by ≥

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		All (*n*=34)	Immunosuppressant use at enrolment		Gender	
			No (*n*=14)	Yes (*n*=20)	Female (*n*=11)	Male (*n*=22)
Frequency (n, % within stratification group)	IGA rating at the 16+/-4 week follow-up					
	Clear	6 (17.6%)	4 (28.6%)	2 (10.0%)	3 (27.3%)	3 (13.6%)
	Almost clear	14 (41.2%)	6 (42.9%)	8 (40.0%)	2 (18.2%)	12 (54.5%)
	Mild disease	9 (26.5%)	2 (14.3%)	7 (35.0%)	4 (36.4%)	4 (18.2%)
	Moderate disease	4 (11.8%)	1 (7.1%)	3 (15.0%)	2 (18.2%)	2 (9.1%)
	Severe disease	1 (2.9%)	1 (7.1%)	0	0	1 (4.5%)
	Change in IGA severity between baseline and the 16+/-4 week follow-up					
		All (*n*=28)	No (*n*=13)	Yes (*n*=15)	Female (*n*=8)	Male (*n*=20)
	Increase in severity	1 (3.6%)	0	1 (6.7%)	1 (12.5%)	0
	No change in severity	1 (3.6%)	1 (7.7%)	0	0	1 (5.0%)
	Improvement by one category	5 (17.9%)	2 (15.4%)	3 (20.0%)	2 (25.0%)	3 (15.0%)
	Improvement by two or more categories	21 (75.0%)	10 (76.9%)	11 (73.3%)	5 (62.5%)	16 (80.0%)

Table 5. IGA scores at follow-up

Statistic	Measure	All (*n*=54)	Immunosuppressant use at enrolment		Gender	
			No (*n*=25)	Yes (*n*=29)	Female (*n*=19)	Male (*n*=35)
Mean (SD)	DLQI score at baseline	18.26 (6.18)	19.48 (7.50)	17.21 (4.64)	20.11 (5.13)	17.26 (6.53)
Frequency (n, % within stratification group)	DLQI scores 'no impact' at baseline (0-1)	0	0	0	0	0
	DLQI scores 'small impact' at baseline (2-5)	1 (1.9%)	1 (4.0%)	0	0	1 (2.9%)
	DLQI scores 'moderate impact' at baseline (6-10)	4 (7.4%)	3 (12.0%)	1 (3.4%)	0	4 (11.4%)
	DLQI scores 'very large impact' at baseline (11-20)	29 (53.7%)	9 (36.0%)	20 (69.0%)	9 (47.4%)	20 (57.1%)
	DLQI scores 'extremely large impact' at baseline (21-30)	20 (37.0%)	12 (48.0%)	8 (27.6%)	10 (52.6%)	10 (28.6%)

Table 6. DLQI scores at baseline

		Stratification				
		All (*n*=42)	Immunosuppressant use at enrolment		Gender	
			No (*n*=16)	Yes (*n*=26)	Female (*n*=14)	Male (*n*=27)
	DLQI rating the 16+/-4 week follow-up					
Mean (SD)	DLQI score	7.86 (9.49)	4.44 (7.08)	9.96 (10.27)	8.57 (9.25)	7.52 (9.94)
Frequency (n, % within stratification group)	No impact (0-1)	14 (33.3%)	8 (50.0%)	6 (32.1%)	5 (35.7%)	9 (33.3%)
	Small impact (2-5)	9 (21.4%)	4 (25.0%)	5 (19.2%)	1 (7.1%)	8 (29.6%)
	Moderate impact (6-10)	7 (16.7%)	2 (12.5%)	5 (19.2%)	3 (21.4%)	3 (11.1%)
	Very large impact (11-20)	6 (14.3%)	0	6 (23.1%)	3 (21.4%)	3 (11.1%)
	Extremely large impact (21-30)	6 (14.3%)	2 (12.5%)	4 (15.4%)	2 (14.3%)	4 (14.8%)
	Change in DLQI severity between baseline and the 16+/-4 week follow-up					
		All (*n*=40)	No (*n*=16)	Yes (*n*=24)	Female (*n*=13)	Male (*n*=27)
Mean (SD)	Absolute change in DLQI score	8.98 (7.91)	12.13 (7.97)	6.88 (7.30)	10.54 (9.23)	8.22 (7.26)
	Percentage change in DLQI score	58.85% (42.11%)	75.90% (34.34%)	47.48% (43.60%)	54.64% (44.31%)	60.88% (41.73%)
		All (*n*=30)	No (*n*=11)	Yes (*n*=19)	Female (*n*=12)	Male (*n*=18)
Frequency (n, % within stratification group)	MCID reduction	32 (80.0%)	14 (87.5%)	18 (75.0%)	10 (76.9%)	22 (81.5%)
	DLQI MCID and EASI 50% reduction or greater	16 (53.3%)	8 (72.7%)	8 (42.1%)	7 (58.3%)	9 (50.0%)

Table 7. DLQI scores at follow-up

2 categories, and in an additional 5 (17.9%) an improvement of one category was observed. For one patient there was no change and for another and increase in IGA was observed.

A Wilcoxon Signed Rank test indicated that the IGA scores at the 16+/-4 weeks follow-up (median = 1) were significantly lower than at baseline (p<0.001).

DLQI Scores

Baseline DLQI scores were available in 54 of 57 patients (mean 18.26; SD 6.18, corresponding to 'very large' impact) (Table 6). DLQI scores were available at baseline and week 16+/-4 in 40 patients. The mean change in DLQI score was an improvement of 8.98 points (SD= 7.91; range = 14 to 29 points). A MCID was observed in 32 patients (80.0%). Of the 30 patients for whom both EASI and DLQI change scores were available at the 16+/-4 weeks follow-up, 16 (53.3%) achieved an EASI-50 and MCID in DLQI scores.

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		Stratification				
		All (*n*=26)	Immunosuppressant use at enrolment		Gender	
			No (*n*=9)	Yes (*n*=17)	Female (*n*=7)	Male (*n*=19)
Clinician rated response to treatment at the 16$^{+/-4}$ week follow-up						
Frequency (n, % within stratification group)	Much worse	0	0	0	0	0
	Worse	2 (7.7%)	0	2 (11.8%)	1 (14.3%)	1 (5.3%)
	About the same	2 (7.7%)	0	2 (11.8%)	2 (28.6%)	0
	Somewhat better	5 (19.2%)	0	5 (29.4%)	1 (14.3%)	4 (21.1%)
	Much better	17 (65.4%)	9 (100%)	8 (47.1%)	3 (42.9%)	14 (73.7%)

Table 8.
Clinician-rated response to treatment at follow-up

Measure	EASI at the 16$^{+/-4}$ week follow-up	IGA at the 16$^{+/-4}$ week follow-up	DLQI at the 16$^{+/-4}$ week follow-up	Clinician-rated response at the 16$^{+/-4}$ week follow-up
EASI at the 16$^{+/-4}$ week follow-up				
IGA at the 16$^{+/-4}$ week follow-up	0.89 (p<0.001; n=24)			
DLQI at the 16$^{+/-4}$ week follow-up	0.67 (p<0.001; n=32)	0.75 (p<0.001; n=34)		
Clinician-rated response at the 16$^{+/-4}$ week follow-up	0.47 (p=0.51; n=18)	0.66 (p=0.003; n=18)	0.64 (p=0.001; n=25)	

Table 9. Correlations between endpoints at follow-up

A paired-samples t-test indicated that the DLQI scores at the 16$^{+/-4}$ week follow-up (mean 8.09) were significantly lower than at baseline (mean 17.05; t(39)=7.175, p<0.001).

Clinician-rated response to treatment at follow-up

The most common clinician-rated treatment response for the 26 patients for whom data were available at the 16$^{+/-4}$ weeks follow-up was 'much better' (65.4%). Two patients (7.7%) were graded as worse (105 and 125 days since first injection), while a further two were rated as showing no change (Table 8).

Relationship between endpoints at follow-up

Table 9 shows the relationship between endpoints at follow-up. Positive relationships between severity scales were significant and considered moderate to strong, particularly between the EASI and the IGA (r=0.89, p<0.001).

DISCUSSION

The aim of this study was to investigate the treatment efficacy of dupilumab in adult patients with AD treated in EAMS a pre-license access scheme in the UK.

The results demonstrated a significant improvement in AD severity between baseline and 16 $^{+/-4}$ week follow-up, as measured by EASI and IGA. EASI-50 and EASI-75 improvements were observed in 67% and 37% respectively and importantly a minimally clinically important difference of 6.6 points or more was observed in 73%. IGA scores improved by at least two categories for 75% patients, and by one category for 17.9%. This corresponded with improvements in DLQI scores with a minimally clinically important improvement observed in 80%. Furthermore, a clinician-rated treatment response was reported as either "better" or "much better" in 19% and 65% of patients, respectively.

The efficacy of dupilumab in AD has previously been demonstrated in several randomised controlled trials[3,4]. Due to the potential of selection bias within clinical trials it is important that efficacy of new drugs is also evaluated outside the clinical trial setting. In one recently published real-world study of 19 AD patients treated with dupilumab, a median SCORAD decrease of 55% and increase in patients with IGA of 0/1 from 5% to 61% was observed after 16 weeks[11]. Limitations of that study suggested by the authors included the small number of patients and the fact it was based in a single-centre. Importantly, our larger multi-centre real-world study mirrors these results and the efficacy demonstrated within the clinical trial programme despite the fact patients treated within EAMS had more refractory disease (75% having failed 3-4 prior immunosuppressant drugs, reflecting a more severe cohort that those who access in the real-world setting either by licence, "candidates for systemic therapy", or by NICE criteria "failure on 1 immnuosupressant"[12,13,14]). Of the pivotal studies, the CAFÉ trial most closely represents the EAMS patient population, i.e. failure to respond / intolerant/inadvisable for ciclosporin. In CAFÉ, an EASI-50 and DLQI improvement of ≥ 4 was observed in 85% and 88% of patients, respectively. In the present study, we observed a 67% EASI-50 and 80% DLQI ≥ 4 improvement.

As with any retrospective study based on secondary use of data, interpretation of study endpoints depended on the completeness and quality of the source medical records and the reliability of the abstraction of data from the medical records, meaning potential confounders could not be accurately assessed. Full datasets were not available for all patients enrolled in EAMS due to missing baseline or incomplete follow-up data. Quality control was undertaken on a small subset of patients (10%) to minimise disruption at the clinical site. Another potential limitation is that no safety or adverse events data were recorded as part of this aspect of the study. Further data are required from other real-world cohorts and registries to further understand the efficacy and safety of dupilumab on a wider scale.

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In conclusion, dupilumab is associated with significant and clinically-relevant improvements in AD as measured by patient- and physician-reported outcome measures. Importantly, the clinical efficacy, despite the highly immunosuppressant refractory population in this EAMS cohort, is comparable to that previously reported in large randomised clinical trials.

This work was supported by funding from Sanofi Genzyme

Conflicts of interest

LD, RR and RH are employees of and hold stock options in Sanofi Genzyme.
DOK has received honoraria as a speaker and /or advisory board member for Abbvie, Novartis, Lilly, UCB and Janssen. MAJ has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Amgen, Lilly, Sanofi, Leo Pharma and Pfizer. PL has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Almirall, Actelion, Celgene, Janssen, Lilly, Sanofi, Leo, UCB and Novartis. LS has no conflicts of interest. MC has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for Eli Lily, Leo Pharma, Novartis, L'Oreal, Procter and Gamble, Oxagen, Johnson & Johnson, Pfizer, Regeneron, Sanofi, UCB and Hyphens Pharma. SV has received an educational grant from Abbvie. HC has received honoraria for advisory board participation from Sanofi, Abbvie, Novartis and Janssen.

Contributions

Data collection DOK, MA-J, PL, LS, MC, SV, HLC
Data analysis RH ABS, RR, LD, DOK
Manuscript preparation DOK, LD, RR, ABS, RH
Manuscript review MA-J, DOK, PL, LS, MC, SC, HLC

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Clinical Paper

Impact of COVID 19 on red flag discussions for haematological malignancies within the Belfast trust

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Key words: COVID-19, Haematology, Red flag, Malignancy.

Abstract

Introduction: During the COVID-19 pandemic, there have been suggestions that there will be a reduction in cancer diagnoses, causing a detrimental effect on patients[1]. We therefore conducted an analysis to assess if there has been a reduction in new haematological malignancy diagnoses within the Belfast Health and Social Care Trust (BHSCT).

Methods: We observed a significant decline in diagnostic tests used in the diagnosis of haematological malignancies. We therefore decided to analyse the impact of COVID-19 on the volume of tests performed to see if this impacted the number of new cases of haematological malignancies diagnosed. To ascertain the number of new diagnoses referred to Clinical Haematology we decided to analyse the number of new diagnoses discussed at the local Multidisciplinary Team Meetings (MDM) between March and June 2020 and compare this with the same period in 2019. In line with NICE guidelines[2] there has been no change to the referral pathway for patients with new haematological malignancy.

Results: Results show that there is no significant difference between the number of new malignant haematological diagnoses discussed during March to June 2020 and the same period in 2019. This confirms that the number of new diagnoses remains the same within the two time periods.

Conclusion: This analysis highlights that despite a reduction in primary and secondary care diagnostic blood tests, there is no difference in the number of new cases of haematological malignancies discussed at Haematology MDM throughout the first surge of the COVID-19 pandemic locally.

Introduction

During the COVID-19 pandemic in Spring 2020 there was major reconfiguration in primary and secondary care services within the Belfast Health and Social Care Trust (BHSCT)[3]. This led to a reduction in the number of face to face consultations with patients. As such, the number of samples processed by the laboratories was greatly reduced. Overall, (in both primary and secondary care) there was a 55% decrease in haematological samples processed within the BHSCT at the peak of the pandemic compared with the average weekly number pre COVID-19 pandemic.

Due to the reduction in patient consultations and diagnostic blood sampling, there have been suggestions that there has been a reduction in the number of patients with suspected cancers referred to hospital[1].

The objective for this analysis is to assess if the reduction in laboratory usage affected the number of new diagnoses seen by the Haematology team within the BHSCT during the COVID-19 pandemic.

Method

Data was gathered firstly by assessing the number of samples processed by the haematology lab from February 2020 to June 2020. It was then categorised into inpatient, outpatient or primary care samples.

As new patients are referred from many different specialties within primary and secondary care, and furthermore, not all patients receive treatment (either inpatient or outpatient), we decided to review the number of new patients discussed at the Haematology Multidisciplinary Team Meetings (MDM) in the Belfast City Hospital during March to June 2020 and compared this with the same period in 2019. By following NICE MDM guidelines[2] we felt that the MDM should best reflect the numbers of new patients diagnosed with a haematological malignancy.

Using the numbers of new diagnoses discussed in MDM we then divided these into different diagnostic groups and then use statistical analysis to see how COVID-19 has affected numbers.

Results

Lab usage:

During the five weeks prior to lockdown, the haematology laboratory in the Belfast Health and Social Care trust (BHSCT) was processing an average of 19980 samples per week. On the week Government COVID-19 restrictions commenced (week beginning 15/03/2020)[4] the number of samples dropped to 11017. The week the Government imposed a full lockdown (week beginning 23/03/2020) the

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number of samples processed was 9065 and by mid April (at the peak of COVID-19 cases) this number was 7872. We can see from graph 1 that the greatest reduction in samples was from primary care.

It is interesting to note that the week during which most confirmed COVID-19 cases were diagnosed (week beginning 12th April), corresponded to the week the fewest number of samples were processed[5]. This showed a 79% decrease in primary care samples within the haematology lab compared with a 42% decrease in inpatient and 64% decrease in hospital outpatient samples.

There has been a reduction in nearly all of the different types of haematology profiles tested. The most common blood sample processed by the haematology labs is the complete blood count (CBC). On average, the BHSCT labs are processing 15606 CBC samples per week. This number fell to 8615 on the first week of lockdown and plateaued at 6085 on the week beginning 12th April 2020 (the week with the highest number of new COVID-19 cases)[5].

Another test that is commonly used in haematology (but processed in the Biochemistry laboratory) for the diagnosis of plasma cell malignancy is free light chains (FLC)[6,7]. The average number of samples processed for FLC pre COVID was 313 and during COVID was 184. This is a 41% decrease in samples. However, we are unable to determine how many of these samples were for new patients and how many were performed for monitoring of known patients with a diagnosis of plasma cell disorders.

As many haematological conditions (both malignant and non-malignant) are routinely diagnosed using blood samples from symptomatic patients or diagnosed incidentally[8] when samples are being sent for another reason we therefore conducted further analysis to see how the reduction in samples has affected the number of new malignant diagnoses seen by the Haematology team.

The Haematology Multidisciplinary Team Meeting (MDM):

NICE guidelines state that all patients with a haematological malignancy, non-malignant bone marrow failure or lymphocyte and plasma cell proliferation of uncertain significance are discussed at the weekly MDM[2]. In accordance with NICE guidelines there are two MDMs occurring weekly. One is for leukaemia and myeloproliferative disorders and one for lymphoma and plasma cell disorders.

The trust recommendation for new patient discussions is as follows:

- All patients with a new diagnosis of lymphoma prior to treatment (or as soon as possible after starting treatment)
- All new plasma cell disorders excluding MGUS (only discussed if further investigations are required)
- All new diagnosis chronic lymphocytic leukaemia
- All new diagnosis acute leukaemia

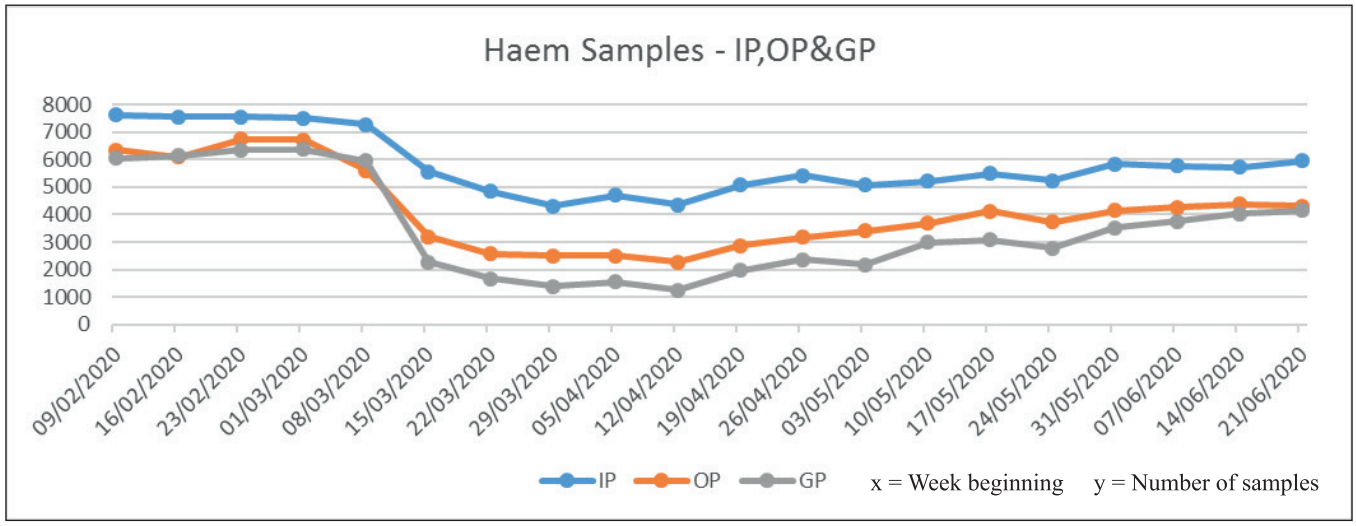
New Haematological diagnosis:

For this analysis, we compared the number of new patients and their diagnosis discussed at Haematology MDM in the Belfast City Hospital from March to June 2020 and the same period in 2019.

This shows that over both four month periods there are similar numbers of patients discussed. Table 1 shows the breakdown of the new cases discussed per month for each diagnostic category that were diagnosed through the laboratories within the BHSCT (any acute leukaemia that was initially diagnosed in another trust has been excluded).

From the data available, there was a mean of 22.5 patients per month discussed in 2019 compared with 20.5 per month in 2020. When the Monthly data was analysed by an unpaired t-test that showed a p value of 0.759. This shows no significant statistical difference between the two time periods. Even if we exclude the number of new lymphoma diagnoses

Graph 1



(IP- Inpatient sample; OP – Outpatient sample; GP – General Practice Sample)

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Table 1:

Diagnosis	Mar-19	Apr-19	May-19	Jun-19	Total		Mar-20	Apr-20	May-20	Jun-20	Total
Plasma Cell	7	1	5	7	20		6	6	1	4	17
Lymphoma	13	3	7	4	27		8	7	5	14	34
CLL	5	1	3	2	11		1	3	0	6	10
Acute Leukaemia	1	0	4	4	9		2	0	4	1	7
Chronic leukaemia	1	1	3	3	8		1	0	1	1	3
MPN	3	1	2	3	9		3	0	2	0	5
MDS	0	1	2	2	5		1	0	0	3	4
Other	0	0	1	0	1		1	0	0	1	2
Total	33	10	30	29	102		26	17	16	32	91

(CLL – Chronic Lymphocytic Leukaemia; MPN – Myeloproliferative Neoplasms; MDS – Myelodysplastic Syndrome)

(as these are mainly diagnosed by biopsy rather than blood test) the p value is 0.407. Therefore, there is still no significant difference between the two timeframes.

Limitations

For the results, there is an assumption that all new patients are discussed in the local MDM, as there has been no change to the NICE guidelines or referral pathways/criteria over this time period. Within the BHSCT, not all new diagnosis MGUS patients are discussed at the MDM. As stated above, only MGUS patients requiring further investigations will be discussed but this policy is unchanged from previous years.

This analysis also does not take into account the actual diagnosis date therefore some patients may have been diagnosed before this period and discussion may have been delayed. Current Northern Ireland Department of Health guidelines state that all patients should have started treatment within 62 days of initial red flag referral and first definitive treatment should be started within 31 days of when the decision to treat was made[9].

We are unable to quantify how many of the free light chain blood tests were performed for new patients and how many were performed for monitoring patients with known diagnoses of plasma cell dyscrasias.

Lymphoma is mainly diagnosed using imaging and biopsy therefore are not generally reliant on blood tests for initial diagnosis.

Discussion:

Clinical Haematology is a specialty that diagnoses and treats a wide range of conditions that can affect the peripheral blood, bone marrow or even the lymphatic system. Each of these conditions presents differently and at different severities.

Patients are referred to the Haematology team from multiple different avenues such as primary care referrals, through the emergency department or from different hospital specialties. Therefore, the number of primary care referrals may not be an accurate representation of new patients diagnosed and treated. This is why, for this analysis, the number of new patients discussed at the MDM was used. As per NICE guidelines[2] all patients with a haematological malignancy or bone marrow failure disorder should be discussed at MDM. Therefore, it is felt that the number of MDM discussions should best reflect the number of new patients referred to Haematology.

The sharp decline in the number of samples processed by the labs within the BHSCT raised the question of how this may affect the number of new haematological conditions diagnosed as many of these affect the peripheral blood.

By comparing the number of new diagnoses discussed at MDM from the first week in March to the last week in June 2019 and 2020 there is no statistical difference between the two time frames. For this analysis, we only counted patients who were initially diagnosed within the BHSCT (this excludes patients with acute leukaemia who were initially referred from other trusts). This is reassuring as the initial fears were the COVID-19 pandemic would have a negative impact on patients and their diagnosis and management[10]. By following the criteria of the BHSCT MDM, the data suggests that there has been no reduction in the number of new referrals. This illustrates that there has been no change to the number of malignancies seen by the haematology team over this time period.

We can also see that there has been a reduction in the number of free light chain samples processed by the labs. However, despite this the number of plasma cell dyscrasias remains stable. This may reflect a reduction in monitoring samples sent due to a reduction in consultations. During this analysis, we were unable to determine how many of the FLC samples were for new patients. As not all new MGUS patients are discussed at MDM (and many are incidental diagnoses), it would be interesting to see whether there has been a reduction in this diagnosis[11].

This analysis has only looked at the number of newly diagnosed patients and how it compares to the same time period in 2019. During the COVID-19 pandemic, there have been some changes to certain treatment regimens as well as

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patient criteria for treatment. Therefore, despite there being no change demonstrated in the number of new diagnoses, we have not analysed whether there has been a change in the number of patients commencing treatment or how this treatment may have differed pre-COVID[12]. As this analysis didn't look at the stage at presentation it will be interesting to see if the overall survival rate remains the same as previous years.

There are many haematological conditions, such as MPN and MDS, that may be diagnosed incidentally on blood tests that were performed for a different reason. Therefore, the long-term effect on these diagnoses will require monitoring over a longer period of time to ascertain the true effect COVID-19 has had[13].

Conclusions

Overall, during the COVID-19 pandemic there has been a major reduction in the number of samples processed by the haematology labs within the BHSCT. The area that has seen the biggest decrease in sample numbers is from primary care. However, despite this there has been a similar number of new patients discussed at the weekly Haematology MDM. The results have shown that there is no significant difference between the numbers discussed in 2019 and 2020. This is very reassuring considering the initial suggestion that there would be a reduction in the number of new cancer diagnoses.

We can see that the number of high grade conditions that may require immediate treatment has remained stable over the two timeframes. This analysis only considered diagnosis and not treatment. Due to COVID-19, there have been changes to some recommended treatments and consequently some patient groups may have been offered only lower intensity treatments to minimise their risk during the pandemic. Therefore, despite the same number of new diagnoses being made, the true long term effects of the COVID-19 pandemic will remain to be seen.

Conflict of Interest: No conflicts of interest to declare.

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Clinical Paper

Diabetes and Covid-19: Clinical implications and novel management strategies

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Abstract

From the outset of the Covid-19 pandemic, diabetes has been identified as attracting higher rates of severe infection and associated mortality. Our understanding of the mechanisms behind these observations continue to develop but it is clear that the comorbidities associated with diabetes play a key role. Here we provide a brief overview of the clinical implications relevant to Covid-19 infection in diabetes and outline the changes we have instituted to adapt the management of both acute hyperglycaemic emergencies and routine diabetes care during the current pandemic.

Introduction

Diabetes is associated with an increased risk for both bacterial and viral respiratory tract infections and this risk is moderated to some extent by glycaemic control. [1,2] In previous novel coronavirus outbreaks, such as the Middle East Respiratory Syndrome (MERS) epidemic, diabetes was associated with an increased risk of infection and an increased risk of mortality when compared to cases without diabetes. [3] Whilst understanding of the interplay between diabetes and Covid-19 continues to develop, it appears to present considerable morbidity and mortality in those affected.

Diabetes and risk of covid-19 infection

The relationship between diabetes and the risk of initial infection with Covid-19 remains unclear. Consideration must be given to the fact that most initial data pertains to hospitalised patients who represent the more severe end of the disease spectrum. An early meta-analysis from Chinese centres found an overall prevalence of 9.7% for diabetes among 1,576 confirmed Covid-19 cases, which is similar to the IDF reported diabetes prevalence for the region (10.9%).[4] Data from the United States however point towards a gross over-representation of diabetes among confirmed cases across all settings, with a prevalence of 30% among 1,320,488 laboratory confirmed Covid-19 cases.[5]

Clinical course in Covid-19 with diabetes

It is clear however, that diabetes has a profound impact on the clinical course for those infected with Covid-19. In a population wide study of 61 million individuals for Public Health England, a prior diagnosis of diabetes conferred an increased odds for in-hospital mortality.[6] Among 23,698 Covid-19 deaths, a third were among those with a prior diagnosis of diabetes, 31·4% in people with type 2 diabetes and 1·5% in those with type 1 diabetes. Compared to those without diabetes, the odds ratios for in-hospital Covid-19 death were 3·51 for type 1 diabetes and 2·03 for type 2 diabetes. A subsequent analysis on the same dataset highlights that overall glycaemic control was a significant modifier of risk.[7] Among patients with type 1 diabetes, for those with HbA1c ≥86mmol/mol, when compared to those with HbA1c 48-53mmol/mol, the mortality was two-fold higher (HR 2.23). A similar relationship was seen in type 2 diabetes (HR 1.61).

The greater severity of covid-19 infection among people with diabetes was also illustrated in the French multi-centre CORONADO study which followed the disease course among 1,317 patients hospitalised with covid-19, all of whom had diabetes.[8] A primary outcome of death or intubation for mechanical ventilation by day 7 was seen in 29% of patients. The mortality rate by day 7 was 10.6% and only 18% were fit to be discharged after 7 days.

The burden of diabetes in intensive care units is seen across multiple cohorts. As a proxy of disease severity, the prevalence of diabetes is greater among hospitalised adults with covid-19 (24%) than in the community (6%) and is greater still among intensive care unit admissions (32%).[9]

Overall, there is a clear picture that disease severity, the need for ICU admission and mortality are significantly higher among patients with diabetes.

The mechanisms which underpin these increased risks are complex. The co-morbidities associated with diabetes undoubtedly exert a significant influence as mediators of risk. The interaction between these factors confer a state of heightened mortality as illustrated in figure 1 below. Frequent concomitant factors such as obesity, hypertension, coagulopathy and acute hyperglycaemia are of particular importance in the pathophysiology of Covid-19.

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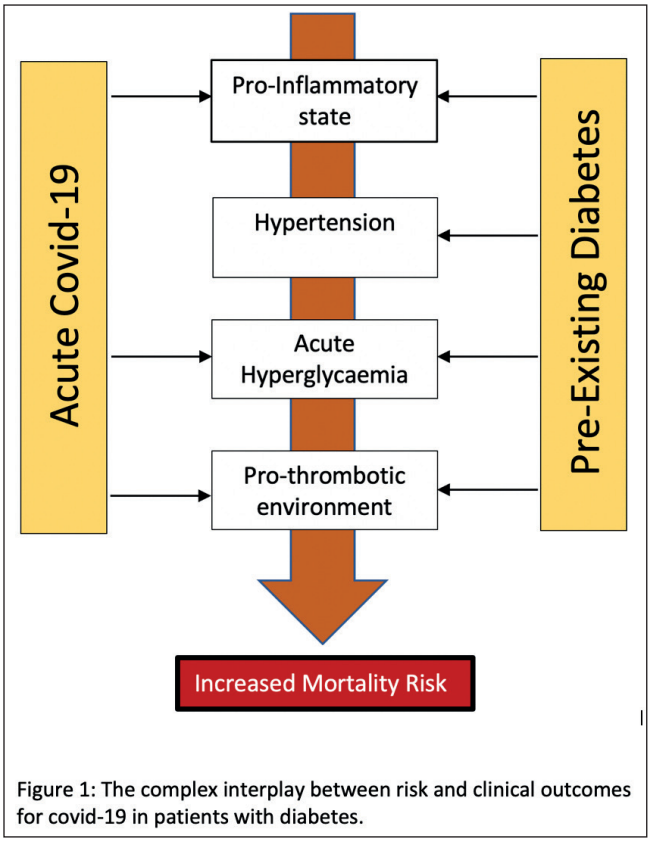

Figure 1: The complex interplay between risk and clinical outcomes for covid-19 in patients with diabetes.

Obesity

Obesity has been shown to be an independent risk for covid-19 severity and mortality. Obesity presents not only mechanical ventilatory constraints but also alters cytokine expression and exerts a pro-inflammatory effect, which may exacerbate the cytokine storm seen in severe covid-19 pneumonitis. Similar to diabetes, there is a high prevalence of obesity among patients requiring intubation and mechanical ventilation. [10] It is also an independent predictor of mortality and the requirement for hospitalisation.[11] One large primary care analysis demonstrates clearly a trend for rising mortality with increasing BMI, reaching a hazard ratio of 1.92 for BMI ≥40kg/m^2.[12]

Hypertension

Hypertension emerged early in reports of covid-19 as a prevalent comorbidity and as having particular association with more severe disease. Early data from China identified hypertension as the most common comorbidity (21.1%) and when present, the odds of severe disease were more than doubled (OR 2.36).[4] A similar picture was highlighted in large European and North American observational studies, principally that a diagnosis of hypertension is more common among positive cases than controls and that the odds of severe covid-19 infection were increased.[13,14] Given that SARS-CoV2 exploits the ACE2 receptor for cell entry, concern quickly arose as to the whether use of renin-angiotensin-inhibitors, frequently used in patients with diabetes, might pose a risk by up-regulating ACE2 receptors and facilitating increased viral entry potential. However, these concerns appear unfounded. Systematic reviews suggest that the prior use of ACE-inhibitors (ACEi) and Angiotensin Receptor Antagonists (ARB) does not increase the odds of infection nor of severe disease.[15,16] There is no evidence to support the withdrawal of ACEi or ARB in patients with covid-19 unless otherwise indicated, with one large retrospective analysis in Chinese centres actually suggesting a reduction in 28-day mortality in patients who continued ACEi or ARB when compared with other anti-hypertensive agents (HR 0.31 vs 0.49).[17]

Coagulopathy

Diabetes is in itself a relatively prothrombotic state, with alterations in the coagulation cascade and fibrinolysis.[18] Severe covid-19 likewise is associated with widespread coagulopathic change and endothelial dysfunction culminating in diffuse microangiopathy and alveolar damage.[19] A retrospective review of Chinese patients with diabetes and Covid-19 found that those who ultimately died had significantly higher prothrombin time 15.2s vs 13.6s and D-Dimer 4.95 vs 0.41μg/mL on admission. [20] The combination of diabetes, obesity, and acute hyperglycaemia present a particular burden for thromboembolic disease in the setting of Covid-19. The precise role of anticoagulation in this setting and optimum therapeutic approaches have yet to be determined

Acute Hyperglycemia

The role of acute hyperglycaemia, as distinct from background glycaemic control referenced above, appears to bear particular relevance in patients with and without diabetes. In the CORONADO study, the plasma glucose on admission was found to have an association with both mortality and the requirement for intubation and ventilation, with the odds rising in line with plasma glucose.[8] Interestingly, this relationship was not found for HbA1c in this cohort. Similarly, a multi-centre study of 1,122 patients admitted to US hospitals with Covid-19 found that the overall mortality rate for patients without diabetes or uncontrolled hyperglycaemia (at least 2 glucose readings >10mmol/l) was 6.2%.[21] The mortality rate among those with prior diabetes was more than doubled at 14.8%. However, most strikingly, the mortality among those with uncontrolled hyperglycaemia, but no prior diagnosis of diabetes, was highest at 41.7%. These findings were replicated in a large Spanish registry analysis where acute hyperglycemia without prior diabetes was independently predictive of disease severity and overall mortality.[22] It is unclear to what extent acute hyperglycaemia per se exacerbates the clinical course or whether severe disease and the associated pro-inflammatory state is reflected in insulin resistance and hyperglycaemia. The ACE2 receptor is expressed on the pancreatic beta cell and acute hyperglycemia might therefore correlate with greater viral exposure and subsequent beta cell dysfunction. The role of acute glycaemic control and the most effective glucose targets in patients with Covid-19 have yet to be elucidated.

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New Onset Diabetes

Some UK centres have reported an increase in presentations with new type 1 diabetes among children in comparison to the preceding five years along with an increase in presentations with severe ketoacidosis.[23] In contrast, results from a German multi-centre study found no overall increase in new presentations with type 1 diabetes[24] but another did find a significant rise in presentations with severe ketoacidosis.[25] However, it is clear that the sequelae of covid-19 infection present challenges to the management of diabetes particularly for those hyperglycaemic emergencies.

Hyperglycaemic Emergencies

Early in the course of the pandemic, many centres including those in the UK saw an increase in presentations with diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS).[26,27] In the setting of Covid-19 infection, there is an upregulation of pro-inflammatory cytokines culminating in reduced insulin output and often severe insulin resistance.[28] This response may be seen in those without prior diabetes but when coupled with the insulin resistant state of type 2 diabetes or the insulopenic state of type 1 diabetes, hyperglycaemic emergencies such as DKA or HHS may ensue rapidly. A review at one UK centre compared adult DKA attendances before and during the Covid-19 pandemic.[29] Although there was a downturn in medical admissions of one third, the absolute number of cases presenting with DKA remained similar between the two periods. The proportion of DKA among patients with type 2 diabetes however rose from 17% pre-pandemic to 37% in the observation period.

The propensity for insulin resistance and hyperglycaemic emergencies coupled with resource demands during covid-19 have required changes in the management of these emergencies. Our response locally has been to adapt existing protocols for DKA and HHS for use during the covid-19 pandemic. We have sought to highlight the tendency toward hyperglycaemic emergencies in patients with Covid-19 and its associated insulin resistance. Central to change in management was to rationalise fluid and electrolyte replacement in patients with severe pneumonitis, to mitigate the risk of fluid overload and third-space effect. The concomitant risk profile in these patients for severe disease and mortality was a critical consideration and early referral for intensive care unit management, where appropriate, is recommended.

Alongside this upstroke in DKA/HHS there has also been a considerable burden of hyperglycaemia in non-diabetic patients with covid-19.[22] A number of reports describe marked insulin resistance in cases of severe Covid-19 with very high insulin requirements.[30] There appears to be some correlation between markers of cytokine release, disease severity and the resulting degree of insulin resistance.[28] Coupled with the now-widespread use of Dexamethasone[31] for covid-19, along with prolonged enteral feeding in intubated patients, there are marked demands on diabetes management resources for acute services. In response to this, a number of sites have been forced to implement DKA/HHS management using subcutaneous insulin where resources may be inadequate to meet the demands for typical intravenous insulin. Diabetes UK have subsequently published guidance on the management of DKA using of subcutaneous insulin for less severe cases of DKA in the UK.[26]

Likewise, existing guidance has been modified for the management of steroid-induced hyperglycemia and covid-19 related hyperglycaemia for use in hospital inpatients.[32]

Drug Management

Adjustments to diabetes medications are integral to the management of many hospitalised patients but there are particular concerns in the setting of covid-19. A summary is provided in table 1 below.

Metformin use should generally be suspended until the patient's renal function and clinical status are known. It is often withheld until the patient recovers, however recent observational evidence suggests a potential survival benefit in women.[33] Where renal function and clinical condition allow, Metformin may be continued.

SGLT2 inhibitors should be held owing to the risk of volume contraction, renal impairment and euglycemic ketoacidosis in the setting of covid-19.

DPP4 inhibitors and GLP-1 analogues are generally safe to continue though the latter may cause nausea in patients who are acutely unwell. Both classes have anti-inflammatory properties and DPP4 is also a target receptor for SARS-CoV2. Observational data suggest a survival benefit in patients supplemented with Sitagliptin with a two-fold reduction in mortality (HR 0.44) but randomised controlled trial data are lacking.[34]

Sulphonylureas do not pose particular risk or benefit but it is advisable to stop these drugs in patients unable to eat or drink. They may be useful in the setting of steroid induced hyperglycaemia, but their use may be limited where there is severe insulin resistance.

Drug Class	Advice
Metformin	Review renal function and clinical status. Continue where possible.
SGLT2 inhibitors	Hold for all acutely unwell patients until recovery.
DPP4 inhibitors	Safe to continue.
GLP1 Receptor Agonists	Safe to continue. May cause GI side effects in those unable to eat in the setting of acute illness.
Sulphonylurea	Hold initially in patients not eating. May be useful in milder cases of steroid-induced hyperglycaemia.

Table 1:
Diabetes medication advice in the setting of Covid-19

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Outpatient Management

Addressing covid-19 has demanded significant restructuring of diabetes care delivery across Northern Ireland. Given the particular risks faced by patients with diabetes, maintaining care, support and education has been imperative. As has been the case in most settings, review consultations have been delivered virtually with face-to-face care restricted to emergencies-only across adult, transition and antenatal services. Direct patient contact has generally been reserved for high acuity situations such as new diagnoses of type 1 diabetes, diabetic emergencies, high risk pregnancies and active diabetic foot disease. There is concern, however, that the deferral of routine screening services for patients with diabetes will lead to an inevitable backlog of untreated complications in the post-Covid period.

The use of telemedicine has proved invaluable in delivering multidisciplinary education to patients. This has enabled us to continue routine diabetes monitoring as well as initiate new medications and diabetes technology remotely.

To facilitate patient access to specialist advice, a regional diabetes helpline and email address were established to offer specialist diabetes nursing support directly to patients 7 days per week.

Summary

Patients with diabetes face a more severe clinical course and significantly increased mortality when infected with Covid-19. The concomitant risk factors associated with diabetes appear to play a key role as mediators of this response. Increases in demand for diabetes services and the reconfigurations of secondary care have necessitated considerable adaptations in the provision of diabetes care and the institution of Covid-19 specific treatment approaches. Our understanding of how best to manage diabetes in this setting continues to develop.

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Clinical Paper

A *surge* in appendicitis: Management of paediatric appendicitis during the COVID-19 surge in the Royal Belfast Hospital for Sick Children.

Colvin D, Lawther S

ABSTRACT

Background

Traditional surgical dogma is that paediatric appendicitis necessitates an appendicectomy; however there is an increasing cohort of evidence suggesting that non-operative management (NOM) using antibiotic therapy is safe and effective. During the COVID-19 surge (April – June 2020) with centralization of paediatric surgical care and risks from anaesthetics to both patients and staff a NOM pathway was used to manage clinically diagnosed appendicitis in the Royal Belfast Hospital for Sick Children (RBHSC).

Methods

Prospective data collection was undertaken of all children (<16 years) diagnosed with appendicitis who entered the NOM pathway in RBHSC from 01/04/2020 to 30/06/2020. This was compared to a cohort from the same timeframe in 2019. Primary end-points were inpatient success rate of NOM and 30-day success rate of NOM (success defined as no appendectomy performed).

Results

47 patients completed the NOM pathway, with 43% (20/47) suspected to have complicated appendicitis. The cohort was similar to that of 2019 in terms of age (p=0.1) and sex (p=0.8), but was 155% larger (42 v. 20).

For those with simple appendicitis, there was a 96% (26/27) success rate of NOM on discharge, with a 93% (25/27) 30-day success rate. For complicated appendicitis, there was a 40% (8/20) success rate on discharge, with a 30% (6/20) 30-day success rate.

Conclusion

The use of a NOM pathway for paediatric appendicitis during the COVID-19 surge in Northern Ireland was safe and effective for staff and patients. With a small sample size and restricted follow up more evidence is required to prove if this is an effective treatment modality with a return to normal theatre availability. In the interests of antibiotic stewardship we would not advocate NOM pathways utilisation by non-surgical clinicians.

Key words

COVID-19, appendicitis, paediatric, antibiotics, non-operative

Background

Traditional surgical dogma is that paediatric appendicitis necessitates an appendicectomy, however there is an increasing cohort of evidence to suggest that non-operative management (NOM) with antibiotic therapy has a role.

Prospective studies utilising antibiotic therapy in simple or uncomplicated paediatric appendicitis have resulted in 92-94%[1,2] success rates as an inpatient, with 30 day success rates of 89%[2]. In complicated appendicitis (perforation or abscess) primary antibiotic therapy can achieve an inpatient success rate of 66%[3]

Setting

During the primary surge of COVID-19 in Northern Ireland (April – June 2020), working practices for children with acute surgical conditions changed. All children (<16 years old) with suspected appendicitis were referred to the general surgery team in the Royal Belfast Hospital for Sick Children (RBHSC), whereas previously, for some children their care was provided by adult surgical services in district general hospitals. All elective operations were appropriately suspended in RBHSC to allow for this increase in emergency care, as well as reducing the potential risk to patients of anaesthesia during the pandemic[4].

In an effort to protect theatre staff from potentially COVID-19 positive patients and the potential risks of anaesthesia in a COVID-19 positive patient a decision was made by the surgical team to develop a NOM pathway. This utilizes a scoring system[5] to discriminate between simple and complicated appendicitis, and components of our department's original post-appendicectomy antibiotic pathway with separate arms for suspected complicated and simple appendicitis.

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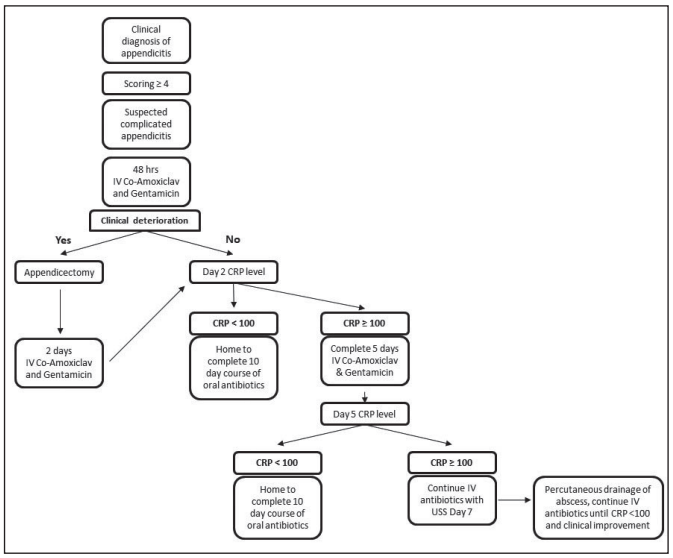
Aims

This paper outlines our experience during the COVID-19 surge and compares it to our caseload from the same timeframe in 2019 when patients were managed primarily operatively.

Patients and methods

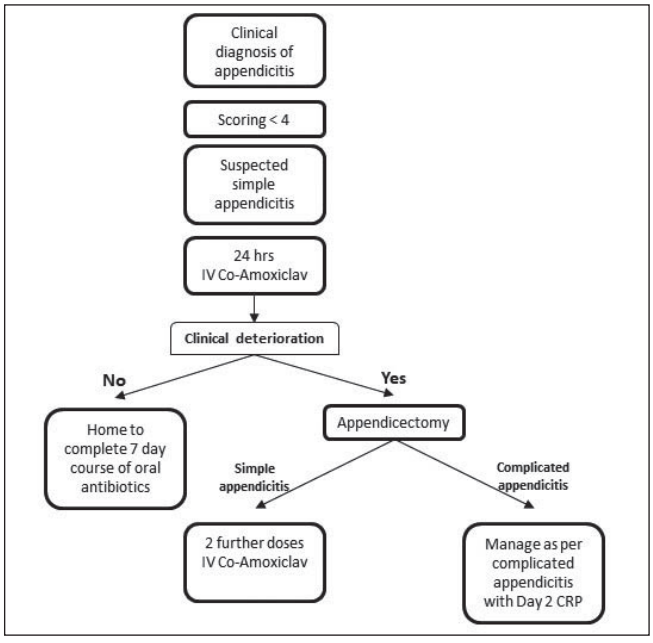
Figure 1



We prospectively collected data on all patients diagnosed with appendicitis <16 years old managed in RBHSC from 01/04/2020 to 30/06/2020, during the COVID-19 surge phase in Northern Ireland. Not included were patients who were commenced on antibiotic treatment by clinicians outside of the Paediatric Surgical team in RBHSC or did not follow the NOM pathway.

Primary endpoints included inpatient success rate of NOM and 30 day success rate or NOM (success meaning no appendicectomy performed during admission or within 30 days of discharge).

Figure 2



The NOM pathways are outlined in **Figures 1 & 2**. During NOM treatment if the patient exhibited clinical deterioration on review by a consultant surgeon, they would proceed to an appendicectomy.

These findings were then compared to previously collected data on patients managed in RBHSC from 01/04/2019 to 30/06/2019 on the aforementioned post-appendicectomy pathway using Student t-test, or Fischer's exact test where applicable. Significance was set at $p < 0.05$.

Results

During this 3 month surge phase, 51 patients with acute appendicitis were managed in RBHSC with 47 entering the NOM pathway (92%). Median age of all patients was 10 years (IQR 8-12 years), and 71% (36/51) were male. None of the patients provided a positive COVID-19 swab on admission. 10% of patients (5/51) underwent an ultrasound to aid diagnosis.

Table 1

NOM pathway appendicitis	April – June 2020 (COVID SURGE)		April – June 2019 (Comparison)		
	N =	%	N =	%	p=
Patients	47		20		
Age (median)	10 years		9 years		0.1
Male	33/47	70%	13/20	65%	0.8
Average length of stay	3.2 days		3.5 days		0.7
Successful NOM on discharge	34/47	72%			
Re-admission	6/34	18%	1/20	5%	0.2
Successful NOM 30 days post-discharge	32/47	68%			

Overall 72% (34/47) of patients were successfully managed with antibiotics alone until discharge with an 18% (6/34) readmission rate at 30 days. 2 of these readmitted patients went on to have an appendicectomy (**Table 1**). In comparison to the same time frame in 2019, there was an increase in admissions from 20 to 51 cases (155% increase).

For suspected simple appendicitis, 96% (26/27) were successfully treated with antibiotics on their initial admission, with a 30 day readmission rate of 19% (5/26). 1 of these patients required an appendicectomy on readmission giving a 30 day success rate for NOM of 93% (25/27).

Table 2 outlines the results of patients suspected to have complicated appendicitis. 40% (8/20) of patients were successfully managed with NOM, 3 (15%) required abscess drainage and 9 (45%) proceeded to appendicectomy. Of the NOM patients, 2/8 (25%) were readmitted within 30

Table 2

Complicated appendicitis	April – June 2020 (COVID SURGE)		April – June 2019 (Comparison)		
	N =	%	N =	%	p=
Complicated appendicitis	20/47	43%	12/20	60%	0.3
Age (median)	10 years		9 years		
Male	14/20	70%	7/12	59%	0.7
Average length of stay	5.2 days		5.1 days		0.9
Successful NOM on discharge	8/20	40%			
Re-admission	5/20	25%	1/12	8%	0.4
Re-admission NOM	2/8	25%			
Re-admission (Had operation)	3/12	25%	1/12	8%	0.6
Successful NOM at 30 days	6/20	30%			

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days, giving a 30 day success rate for NOM in complicated appendicitis of 30% (6/20). Both of the readmitted patients subsequently underwent an appendicectomy on readmission. All patients who were suspected to have complicated appendicitis and had an appendicectomy had this diagnosis confirmed on histopathological assessment.

Discussion

The lifetime risk of appendicitis is between 6-9%[6,7] with a known peak between 10-20 years old[8]. For over a century[9,10] an appendicectomy has been the mainstay of treatment, however in an effort to reduce morbidity and the risk of removal of a normal appendix, NOM in children has been shown to be effective[11].

NOM of appendicitis in environments without access to emergency surgical care is also well established[12,13]. During the COVID-19 surge it appeared to be an appropriate step to utilise antibiotics as the primary treatment modality for appendicitis with the understanding that the established practice of appendicectomy was available if there was any evidence of clinical deterioration. Although only 1-2% of COVID-19 cases have been in children, the risks to staff of general anaesthesia in a COVID-19 positive patient were significant[14] with aerosolization of virus and contamination of the theatre environment. Previously patients with appendicitis would undergo appendicectomy on the day of admission, or if admitted overnight, the following day. During the surge period there was no rapid method for identifying COVID-19 positive patients in the normal timeframe between admission and theatre. Every procedure therefore required full personal protective equipment (PPE) and theatre deep cleaning as asymptomatic carriage and transmission to healthcare workers by children has been well documented[15]. From August 2017 to January 2019; 56% of emergency appendicectomies were performed laparoscopically in RBHSC. During the COVID 19 surge there was concern that uncontrolled expulsion of laparoscopic gas and surgical smoke plume may lead to virus transmission to staff from even asymptomatic patients. With a lack of effective PPE and surgical equipment to improve staff safety, the initial departmental decision was to use the open approach when surgical intervention was deemed necessary.

Our results for suspected simple appendicitis managed non-operatively are in line with international results (96% and 93% at discharge and 30 days vs. 92-94%[1,2] and 89%[11] respectively). Relying on clinical diagnosis without radiological (again in an effort to reduce staff exposure) or intra-operative evidence would suggest that some patients may have been over treated, however our department's negative appendicectomy rate over the preceding two years has been 3% with no change to personnel.

For complicated appendicitis 40% were successfully managed non-operatively which is lower than other centres (66%)[3]. The majority of patients undergoing an appendicectomy for failed NOM were operated on within 24 hrs of commencing treatment and it may be reasonable to suggest that if this had been a randomised trial, a longer period of NOM may have been tolerated by the clinical team. It was hypothesised that the rate of complicated appendicitis would increase, expecting parents to be reluctant to attend the emergency department early in a disease process with concerns about coronavirus transmission. However in comparison to the previous year, this proportion of complicated appendicitis fell (60-43%).

Recurrent appendicitis

For suspected simple or uncomplicated appendicitis, long term recurrence rates with histologically confirmed appendicitis have been published from 16-17%[16,17] over follow up periods of up to 5 years.

For complicated appendicitis, long term recurrence rates vary depending on the feature which defines complicated. In acute perforated appendicitis, recurrence rates of 8% at 7 years follow up have been documented in retrospective studies[18]. For those with an appendix mass, one systematic review calculated 20.5% recurrence rates (with follow up ranging from 6 months to 13 years)[19]. These findings form the statistical basis for informed consent with patients and their parents regarding interval appendicectomy during our outpatient review in RBHSC following NOM.

Recommendation

Utilizing this pathway during the COVID-19 surge appears to have been a safe and appropriate step. Most patients with presumed simple appendicitis can be treated with antibiotics alone and there are some patients with suspected complicated appendicitis who can be managed non-operatively. However drawing conclusions that abandoning primary appendicectomy for both complicated, and simple appendicitis would not be advocated by our team. Without review by an experienced surgeon, over-treating abdominal pain in the emergency department, of which appendicitis typically accounts for 1%[16], may lead to poor antibiotic stewardship. There is also a concern about long term sequelae of NOM; recurrent appendicitis, adhesions, chronic abdominal pain and the risk of a missed neuroendocrine tumour. All patients involved in this pathway have been offered an outpatient discussion regarding an interval appendicectomy.

With an ongoing concern about a second spike in COVID-19 cases, or other future pandemics, we believe that similar NOM pathways in similar settings may be of benefit for the health service in Northern Ireland, without detriment to our paediatric patients.

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Clinical Paper

Developing a Communication System During the COVID Crisis for the Relatives of Critically Ill Patients

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Provenance: Externally peer reviewed

Introduction

Communication was tested in many ways during the coronavirus disease (COVID) crisis of 2020, with the most profound effects felt amongst the relatives of those patients who were in hospital, particularly those patients in intensive care where the patient themselves is unable to communicate with their family for various reasons. The Nightingale hospital COVID Intensive Care Unit (ICU) was set up in Belfast in response to the COVID threat. During its period of operation, a total of 47 patients were admitted and cared for within this ICU. 5 of these patients unfortunately died during their hospital stay. Due to the restrictions in place during this time, visitors were not permitted to see their critically unwell relatives in hospital. This was an extremely distressing reality that our patients' relatives faced and for the most unfortunate ones, they didn't get to say goodbye to their loved ones in the way that they usually would do in hospital. It is well recognised that good communication is crucial in healthcare, especially when it comes to the critically unwell. Incomplete communication with family members can have a hugely negative impact on the family [1] and increases complaint rates [2]. There are many psychological effects of critical illness on family members and effective communication plays an important role in ameliorating these effects.

The Nightingale hospital was also an extremely challenging new working environment for staff. Altered shift patterns and the wearing of personal protective equipment (PPE) made communication frustrating for them. Staff were unable to provide daily communication with family via their usual methods therefore innovative solutions were required to overcome this problem. In an effort to ease work burden on the intensive care staff and more importantly to ensure that families were being adequately communicated with, we formed a unique phenomenon to our trust in what became known as 'The Family Communications Team' (FCT). It consisted of three anaesthetic trainee doctors working from a remote site that was separate to the ICU to provide daily communication with patient relatives. A rapport was formed with patients' relatives and they were supported as best possible on their emotional journey. This report shows how this communication system was effective and how it helped to ease the suffering of those families who were the most severely affected during the COVID crisis in Northern Ireland.

Initial challenges

When the decision was made that there was a role for FCT to update relatives of the patients in the COVID ICU there were many issues that needed to be addressed before commencing. These included how the FCT would access the clinical information without adding to the clinical team's workload at an already stressful and busy time when one of its main aims was to reduce their burden. The FCT needed to access information in a timely manner so that relatives were not waiting until late at night for phone calls. There also needed to be a system in place for adequate documentation of the communication provided. As well as these issues, there was also initially a concern regarding staffing numbers and whether the team would be suitably equipped to cover a service over seven days a week.

Following several discussions and suggestions it was decided that 'Microsoft Teams' would be a useful platform to use. The NHSx Website was an excellent reference for COVID Information Governance advice with regards to video conferencing, using third party applications and working from home. It confirmed that due to unprecedented times it allowed for different ways of working as long as due care regarding encryption was taken. [3] The use of Microsoft Teams has been endorsed throughout the Belfast Trust since the outbreak of the pandemic. It enabled local and remote access to a series of live documents that could be edited and archived as necessary. This meant that the FCT were able to access clinical information as it was being updated continuously without needing to disturb the clinical team.

As the FCT service was commenced at the beginning of the outbreak, we were unsure of patient numbers and how many people would be required to staff the FCT to sustain the service, especially since the Nightingale unit could potentially accommodate 200 patients if required. The service was initially set up as a group of three anaesthetic registrars who due to pregnancy were working non-clinically during the pandemic in accordance with guidance. The service was also discussed with a number of other specialties

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who had staff working non-clinically and had offered to help out. However, it soon became clear that prior knowledge of working in ICU would be required to interpret the patient information and adequately explain this to the relatives. Fortunately, due to numbers remaining fairly low in Northern Ireland during the initial wave of COVID-19 we managed to sustain the service with just three members of staff.

Method

The clinical team were using Microsoft Teams for their handover document which was updated continuously by the doctors throughout both day and night shifts. Following the daily consultant ward round the clinical team were also completing a brief relative communication template. This document used a code to outline the patient's trajectory over the previous 24 hours and summarise any key points. (Appendix 1) As the FCT were able to access both the clinical handover and the relative communication template documents together this ensured that up to date information was being provided to families. With the added benefit of the team consisting of anaesthetic doctors, the team were able to apply their own knowledge and experience to each patient, discuss the likely trajectory for the patient and answer specific questions. The FCT were also available on a daily basis via telephone for staff in the ICU regarding any patient issues or information that the staff wanted families to know. This worked both ways, as families were able to leave messages with the FCT for example often family members would thank nursing staff especially for their care and attention.

When patients were admitted to the COVID ICU a prompt script for the initial conversation to relatives was used to explain to them what to expect with regards to communication and updates whilst their relatives were in ICU. This outlined that they would get one phone call to one relative every day. The FCT explained there would be a small team of doctors working in the communications team and that we were all used to working in intensive care however at this time were not looking after their relatives directly. Instead we were working closely to support the ICU team and gather all the relevant information to pass onto the relatives. We would also be in a position to feedback any issues to the clinical team. It was clearly stated that if their relative had any sudden deterioration or change in condition between the daily updates that a member of the clinical team would contact them directly in the interim. After each daily discussion with relatives, a summary of the conversation was documented into a table on the relative communications document and this was then archived on a weekly basis as a record of what information had been discussed and any queries that were raised by the families. These archives have since been printed out and filed as hard copies in the patients' notes as a record of the communication that took place with their relatives.

Ongoing challenges

One of the main challenges faced during the process was communication with non-English speaking families which required the use of interpreters. Initially we used the Health and Social Care Northern Ireland (HSCNI) Interpreting services and booked an interpreter to come to the office in person. Using speakerphone, we were able to communicate with these relatives. However, as calls were covered from home at the weekends, we found it easier to use the Big Word service and conference calls for communicating with these families.

Another challenge were video calls. As time progressed and patients were in the unit for increasingly prolonged admissions the hospital acquired some tablet devices. The Intensive Care Society suggested considering video call communications. [4] This brought its own challenges, both logistically and ethically. It was impossible for unconscious patients to consent to this and it was difficult to control who had access to the video calls at the relatives end and whether they could be recording them to share with others. Patient dignity needed to be maintained on these calls as well as respecting the confidentiality of other patients in nearby beds. It was even more difficult to facilitate this for the non-English speaking relatives without the use of interpreters and the clinical team were unable to communicate on the calls as they were in full PPE. The commonly used platform 'Zoom' is not formally encrypted, however a standard operating procedure was drafted to enable video calls to take place for relatives using this App. The option of video calls was mentioned to families during their daily update and using an email address they provided to us we agreed to try and facilitate a video call if the clinical team were available. The FCT advised relatives to speak so the patient could hear familiar voices. Communication from the clinical team would be very limited due to PPE therefore the FCT would phone the relatives back after the video call to answer any questions they may have after seeing their relative in intensive care.

Collecting Results

A short questionnaire was sent via email to patients for the attention of their relatives at approximately 6 weeks following hospital discharge. (Appendix 2) These email addresses were provided by patients after a consent process. The results and feedback from these questionnaires have been used to evaluate this service alongside the personal experience of the FCT and feedback from the clinical team.

Results

Out of the 47 patients that passed through the Nightingale COVID ICU, 43 patients' families were communicated with using the FCT. For those 4 families that didn't receive communication, their relative was admitted and discharged from the ICU before the set-up of the FCT. They were communicated with by other means, but this proved suboptimal as is demonstrated in our results.

The response rate for the questionnaire sent to relatives following hospital discharge had a 60% response rate. This

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questionnaire didn't go to those families whose relatives had died in ICU, as we didn't have access to their email address and didn't want to ask for it as we felt that would have been insensitive. Of those who responded, 91% rated the standard of communication received from the FCT as 'good' or 'very good' compared to 33% who did not receive communication by the FCT. 68% of the respondents felt that the communication they received from the FCT helped them to understand their relatives stay in ICU a 'great deal' whereas none of the relatives answered this response when they were not communicated with by the FCT. 59% of relatives felt that communication by the FCT helped them cope a 'great deal' better with their relatives stay in ICU.

Any comments given were positive (some examples are displayed below). The FCT received positive feedback on an almost daily basis from families that were extremely thankful for communication updates. When this praise was passed on to nursing staff it helped morale in what were extremely challenging and uncertain working conditions. It was obvious from the documentation of the daily discussions that the team built a rapport with families and they felt supported at a difficult time. When these patients were all followed up at a virtual 6 week follow up clinic, several of them commented on how pleased they were that their families had received excellent communication and were comforted to know that their relatives were being updated daily during their ICU stay.

Examples of comments received from families:

'The phone calls were very detailed letting us know fully the situation and helping us to understand all that was going on. We were able to ask questions and felt we were getting the answers we needed.'

'I appreciated the consistency that I spoke to the same doctor every day'

'Communication was good and explanations given in plain language, also questions were answered or addressed immediately. Thank you all'

'We would like to thank Dr.X from the bottom of our hearts, she helped our family through the most difficult period that we have ever experienced'

'The anxiety I had was unbearable but thanks to Dr X I somehow managed to cope just about and continue being strong for the rest of our family'

'The doctors were amazing, ringing me every day with a detailed update. They explained things in simple terms when I didn't understand and no question was too much or too silly for them. I genuinely can't thank them enough for the support and time they gave me'

Examples of comments received from patients:

'My wife and son received great updates on my progress. The team always portrayed a very caring attitude. Receiving updates at the same time every day was important'

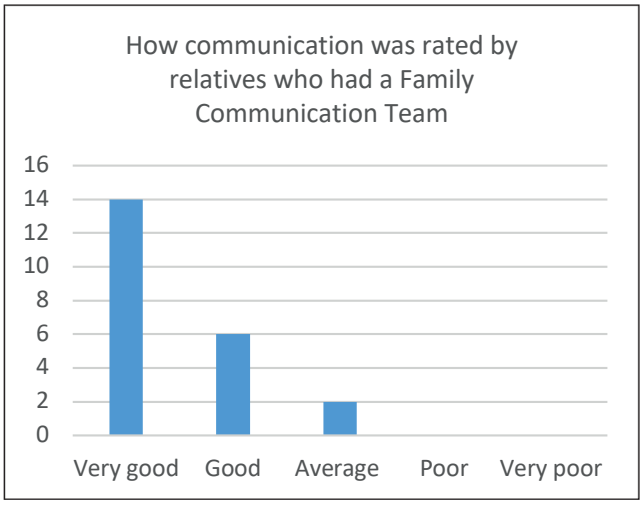
'She found the family updates extremely useful and she was very grateful for the regular and compassionate calls'. (patients commenting on his wife's experience).

'She developed a relationship with the doctor. It gave her hope' (patient commenting on his wife's experience)

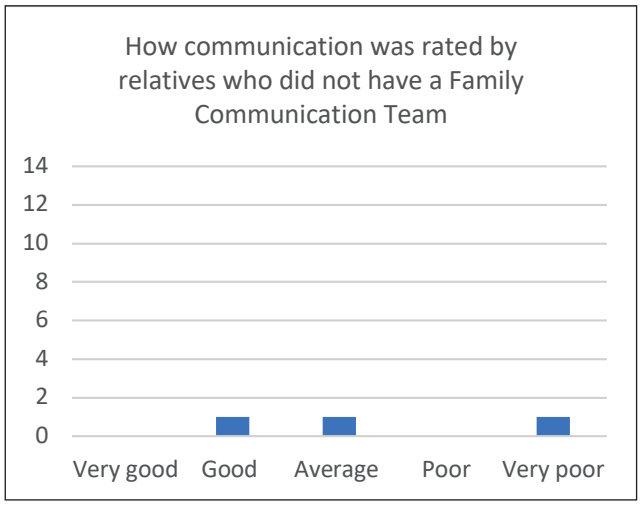
Results

Graphs 1 and 2 shows how families rated the communication they received whilst their relative was in intensive care.

Graph 1



Graph 2



Graphs 3 and 4 shows how the communication families received helped them understand their relative's stay in intensive care better.

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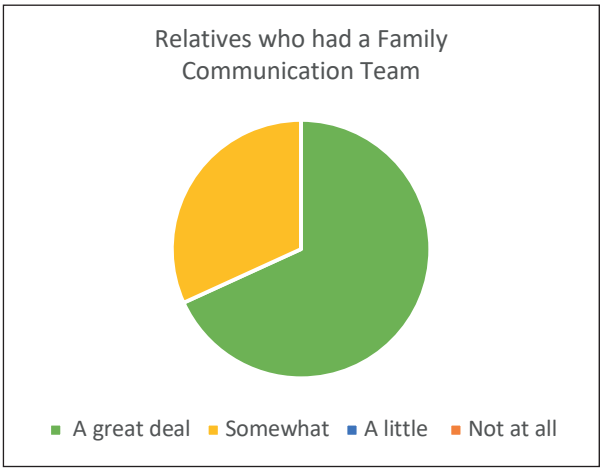
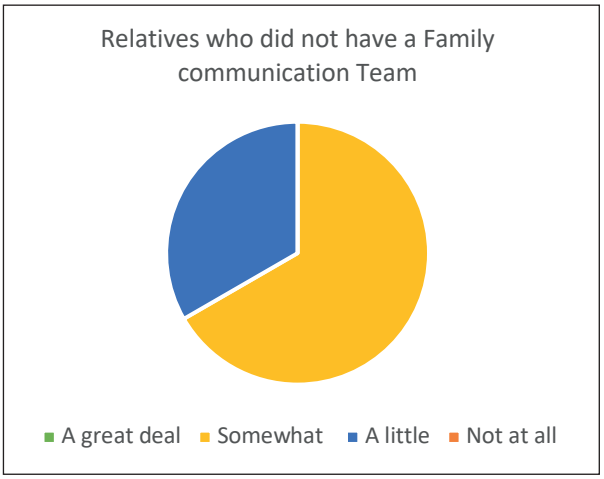
Graph 3

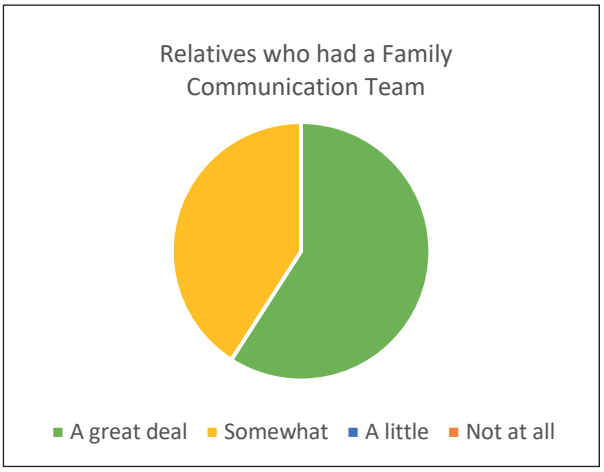


Graph 4

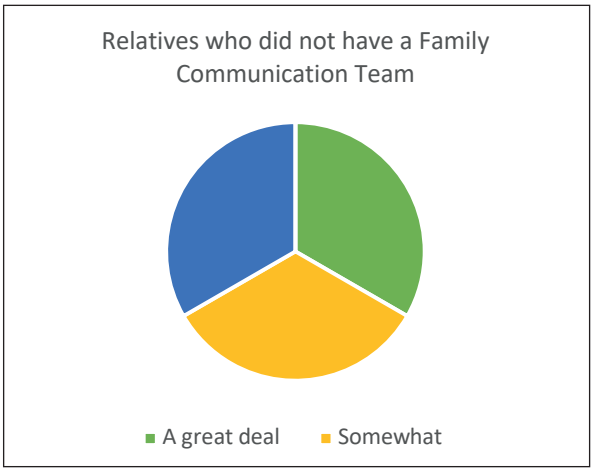


Graphs 5 and 6 shows how the communication families received helped them cope with their relative's stay in intensive care better.

Graph 5



Graph 6



Discussion

The severe restrictions put in place for hospital visiting during the COVID crisis, meant that there were limited options for families as they could not visit hospital. Furthermore, usual communication via telephone to families from the clinical staff was made more challenging due to staff workload and the wearing of Personal Protective Equipment (PPE). This unique situation created ethical grey areas when it came to communicating and updating the patients realtives[5]. Guidance on information governance states that in circumstances such as these, it may be more harmful to patients not to share information than it is to share it [6]. After addressing these many challenging, the formation and delivery of the FCT within the Nightingale ICU eased workload of the clinical staff and kept relatives informed to the best of our ability at the time. When feedback from the relatives who did receive communication from the FCT was compared to those who didn't, we feel that there is a clear benefit shown from the use of the FCT and the feedback has been overwhelmingly positive.

The benefits of the FCT were many, to both the relatives and the staff working in the unit. There was an understanding for these families that it was very difficult and unusual not being able to visit their relatives. The FCT dedicated significant time explaining things to the relatives and listening to their concerns. It was also appreciated that the clinical team were wearing PPE at all times in the unit so were unable to answer phone calls from relatives looking for updates. We anticipated this would not only be frustrating for staff but would certainly add to relatives' anxiety when they couldn't get through on the phone to someone with knowledge of their loved one. Knowing that they would get a call at a similar time each day helped to reduce the volume of calls into the unit and allowed the clinical team to concentrate on their clinical workload. It also meant that as opposed to relative led updates on patients by calling into the unit at any time of day or night, they instead were receiving a more comprehensive overview of the last 24 hours and as a result they were better informed overall. Lastly, as documentation was able to be accessed via Microsoft teams it meant that

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infection control was adhered to, which further reduced risk of spread to patients and staff.

From the doctors who were providing the communication, they overall felt that they were contributing to an important service and felt that what they were doing was making an impact. Despite this, communication was certainly emotionally challenging at times and there were difficult discussions that took place via telephone. Recognising that these challenging and emotive discussions could take their toll on the individual after continuous exposure [7]; the members of the FCT were able to reflect on these conversations together and support each other as needed.

As a small team of three doctors making up the FCT we were initially wary of the same person providing the communication to the same relatives everyday but we soon found that the relatives appreciated the continuity of care. They found it reassuring to get a phone call at a similar time each day from the same person and we were able to build up a good rapport with them as some patients were in ICU for many weeks. The relatives commented if we were off a day that they were glad to have their 'usual doctor' back and often the communication was as much about giving them someone to listen to their concerns and have a chat in general about how they and the rest of the family were coping. Being part of the FCT we have learnt many new skills and have experienced first-hand the impact that providing personal communication can have on relatives who are going through very difficult situations. We realised the importance of providing attention to detail to each individual family and showed compassion by being mindful of the difficult circumstances they were facing.

Challenges faced during the process of running the FCT were dealt with accordingly, with the main one being the use of interpreters. The Big Word Interpreting service is used widely by the health service and is available 7 days a week. This allowed the FCT to communicate daily with relatives and we were reassured that they were being communicated with in the appropriate language. The calls generally took longer, as was expected with a three-way conversation and there were several times that the FCT were left feeling uncertain as to whether relatives truly understood what was happening. The only way to try and alleviate this concern was repetition of information and trying to ascertain from the interpreter whether they felt that relatives understood what we were saying. There were a few occasions when these relatives appeared to have picked up information wrongly and we are still unsure if this was due to the interpreters providing the information or due to a lack of understanding on the relative's part. It is evident that the use of interpreters for communication in healthcare results in an alteration of linguistic features such as content, meaning and reinforcement. Overall, this will inevitably mean conversational loss [8]. The FCT tried to reduce this as best as possible, but it still had its faults. Phone calls with the use of interpreters was problematic at times despite our best efforts and it was difficult to form a rapport with these relatives.

Despite the many challenges encountered with the video calls they proved to be some of the most rewarding interactions throughout the whole process. Feedback from the relatives on the phone call following the video call was always very positive and they took much comfort from seeing their relative and being able to speak to them even if they were not able to communicate back to them. Video calls were also used on occasion for those patients who were seriously ill and not expected to survive and gave relatives a chance to say their goodbyes. This proved a very emotional experience for everyone involved but the families thanked us for the opportunity to do this at a time when there was no hospital visiting allowed even in end of life care.

An area of weakness that was identified from the feedback received was that it didn't include those relatives of patients who died in the ICU during this time and one could argue that it would have been these families that would have been most useful to hear from. However, as the nature of this project was never for the doctors' gain, it was felt insensitive and unnecessary to ask these families to answer a questionnaire at what is undoubtedly an extremely upsetting time for them. We did not contact families after death as we felt this needed to be done by someone who was aware of the bereavement services available for families to access.

Despite telling the relatives the feedback form was for ICU communication some of the comments received implied that the relatives had scored the questionnaires on communication during their relative's entire hospital stay. This was difficult for relatives as they were not offered a forum to feedback opinions on communication outside of ICU. This further highlights the impact of the quality of communication received by relatives and its bearing on their overall experience whilst their loved ones are in hospital. Verbal feedback received at the ICU follow up clinic informed us that many relatives felt let down by the quality of communication once their relative left ICU so overall the results may have been more positive.

After showing the benefit of this system, we hope that it will be potentially be employed again in future, especially if another pandemic were to arise but potentially there is a place for a system like this in the normal ICU setting.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix 1

Critical Care Communication Bulletin Date

I – Improving P – Progressing S – Stable C – Cause for Concern D – Deteriorating

Patient Name	Progress	Information for Relatives

Improving: Doctors would hope to hope to transfer him/her to a ward over the next few hours.

Progressing: Making progress and requiring less support from the breathing machine.

Stable: Stable for now, but still requiring the breathing machine and high concentrations of oxygen

Cause for concern: Giving the doctors concern as he/she is not making the progress they would have hoped to see, despite full support for his/her condition. All possible treatment is continuing, and he/she is being reviewed by the doctors regularly.

Deteriorating: Requiring increasing support to maintain Resp/CVS; doctors concerned about progress. Eg needs high concentrations of oxygen, his/her circulation is failing, needs strong drugs to maintain his/her blood pressure. All possible treatment is continuing, and he/she is being reviewed by the doctors regularly. If there is any further deterioration, they will contact you directly before the next bulletin.

Appendix 2

Communication Feedback

Your experience of communication during your relative's intensive care stay.

1. Did you receive daily updates from the family communications team? (6th April onwards)
   - ☐ Yes
   - ☐ No

2. How would you rate the communication that you received while your relative was in intensive care?
   - ☐ Very good
   - ☐ Good
   - ☐ Average
   - ☐ Poor
   - ☐ Very poor

3. Did the communication you receive help you understand your relative's stay in intensive care better?
   - ☐ A great deal
   - ☐ Somewhat
   - ☐ A little
   - ☐ Not at all

4. Did the communication you receive help you cope with you relative's intensive care stay better?
   - ☐ A great deal
   - ☐ Somewhat
   - ☐ A little
   - ☐ Not at all

5. Any additional comments?

   _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____

We greatly appreciate you taking the time to complete this and hope your feedback can help to improve this service.

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Medical Education

'Working together' - A new approach to Reviewing the Quality of Postgraduate Medical Training Posts in Northern Ireland?

Blayney GV[1], Phillips SA[2], Gardiner KR[3].

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Provenance: Externally peer reviewed

Abstract

Many of us are involved in the education and training of junior doctors. Maintaining and improving the quality of such training is the common goal of all medical educators, including those working in the Northern Ireland Medical and Dental Training Agency (NIMDTA) and within our hospitals – the Local Education Providers (LEPs). The development of NIMDTA's Placement Quality Initiative (PQI) aims to create a more collaborative working relationship between NIMDTA and the LEPs, working together, to achieve a shared goal and develop and implement strategies to improve current practice. We review the PQI process, from both a trainee and trainer's perspective, and ascertain if this approach has facilitated positive, reproducible changes in training programmes that are felt at ground level.

Key Words: Placement quality; trainee; training post; junior doctor

Introduction

The ability of trainees to maximise their potential is directly influenced by the quality of training they have access to; the common goal of all medical educators being the maintenance and continued improvement in the quality of education and training being delivered. The General Medical Council (GMC) stipulates that postgraduate deaneries must have effective educational governance systems and processes to monitor training sites, to ensure that the standards set out in 'Promoting Excellence' [1] are being met. These should continuously improve the quality and outcomes of education and training by reviewing the quality of teaching, support, facilities and learning opportunities available on placements. Such reviews need to be robust, ongoing processes which ensure that training is taking place in a supportive and constructive environment, with evidence of good educational practice.[1]

The Northern Ireland Medical and Dental Training Agency (NIMDTA) manages postgraduate medical training within Northern Ireland (NI). In November 2020 there were 24 hospital sites acting as Local Education Providers (LEPs) in NI, with 1734 trainees currently in a training post. In compliance with the GMC's Quality Assurance Framework, a key component of NIMDTA's Quality Improvement Framework is a Deanery visit to each LEP on a 5-yearly cyclical basis.[2] Primary, independent and qualitative data obtained through face-to-face interviews with trainees, trainers and educational management leads during visits, is triangulated with self-assessment LEP reports and Trainee surveys. In addition, visits provide the opportunity to explore areas of good practice and concerns and provide feedback.

Deanery visits have often generated a significant workload for both the Deanery and LEPs, which is out of proportion to the improvement achieved; repeat visits sometimes identifying unresolved issues. Therefore the existing visit process is not always effective in improving the quality of the training experience and LEPs can find engagement with the process difficult, as interactions can be perceived as hierarchical, if not confrontational, with the Deanery sitting 'across the table'. Furthermore, available monitoring tools, such as the GMC's National Trainee Survey (NTS), may not provide detailed local information, enabling only limited interpretation for smaller training units and there is more limited trainer engagement in the process. Three of the most recent large-scale NHS reviews (Keogh, Francis and Berwick), have highlighted that junior doctors' views about their training experience need to be heard and that an effective programme of monitoring, including the use of trainee surveys, should be ensured.[3-5] All three reports support the thought that quality and safety in the NHS requires a simple monitoring process, delivered at local level.[3-5]

In response to the administrative burden and limited improvements achieved using established practices, NIMDTA developed a Placement Quality Initiative (PQI) as an alternative method of meeting the GMC's quality assurance standards. The objectives of the PQI are to improve the quality of medical training posts through review of current placements, active engagement with trainees, trainers and providers, and the development and implementation of strategies to improve current practice. This approach aims to create a more collaborative working relationship between

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NIMDTA and LEPs, working together, 'around the table', to achieve a shared goal.

In 2018 the PQI began by reviewing two training programmes – Obstetrics and Gynaecology and the Foundation Year 1 Programme. Review of Psychiatry specialities and Core Surgery were undertaken during 2019-20. Over the last two years the PQI team have obtained feedback on training placements from almost five hundred doctors in training.

We sought to answer the question: Does the PQI process, through a more collaborative approach, utilising shared and agreed goals, provide a more effective method to address the requirement on the Deanery to quality assure postgraduate medical training?

Method

The PQI process of reviewing training programmes is outlined in Figure 1. The process starts by collecting all existing information on training quality. This includes data available from previous Deanery visits, GMC NTS and specialty-specific data and reviews such as The Royal College of Obstetricians (RCOG) Training Evaluation Form (TEF) and Attrition: Solutions Focus Group Report.[6, 7] The curriculum requirements of the training programme and the current training structures within NI are also considered. Following this a programme-specific, online, anonymised trainee questionnaire is developed in cooperation and agreement with trainees and trainers. Trainees are asked to provide their opinions on their current training post, including access to curriculum-specific areas of training. Additionally, the survey provides a number of opportunities for free-text comments, facilitating the broadest range of trainee feedback to be obtained. The data collected is then analysed and presented at a series of meetings both regionally to the Head of School and Training Programme Directors and then specific information is presented to Lead Educators, Directors of Medical Education (DMEs) and Education Managers in LEPs.

Meetings with each LEP are attended by both educators and non-medical Trust leaders and administrators. Areas of strength and weakness are discussed and good practice from other units shared to enable development of collaborative improvement solutions. Actions to address identified areas for improvement are then agreed by both NIMDTA and the LEP. A report of the Regional PQI Review, along with key recommendations, is then made available to all educators and published on the Deanery website. Following a period to allow for the implementation of improvement strategies (12-18 months) trainees are re-surveyed to evaluate progress in achieving agreed development needs. A follow-up report is then disseminated and published.

At the beginning of the PQI process the team conducted an awareness campaign, presenting the PQI concept to Lead Educators, through educational committees and meetings (Department of Health Medical Leaders' Forum, Trust Board meetings, Trainer Education Days) and to trainees through the NIMDTA Trainee Forum, BMA Junior Doctors' Committee and articles in trainee newsletters. Engagement of trainees, trainers and LEPs in the process was considered essential in bringing about positive change in the quality of training placements and early socialising and promoting of the PQI concept was an important step in achieving this.

In order to address the question as to whether the PQI process provides a more effective method to deliver quality improvement in training placements than the current

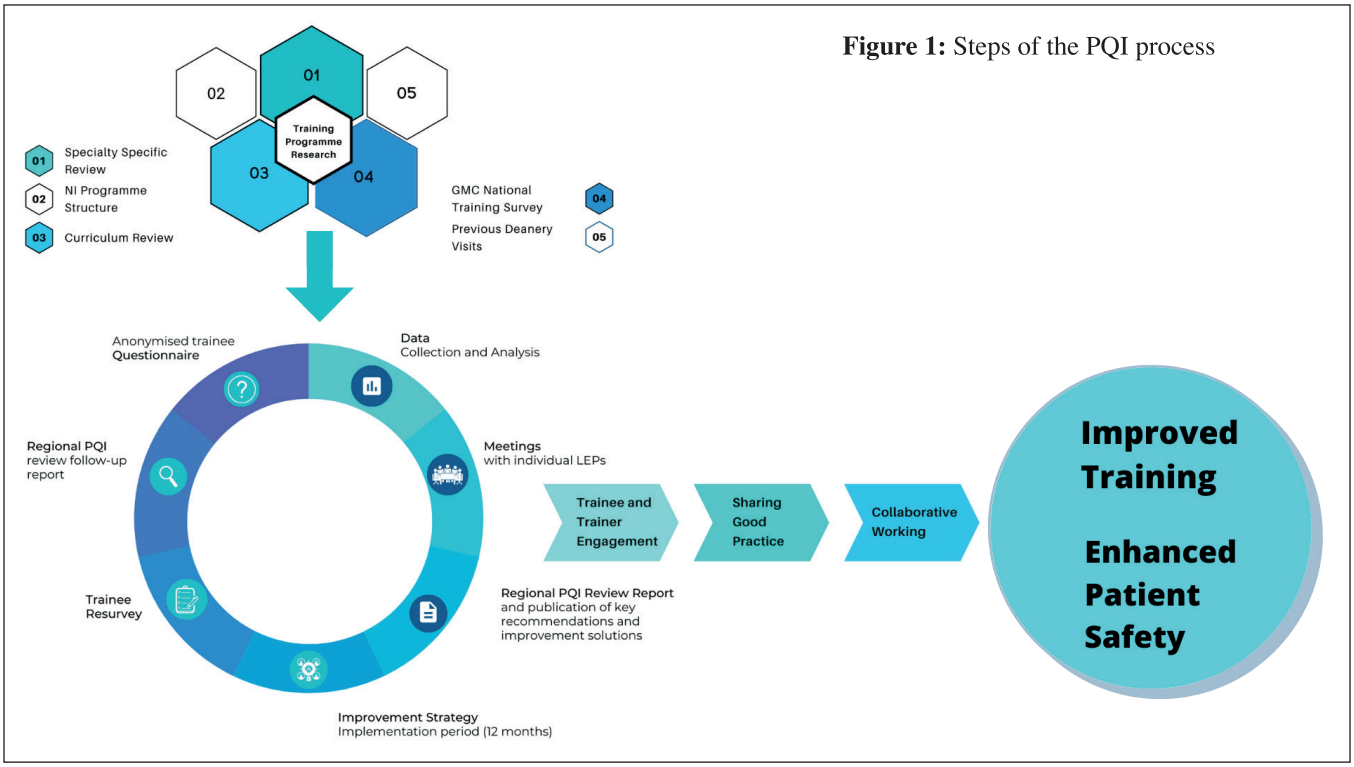

Figure 1: Steps of the PQI process

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Deanery approach, feedback on the process was obtained through an online survey (Appendix 1). The 'Experience of Placement Quality Review Questionnaire' was released to all those involved in post-graduate medical education who had participated in any of the PQI processes. This included Clinical and Educational Supervisors, College Tutors, Training Programme Directors and Heads of School, DMEs and medical and non-medical LEP members involved in education such as Medical Directors, Clinical Directors and Education Managers. Trainee opinion on the PQI process was also obtained through a short 6-question anonymised trainee questionnaire (Appendix 2).

Results

Trainer opinion

The 'Experience of Placement Quality Review Questionnaire' was open online for a 3-week period in Oct 2020. The survey response rate was 40% (40 responses). Respondents had participated in the PQI review of at least one of the programmes reviewed with 13% being involved in the review of all programmes. There were responses from all categories of participant and from all five LEP Trusts in NI.

The majority of educators (70%) agreed or strongly agreed that

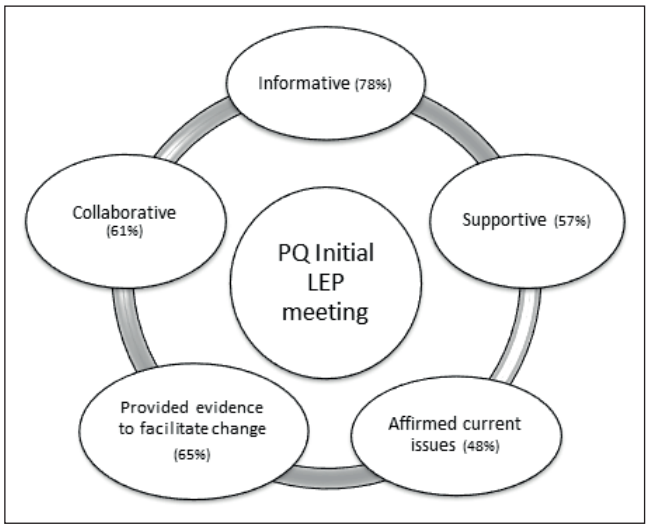

Figure 2: Educator feedback on the PQI process

an anonymised trainee survey provided an accurate picture of the quality of training within a unit and 91% indicated that the NIMDTA PQI team had a good understanding of the training programme and training structure under review. Comments were that the survey provided trainees with a 'safe space' to report issues and that repeating surveys at varying times could strengthen and improve the accuracy of findings. Feedback on the initial PQI meetings, during which the trainee survey results were presented, was very positive with the process being regarded as informative, supportive and collaborative, affirming current issues and providing useful evidence to facilitate change (Figures 2 & 3). The majority of educators (87%) reported that trainee feedback from the survey was disseminated to the wider clinical team through email or a

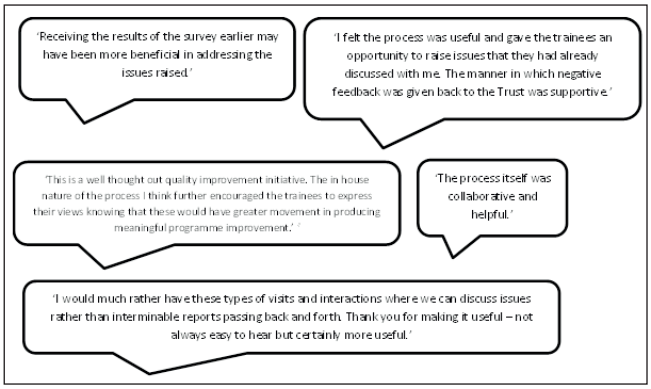

Figure 3: Educator feedback regarding the PQI initial meeting with LEPs

local departmental meeting. Within the wider clinical team it was reported that 61% welcomed the feedback, two thirds of whom were prepared to implement changes in response. The PQI reports generated following the initial review were well received; with one educator highlighting that it was 'useful as a starting point, especially when there is pushback from clinical management teams'.

Almost all of the educators who responded to the PQI Review questionnaire (95%) reported having gained new insight into training in their unit through the process, with 87% agreeing that highlighting areas of regional and reproducible good practice was helpful. A further 57% agreed that trainee feedback accurately captured the quality of training. There were some concerns that a lower survey response rate in a few units might mean that the results were not reflective of training quality, that trainee dissatisfaction could drive increased participation and that some trainees might avoid providing negative feedback due to fear of loss of anonymisation.

Overall, 74% of trainers agreed that the PQI fulfilled its aims and has created a more collaborative approach to improving the quality of training posts. Only 22% felt that the process engaged trainers less than Deanery Visits.

Trainee opinion

The PQI review of the O&G training programme was one of the first PQI reviews in 2018 and has advanced beyond the initial PQI assessment and feedback phase. Trainees in O&G have had time to observe potential improvements in training practices and to complete a re-survey of their training experience. Trainee opinion of the PQI process was therefore determined by sending current O&G trainees a short, anonymised, online survey in October 2020. The response rate was 34% (30 trainees) with responses from all levels of training. Almost two thirds (65%) agreed or strongly agreed that an anonymised trainee survey provides an accurate picture of the quality of training within a unit, with a similar percentage feeling confident to express their opinion, both positive and negative, through the PQ surveys. In view of NI being a small Deanery, a few concerns were expressed that trainees might be more easily identifiable and comments might potentially impact future career prospects.

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Of the respondents that still worked in the same unit, 31% saw definite improvements in training opportunities. Almost two thirds (61%) felt that the PQI process provided useful information to initiate positive change using a collaborative and supportive approach. Requests were made for the results of the PQI Reviews to be communicated directly to trainees.

Discussion

The primary objective of NIMDTA's Placement Quality Initiative (PQI) is to produce meaningful improvement in the quality of the training experience provided by medical training posts. This new approach to reviewing training placements aims, through active engagement with trainees, trainers and LEPs, to develop and implement strategies to improve current practice and to enhance working relationships between the Deanery and LEPs. Trainee and trainer feedback, both formal and informal, has highlighted the PQI as a collaborative and less confrontational approach to assessing and improving training quality with measurable results already observed on the ground. A Regional Unit Prospectus for O&G Training in NI and a 'Train in O&G in NI' leaflet outlining the structure of the O&G training programme, were produced in collaboration with trainers and trainees in the five LEPs, following the O&G PQI Review in 2018.[8] This has improved the information available to trainees about the training programme and training sites so that now the majority of trainees report having sufficient knowledge to make informed decisions in regard to placement options, compared to only a third prior to these publications.[9]

As highlighted in the Berwick, Francis and Keogh reports, junior doctors' views about their training experience need to be heard.[3-5] The PQI provides a platform for this to occur. As part of the development of the PQI process, the PQI team reviewed the quality management infrastructure in other UK Deaneries. Health Education England (HEE) conduct the National Education and Training Survey (NETS) twice a year for all healthcare trainees and students to provide insight into the quality of training placements, identify areas of good practice and areas for improvement.[10] NHS Education for Scotland developed the Scottish Training Survey in 2013 to add value to GMC NTS data, produce robust indicators for quality management and to capture data about each training post.[11] NIMDTA's Placement Quality Initiative described here, is a novel and effective way of meeting the GMC standards for quality managing postgraduate training posts. It is a process which is replicable for other training programmes and regions and has been shown to promote collaborative working between trainees and trainers, LEPs and the Deanery.

A potential weakness of the PQI, suggested by trainee and trainer feedback, was the concern that lower survey response rates or participation being driven by trainee dissatisfaction may impact on the reliability of data obtained. In the six trainee surveys conducted to date, we have obtained opinions from almost five hundred NI trainees and the trainee survey response rate has ranged from 42% to 74% in the most recent survey. We highlight that the data obtained through the surveys is triangulated with other data sources, including the GMC NTS and published specialty-specific data, providing a broader view of the training experience; a key strength of the initiative. As more training programmes become involved in the PQI process and recommendations, good practice and improvement initiatives are disseminated and published, trainers and trainees are developing an increased familiarity with the process. It is anticipated that this will promote better engagement in the PQ process that will improve and maintain a high survey response rate in future training programme reviews.

The PQI approach represents a culture change in the monitoring and improving of the quality of training posts across Northern Ireland. Working together in a less hierarchical, 'around the table' relationship has improved the ability to affect change and has created engaging partnerships which align key medical education goals between LEPs and the Deanery. The improvement methods employed by PQI allow data-driven good practice to be shared, changing perspectives and moving away from a Deanery inspectorial approach. Doing so has promoted engagement and created a collaborative, outcome focused strategy to promoting training quality. We know that doctors who feel highly valued and motivated are better equipped to deliver high-quality care and meet the needs of patients and the wider NHS.[12] They can also be effective powerful agents for change and their views about their training are essential in the integration between clinical practice and education.

Conclusion

NIMDTA's Placement Quality Initiative aims to improve the quality of medical training posts through review of current placements, active engagement with trainees, trainers and providers, and the development and implementation of strategies to improve current practice. It is a driver for change which diminishes hierarchical interactions between Local Education Providers and the Deanery. It promotes collaborative working relationships to generate practical improvement strategies and observable change in the quality of postgraduate medical training which is experienced at trainee level. The PQI approach has facilitated positive changes in the training programmes reviewed to date and continues to adapt and be tailored to upcoming specialty reviews. There is potential to integrate this method with the existing Deanery visit programme to enhance the monitoring of training placements and produce improvements in the overall quality of training, providing an enriched training experience, better quality of trainees and ultimately improved patient safety.

Acknowledgements

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Appendices

Available as online content

1 - Trainer survey

2 - Trainee survey

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Medical Education

Performance of Queen's University Belfast graduates at core and speciality application

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Abstract

Introduction:

The general medical council (GMC) conducts the National Training Survey (NTS) annually. Part of the survey illustrates the statistics of United Kingdom medical school graduates in core and speciality application. We aimed to review the speciality training application and performance of graduates of Queen's University Belfast (QUB), and compared with graduates of medical schools in England, Scotland, and Wales.

Method:

The progression reports from the GMC NTS 2016-2019 were accessed on the GMC website. All data available were extracted in April 2020. The mean results for all graduates of 33 UK medical schools in Northern Ireland, England, Scotland, and Wales were collated from the NTS. Applications to the seven specialities with the greatest number of posts available across the UK were analysed.

Results:

No differences were noted in the majority of the application stages when comparing graduates from QUB with other UK medical school graduates. However, QUB graduates were less likely to be invited for an interview when applying for core surgical training AND receive an offer for Core Anaesthetic and ACCS Training. QUB graduates were less likely to apply for General Practice training.

Conclusion:

Our study evaluates the performance of QUB graduates compared to other UK medical graduates in core/speciality application. Based on our findings, QUB and postgraduate deaneries may consider focussing on strengthening applications for aspiring surgeons, improving interview performance for anaesthetics and ACCS applicants, and attracting trainees to pursue a career in General Practice.

Key Words

Career progression, Speciality training, National training survey

Introduction

In the United Kingdom (UK), medical school graduates are required to complete a two-year foundation programme before applying for specialist training positions. Despite an increasing number of medical graduates choosing not to apply immediately for core/speciality training, nearly 90% of doctors will still enter core or speciality training within three years of completion of the foundation programme.[1]

Speciality training pathways can take 3 to 8 years before obtaining the certificate of completion of training (CCT). The training period can be longer for several reasons including less than full-time training (LTFTT), out of programme research, career break, undertaking fellowship(s), and working overseas.[1]

The General Medical Council (GMC) has conducted the National Training Survey (NTS) annually since 2006 to monitor and report on the quality of postgraduate medical education and training in the UK. Further information regarding speciality and core training applications has been made available from 2016.[2] More than 75,000 doctors in GMC approved training posts completed the NTS in 2019, making this one of the largest postgraduate training surveys.[3]

We aimed to review the core and speciality training applications using the NTS data, specifically focused on the performance of Queen's University Belfast (QUB) graduates in the seven clinical specialities with the greatest number of posts available across the UK, and whether there were any performance differences when compared to graduates of medical schools in England, Scotland, and Wales.

Method

The progression reports from the GMC NTS 2016-2019 were accessed on the GMC website.[2] All data available were extracted and analysed in April 2020. Information on the stages of core or speciality application was obtained 1. Position applied for, 2. Applicant invited to attend an interview, 3. Applicant attended interview, 4. Applicant appointable to a position.

The mean results for all graduates of 33 UK medical schools in Northern Ireland, England, Scotland, and Wales were collated from the NTS for applications to the seven

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specialities with the greatest number of posts available across the UK - General Practice; Core Medical Training; Core Surgical Training; Core Anaesthetic and Acute Care Common Stem (ACCS) Training; Paediatrics; Obstetrics and Gynaecology; and Clinical Radiology.

Once collated, these data were compared with emphasis on variation between QUB and the other UK graduates. We aimed to review the speciality training application and performance of graduates of QUB in the seven specialities listed above, and whether there were any differences when compared to graduates of medical schools in England, Scotland, and Wales.

The NTS reported their data in the following categories: 1. Above outlier at 95% Confidence interval (CI), 2. Not an outlier, and 3. Below outlier at 95% CI. The data are presented in both box and whisker plot and numerical table. The number of applicants, mean, 95% lower and upper confidence interval were provided for all the 4 stages of application. Outliers (defined as below 2 confidence intervals) are highlighted in red in the NTS and regarded as statistically significant.

Results

984 QUB graduates completed the 2-year foundation programme and applied for core and/or speciality training positions from 2016-2019, with a range from 237 to 244 applicants per year. In comparison, a total of 27,397 graduates from the rest of the UK medical schools applied from 2016-2019, ranging from 6,699-7,001 applications per year. Table 1 shows the number of Foundation Year 2 (FY2) doctors who applied for nationally recruited specialities from QUB compared to the UK total per year.

Table 1: Number of FY2 doctors who applied for nationally recruited specialities from QUB compared to the UK total per year from 2016-2019.

Year	FY2 doctors who applied for nationally recruited specialities	
	QUB	Total
2016	263	7,264
2017	240	7,217
2018	244	6,943
2019	237	6,957
Total 2016-2019	984	28,381

Tables 2-8 show the mean percentage of candidates at all four stages of the application process for Core Medical Training; Core Surgical Training; Core Anaesthetic and ACCS Training; General Practice; Paediatrics; Obstetrics and Gynaecology; and Clinical Radiology, respectively. For the majority of factors considered, graduates from QUB were equivalent to other UK medical school graduates , with Core Medical Training, Paediatrics, Obstetrics and Gynaecology, and Clinical Radiology.

Outliers were noted in the following categories. First, QUB graduates were less likely to be invited to the interview stage for core surgical training (Table 3). For those who had attended an interview for Core Anaesthetic and ACCS Training (Table 4), they were less likely to receive an offer. It is also important to highlight that QUB graduates were less likely to apply for training programs in General Practice and less likely to be appointable to these positions after being interviewed (Table 5).

Table 2: Mean percentage of candidates at each stage of the application process for Core Medical Training based on the country of their medical school (for primary medical qualification) for years 2016-2019. Statistically significant results are highlighted in red.

Core Medical Training				
Stage	Country of medical school			
	Northern Ireland (QUB)	Wales	England	Scotland
Applied	16.9	12.6	15.4	15.5
Invited to interview	86.7	89.7	89.5	93.2
Attended interview	100.0	100.0	99.9	100.0
Appointable to position	85.4	91.0	91.5	89.1

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Table 3: Mean percentage of candidates at each stage of the application process for Core Surgical Training based on the country of their medical school (for primary medical qualification) for years 2016-2019. Statistically significant results are highlighted in red.

Core Surgical Training				
Stage	Country of medical school			
	Northern Ireland (QUB)	Wales	England	Scotland
Applied	7.7	8.2	9.7	10.0
Invited to interview	80.3	94.4	92.0	90.3
Attended interview	100.0	100.0	99.3	99.3
Appointable to position	82.0	61.9	75.4	73.0

Table 4: Mean percentage of candidates at each stage of the application process for Core Anaesthetic and ACCS Training based on the country of their medical school (for primary medical qualification) for years 2016-2019. Statistically significant results are highlighted in red.

Core Anaesthetic and ACCS Training				
Stage	Country of medical school			
	Northern Ireland (QUB)	Wales	England	Scotland
Applied	6.8	5.0	6.8	6.4
Invited to interview	94.0	92.6	93.3	88.6
Attended interview	100.0	100.0	99.7	100.0
Appointable to position	64.0	63.5	81.5	80.1

Table 5: Mean percentage of candidates at each stage of the application process for General Practice based on the country of their medical school (for primary medical qualification) for years 2016-2019. Statistically significant results are highlighted in red.

General Practice				
Stage	Country of medical school			
	Northern Ireland (QUB)	Wales	England	Scotland
Applied	19.1	17.7	23.6	20.1
Invited to interview	91.5	96.4	93.2	94.3
Attended interview	100.0	100.0	99.9	99.7
Appointable to position	87.2	93.5	93.3	91.0

Table 6: Mean percentage of candidates at each stage of the application process for Paediatrics based on the country of their medical school (for primary medical qualification) for years 2016-2019. Statistically significant results are highlighted in red.

Paediatrics				
Stage	Country of medical school			
	Northern Ireland (QUB)	Wales	England	Scotland
Applied	2.8	2.9	3.5	3.0
Invited to interview	92.9	93.5	94.5	95.9
Attended interview	100.0	100.0	99.9	100.0
Appointable to position	92.3	100.0	94.7	92.6

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Table 7: Mean percentage of candidates at each stage of the application process for Obstetrics and Gynaecology based on the country of their medical school (for primary medical qualification) for years 2016-2019. Statistically significant results are highlighted in red.

Obstetrics and Gynaecology				
Stage	Country of medical school			
	Northern Ireland (QUB)	Wales	England	Scotland
Applied	1.8	1.5	2.6	2.2
Invited to interview	100.0	93.8	92.1	90.5
Attended interview	100.0	100.0	100.0	100.0
Appointable to position	88.9	93.3	84.4	86.6

Table 8: Mean percentage of candidates at each stage of the application process for Clinical Radiology based on the country of their medical school (for primary medical qualification) for years 2016-2019. Statistically significant results are highlighted in red.

Clinical Radiology				
Stage	Country of medical school			
	Northern Ireland (QUB)	Wales	England	Scotland
Applied	2.9	2.3	3.4	2.8
Invited to interview	75.9	72.0	85.1	84.6
Attended interview	100.0	94.4	99.7	100.0
Appointable to position	63.6	47.1	77.3	79.2

Discussion

There were no differences in the performance of QUB graduates compared to graduates of other UK medical schools in recruitment and selection to training pathways with the exception of the following. QUB medical graduates were:

- Less likely to be invited to interview for Core Surgical Training
- Less likely to be appointable to the position for Core Anaesthetic and ACCS Training
- Less likely to apply for General Practice - similar results were noted in Scotland and Wales
- Less likely to be appointable to the position for General Practice

Queen's University Belfast graduates were less likely to be invited to interview for Core Surgical Training positions; with only 80.3% of applicants being invited to interview from 2016-2019 compared with a minimum of 90.3% of applicants graduating from medical schools in other UK nations. However, once they were invited for an interview, no differences were noted in terms of their performance and likelihood of obtaining a training position. Core Surgical Training has an indicative duration of 24 months, requiring a certain set of competencies and exams to be completed before progression to a surgical specialist training post, and remains the pathway for most surgical trainees to pursue a career in surgery (except for cardiothoracic surgery, and trauma and orthopaedic surgery (in Scotland only)).[4]

Applications for Core Surgical Training are competitive (competition ratio of 2.93 in 2019)[5], with portfolio requirements including degrees additional to a primary medical qualification, research publications, and multiple mandatory courses.[6,7] With a self-assessment of a candidate's portfolio being one of the prerequisites to interview[8], poor scoring of self-assessments may have contributed to the reduced likelihood of graduates from QUB being invited to interview for Core Surgical Training - there is no literature available on this topic and further research is required.

Graduates from QUB were less likely to be appointed to Core Anaesthetic and ACCS Training, with only 64.0% of those who interviewed being appointable to a position. Core anaesthetic training is a 24-month programme, whereas ACCS (Acute Care Common Stem) is a 36-month programme with the final 12 months dedicated purely to anaesthetics.[9] The application process for anaesthetic ACCS positions consists of a portfolio station, a presentation station, and a practical skills station.[10] Further coaching support for applicants may improve performance at interview. ACCS training was introduced in 2007, designed to develop competent multi-skilled acute physicians to manage patients with multimorbidity from 'door to discharge'.[11]

Queen's University Belfast graduates were both less likely to apply for General Practice (only 19.1%), and less likely to be appointable to the position following the interview (only 87.2%). It is worth noting that similar results are noted for Scottish and Welsh graduates, suggesting a national issue in General Practice recruitment in attracting UK graduates.

There is a documented shortage of General Practitioners

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throughout the UK, acknowledged by the Royal College of General Practitioners (RCGP)[12], with particular emphasis on Northern Ireland[13]. The Royal College of General Practitioners in Northern Ireland (RCGPNI) released an action plan in 2015, entitled "Delivering change for general practice: A strategy for improving patient care in Northern Ireland"[14], to specifically target the shortage. Part of this strategy aimed to increase the General Practice workforce in Northern Ireland by the year 2020 by "rebalancing" the trainee uptake to increase the number of doctors following the General Practice training pathway - the relatively low proportion of QUB graduates QUB applying to General Practice from 2016-2019 reinforces the need to address this issue.

The importance of recruiting trainees into General Practice has been emphasised in England and despite retirements of senior clinicians there were more General Practitioners in March 2019 than March 2018, largely attributed to the increased number of trainees joining the speciality.[15]

The importance of making certain roles more attractive has been compared to the need to pay bankers large amounts of money to retain their services.[16] This raises the question of which factors would need to be changed to make certain training pathways more attractive. A study examining factors that were critical to attracting NHS foundation doctors into speciality or core training in Scotland, found that the most influential factor was the location, which is an unmodifiable factor, however, supportive culture and working conditions were the next most influential factors - these could be targeted in specialities which are struggling with recruitment, such as General Practice.[17]

General Practice applications were found to be the only speciality in which gender affected three components of selection and recruitment i.e. likelihood of making an application, the likelihood of receiving an offer, and the likelihood of accepting an offer - with women being significantly more likely to apply, more likely to receive an offer, and more likely to accept said offer.[18] Exploration of why there is a significant difference between genders, specifically in General Practice applications, may help to instruct further efforts to increase overall applications to General Practice training posts by graduates of Northern Irish medical schools.

In addition to the observations noted regarding graduates from QUB, there were some points of interest for graduates of medical schools in Wales (Cardiff University and Swansea University). Graduates from these Welsh medical schools had a low rate of appointability after interview in Core Surgical Training, Core Anaesthetic and ACCS Training, and Clinical Radiology, suggesting the area of improvement is different in each region Universities and foundation schools have to reflect and improve the curriculum locally/regionally based on the NTS feedback.

The limitations of this study include the limited existing research available, making interpretation of the results difficult. The gender, age, and socioeconomic data were not available - these data would have been useful to include in the analysis.[19, 18] Factors for not choosing a speciality or being less likely to be appointable are not available, instead, we report trends and highlight areas where QUB graduates performed less well in comparison to other UK medical graduates. These trends are important for medical schools and postgraduate deaneries to evaluate and appropriately modify the curriculum in the interest of workforce planning. For example, QUB has increased the length of General Practice placements in their curriculum. Increased exposure to General Practice in the undergraduate medical curricula is supported by the British Medical Association as part of the strategy to increase recruitment to General Practice training[20], although increased exposure alone may not encourage students to pursue a career in General Practice if that experience is not positive.

Conclusion

In summary, this study evaluates the performance of QUB graduates compared to other UK medical graduates in core/speciality application. Based on our findings, QUB and postgraduate deaneries may consider focussing on strengthening applications for aspiring surgeons, improving interview performance for anaesthetics and ACCS applicants, and attracting trainees to pursue a career in General Practice. Undergraduate and postgraduate training programmes in the United Kingdom should reflect on the NTS for speciality recruitment, curriculum design, career support, and make appropriate adjustments.

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Medical History

Measles: Progress and Failure

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INTRODUCTION

"Every boy should know about Herd Immunity", replied Professor Rutherford Morison to me[1] at the Annual (1938) Dipping of Cheviot sheep. My question to Professor Rutherford Morison had been suggested by my maternal grandfather who was a farmer and landowner of fields near Newcastle-upon-Tyne, where my father had been an Assistant Surgeon to Professor Rutherford Morison. As surgeons they both knew that I should be away from our home where my mother was being treated for post-partum thrombosis. Aged almost 5, I was staying with another famous surgeon, George A. Mason, later CBE, and his family nearby on Cheviot's north side.

MUSGRAVE ENCOUNTERS

My first meeting with Director Ted Badger was in Hut 1, Musgrave Park[1,2,3,4]. He asked me if I had had measles. I replied, "Yes, I had been treated in the dark to protect my conjunctivae". "Good," Badger replied. That was what ophthalmologist Rycroft—my brother's godfather—had told him[5,6]. I asked Badger if he had missed the Faroes in his small yacht sail from Yale[7]. "Yes," he said. "We are going to use measles in our counter-attack against your father's accusers, who are trying to have him court-martialed for attempting to obtain foods rich in vitamin A"[5,8]. I, said Badger, am only a stand-in for Charles A. Janeway (CAJ) (Fig. 1), who was told to stay in Boston at Harvard to continue research with John F. Enders[9,10] on the immunological control of mumps and measles in addition to his own work on plasma fractionation of blood[11,12,13]. This had been ordered by CAJ's neighbor, U.S. Secretary of War Henry L. Stimson (Fig 2). Badger informed me that "The Stimsons own thousands of acres next to the Janeways' estate in the Adirondacks. The Stimsons also have a Long Island estate with its own polo field and Highland games"[14,15,16].

Badger also told me that CAJ's father, Theodore Caldwell Janeway (1872-1917), a graduate of Yale and the College of Physicians and Surgeons of New York, was recruited in 1914 to be the first full-time Professor of Medicine at Johns Hopkins School of Medicine. He resigned this post in 1917 to enter the U.S. Army Medical Services as Major, and was assigned to the Office of the Surgeon General. CAJ's father died of pneumonia on December 17, 1917, when his son, CAJ, was my age.

Theodore Janeway's father, Edward Gamaliel Janeway (1841-1911), a graduate of Rutgers with a Medical Degree from the College of Physicians and Surgeons of New York, had answered a call to Buffalo, NY six days after President William McKinley had suffered an assassin's abdominal wound. Edward Gamaliel Janeway arrived too late to prevent the President's death[11,17].

Edward Gamaliel Janeway was also a contemporary and neighbor of then Secretary of War Henry L. Stimson's father, Lewis Atterbury Stimson (1844-1917). The latter graduated from Yale in 1863 and proceeded to study medicine at Bellevue Medical College in New York City. Lewis Atterbury Stimson had been the first in the U.S. to demonstrate and practice Lister's method of antiseptic surgery, and in 1883 performed surgery on former president Ulysses S. Grant[14,15].

TED BADGER AND THE EPIDEMIOLOGY OF INFECTIOUS DISEASE

As fellow Yalies and Harvard Faculty, Badger and Enders were well acquainted with each other's work. John F. Enders and his group had started their measles research in 1939 at the Enders' estate on Long Island Sound at the time when Badger's group were assessing the long-term health, including measles, of student nurses within the Harvard Medical School and its hospitals[18,19].

Badger later told me, while visiting our Windy Edge, Dunmurry home, that he had spoken to Rycroft further about the importance of vitamin A and health and nutrition for both the prevention of night-blindness and the amelioration of measles[5,8,20,21,22]. CAJ was also passing this information on promptly to his Adirondacks neighbor, Henry L. Stimson. Did my father know that Stimson's father had spread Lister's anti-surgical antisepsis heritage in New York? CAJ's father had been Head of Medicine at Hopkins after Osler and his grandfather, Edward Gamaliel Janeway had galloped to Buffalo from their Adirondack estate to try to save President McKinley.

A late post-mortem showed, "The mortally wounded

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

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president's Rutherford Morison pouch had not been adequately explored"[17]. I knew that my father had worked for Professor Rutherford Morison at the Royal Victoria Infirmary in Newcastle-upon-Tyne and I told Badger that,"In 1938 Professor Rutherford Morison and I had supervised the dipping of Cheviot sheep." Professor Morison had wanted his invention BIPP, a preparation of iodoform, bismuth subnitrate and liquid paraffin developed for treatment of war wounds during World War I added to the sheep dip[23]. This addition was declined, but used for treatment of wounded sheep.

JANEWAY'S STATESIDE CONTRIBUTION

TABLE 1. INCIDENCE OF MEASLES IN ARMED FORCES IN WORLD WAR II, RATES PER 1,000 MILITARY PERSONNEL

REPORTED CASES OF MEASLES IN THE BRITISH ARMED FORCES DURING WORLD WAR II[29]				REPORTED CASES OF MEASLES BRITISH COMMONWEALTH AIR TRAINING PLAN (BCATP) IN CANADA[30]			U.S. ARMY[31,32]	
YEAR	ROYAL NAVY	ROYAL AIR FORCE	ARMY UK ADMISSIONS TO HOSPITAL	RAF IN CANADA	RAAF IN CANADA	RNZAF IN CANADA	US ARMY IN US	US ARMY HOSPITAL ADMISSIONS TOTAL OVERSEAS
1939	0.7	1.8	1.11				1.4	
1940	0.8	2.1	0.55				3.7	
1941	1.2	1.7	0.49	5.5	24.6	15.8	9.8	
1942	0.4	0.7	0.19	5.5	10.6	11.2	4.5	1.58
1943	0.8	1.1	0.57	4.3	3.9	4.4	5.7	0.80
1944	0.3	0.6	0.34	7.5	4.7	6.3	2.7	0.57
1945	0.4	0.5	0.40				0.9	0.42

Having accepted the diktat of the U.S Secretary of War Henry L. Simson, CAJ remained at Harvard[1,2,3,11,12,13,24,25,26,27]. He thereafter did much valuable work on the prevention of epidemics. During World War I the incidence of measles in U.S. troops in Europe had been high[28], but during World War II it was low (Table 1). Geoffrey Keynes and the Lionel Whitbys closely collaborated on aspects of blood transfusion including the administration of immune serum in the treatment of measles[33,34,35,36,37]. The generations-long friendship of the Stimsons and Janeways co-existed with deep experience. CAJ's father Thomas, as Head of Medicine at Hopkins, resigned shortly before his death in

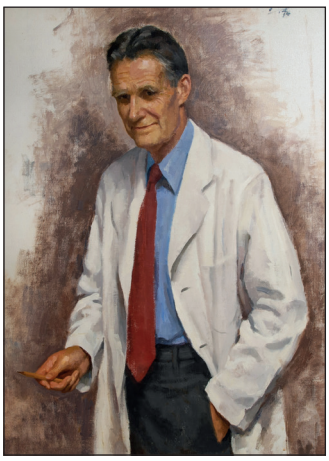

Figure 1
Charles Alderson Janeway, M.D. (1909-1981), Physician in Chief, Children's Hospital, Boston 1946-1976, and Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School. Oil on canvas, 32" x 40", 1975, by George V. Augusta, Jr. (1922-2012). From the portrait collection of Boston Children's Hospital, and reproduced with permission of the artist's estate.

1917, to advise the then U.S. Surgeon General. During World War I he attained the rank of Major and Henry Stimson that of Colonel in U.S. Artillery. John F. Enders had attained the rank of Ensign as a U.S. pilot in World War I.

Late in 1941, after Pearl Harbor, Harvard's Moseley Professor of Surgery, Elliott Carr Cutler, Harvey Cushing's successor as commandant of Harvard's 5th U.S. Army General Hospital[2,3,37] had announced that CAJ would be his Assistant Director and Head of Pathology. This appointment was vetoed by the U.S. Secretary of War, Yale graduate, Henry L. Stimson, who ordered that CAJ should stay at Harvard and continue his work on the fractionation of human blood and the gamma globulins. Stimson and CAJ were both elected to Skull and Bones, "The inner circle of Yale good-fellowship", while undergraduates at Yale[14] (Fig.1) (Fig.2).

Figure 2
Colonel Henry Lewis Stimson (1867-1950), U.S. Secretary of War under President William H. Taft (1911-1913), and later under FDR (1940-1945), by Julius G. Melchers (1860-1932), 1913. Oil on Canvas, 51.5" x 30.74", from the collections of the Center of Military History, Washington, DC. Stimson was appointed Governor-General of the Philippines by President Calvin Coolidge in 1927 and served until 1929, when he was appointed U.S. Secretary of State. In 1939, he was reappointed to his former post of Secretary of War by FDR.

During the U.S.'s engagement in World War I there were 2,370 deaths of enlisted soldiers in the United States and Europe attributed to measles[38]. In World War II, by contrast, even with a quadrupled pool of military personnel for twice the time, the corresponding mortality figure was reduced to 33 deaths[32,38]. The advice to the U.S. Secretary of War Stimson from Enders and CAJ on prevention and treatment was very effective, as was their close collaboration with Geoffrey Keynes and the Whitbys for United Kingdom troops, airmen and Allied Navies[29,35,36,37](Table 1) .

Gamma globulin (human immune serum globulin) obtained as a product of human plasma fractionation was an effective means of prevention or amelioration of measles[11,12,13]. Measles never became a serious military problem during World War II[29,30,31,32,38] (Table 1).

SEQUELAE: THE LEGACY OF JOHN ENDERS

In 1959 CAJ recruited my wife from St. George's Hospital London to be Sidney Farber's intern and later to work in the John Enders Building opened in 1972 at Harvard's Children's Hospital in Boston[1,39].

John Enders, trained by Zinsser[40,41,42,43,44,45], started in 1939 with cultivated human renal cells to allow production of more renal cells to propagate measles virus in quantity[46]. The Edmonston-Enders virus strain is still used in standard measles, mumps and rubella vaccine (MMR)[47,48,49,50]. The wide-spread use of the Enders Measles vaccine led to the

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United Kingdom, the United States and a number of other countries being declared measles-free[51,52]. The World Health Organization (WHO) defines elimination of measles as "the interruption of measles transmission in a defined geographical area that has lasted at least 12 months"[53]. Because of its high infectivity, "the herd protection threshold for measles is the highest of all vaccine-preventable diseases and varies in different settings ranging from 89% to 94%"[53]. Now in 2020, Boston has registered two confirmed cases of measles in the past 4 months[54] (Fig. 3). Air travel to both the U.K. and U.S. warrants closer monitoring: Koplick spots are easily recognizable. The WHO has reported global annual incidence of measles of approximately 6,733,000 cases resulting in 109,638 deaths as recently as 2017[53,62,63]. Complications such as blindness, encephalitis, pneumonia, as well as death, are more frequent among malnourished or vitamin-A deficient children, or those with immune systems weakened by HIV/AIDS or other causes[51,52,62,63]. Measles may disrupt the function of F protein and result in neurological sequelae including "primary measles encephalitis, acute post measles encephalitis, subacute sclerosing panencephalitis (SSPE) and measles inclusion body encephalitis (MIBE)"[64].

WHO has reported that during the period 2000-2017, measles vaccination prevented an estimated 21.1 million deaths worldwide, a decline of 80 percent during that time

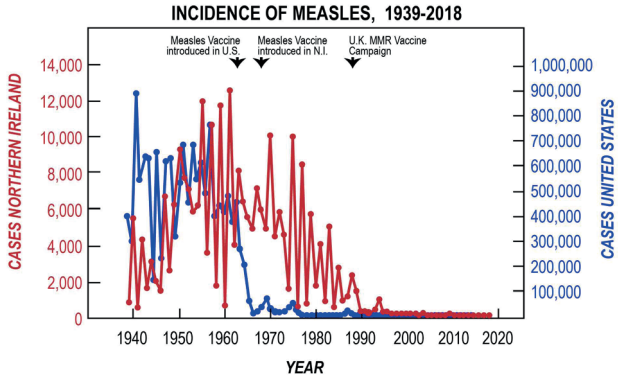

Figure 3

Incidence of Measles in Northern Ireland and the United States, 1939-2018. The incidence of measles in Northern Ireland[55](red) and the United States[56,57,58,59] (blue), reflects natural patterns of outbreaks and acquired immunity prior to the implementation of vaccination programs in 1963 in the U.S[60] and in 1968 in Northern Ireland[61]. In Northern Ireland, the steepest decline in reported cases occurred after the introduction in 1988 of the combined measles-mumps-rubella (MMR) vaccine given at age 15 months[61] . This was followed by a UK-wide campaign for vaccination of all school children in 1994[61]. More recently in Northern Ireland, as in the U.S., cases are mostly "imported" by air-travel[60,61].

period[62]. As of 2017, about 85 percent of children world-wide received one dose of measles vaccine by 12 months of age, but two doses are recommended, since approximately 15 percent of children do not develop immunity after the first dose. WHO estimates that 67 percent of children received a second dose of measles vaccine. At the same time, 8.1 million or 39 percent, of the 20.8 million infants not receiving at least one dose of vaccine, were in India, Nigeria and Pakistan[62], where clinical vitamin A deficiency remains an ongoing public health concern[5].

While WHO has reported an 88 percent global decrease in incidence of measles during the period 2000-2016, from 145 to 18 cases per million persons, by 2019 the incidence had risen again to 120 cases per million, its highest rate since 2001[65]. Sixty-two percent of countries reporting in 2019 included viral genotype information. The WHO reported that twenty out of twenty-four recognized measles genotypes could be eliminated by vaccination[65]. Global estimates of measles mortality increased nearly 50 percent between 2016, which had the lowest rates recorded since 2000, and 2019. Failure to vaccinate is recognized as the main cause of resurgence[65]. The 2020 coronavirus pandemic has led to further decreases in vaccination and surveillance[66].

BELFAST AND BOSTON

The late Distinguished Professor Emerita of Neuropathology Dame Ingrid Allen (Fig. 4) and her colleagues, including Professor Bertus K. Rima of the Center for Experimental Medicine, Queen's University Belfast, identified the primary cell types infected with measles virus as those of the immune system—lymphocytes, macrophages and dendritic cells. In addition, they identified a small number of infected epithelial cells[67]. This group also studied the role of the F-gene as a major determinant of neurovirulence[67].

Figure 4

Professor Dame Ingrid Allen (1932-2020), oil on canvas, 108 cm x 93.5 cm, No. QUB 6, by Tom Hallifax (1965-). From the collection of the Naughton Gallery, Queen's University, Belfast and reproduced with permission.

Professor Allen established the Regional Neuropathology Service for Northern Ireland in 1972 and served as its first leader. In 2006 she began a review of Pathology Services in Northern Ireland which led to the establishment of the Northern Ireland Pathology Network[68]. Post-measles immunosuppression and its long-term immunologic sequelae were elucidated. Measles vaccination (MMR), using Enders' attenuated Edmonston strain aids prevention of all infectious disease and promotes "polymicrobial herd immunity"[69,70]. Recent work by Michael J. Mina, now at Harvard University, and his U.S. and international colleagues, demonstrates that measles causes "elimination of 11 to 73% of the antibody repertoire across individuals"[69,70]. The impairment of immune cells increases the risk of secondary infection

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leading to many of the deaths attributable to measles[69,70]. Adaptive immunity will also play a role in determining response to coronavirus disease vaccines[71].

TUTORING

My Clare College Physiology tutor, E.N. Willmer, FRS, has described in detail Enders' tissue culture technique[46,72]. Willmer opined that herd immunity for measles would require the immunity of at least 96 percent of the population. This prediction to me in 1954 occurred in the Fellows' Garden, that Willmer designed and supervised. The Cam flows past.

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Medical History

James Cardinal: The Celebrated Hydrocephalic

Alun Evans

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Introduction

The Belfast Natural History and Philosophical Society has a proud and illustrious past. It played a central role in the intellectual and scientific development of Victorian Belfast, and beyond, with its close links to The Royal Belfast Academical Institution, or 'Inst', and subsequently Queen's College. It was founded on 5th June 1821 so it will celebrate its Bicentenary this year. It started life as The Belfast Natural History Society but added the 'and Philosophical' to its title in 1842 to reflect its broadening remit.[1] Its object was "… for the cultivation of that science in its various forms, and more particularly for the investigation of the natural history of Ireland."[1]

The Belfast Natural History and Philosophical Society's Centenary Volume is dedicated "To the enthusiasm of the eight youthful founders: Francis Archer, James L Drummond, James Grimshaw, George C Hyndman, James MacAdam, William M'Clure, Robert Patterson and Robert Simms."[2] They shared certain characteristics, especially youth (seven of them were in their early 20s, or younger, and Drummond, their leader, was aged less than 40). Drummond had been appointed to the Chair of Anatomy and Physiology at Inst in 1818.[3]

The Belfast Phrenological Society

The Society's first meetings were convened at Drummond's house at 5 Chichester Street and he was elected its first President.[1] It was written of Drummond that: "His life was not marked by any startling incident, nor was the world enriched by any scientific discovery as the result of his individual exertions; but it may be safely asserted that by his assiduous and unremitting zeal the intellectual life of Belfast was considerably advanced during the first half of the nineteenth century."[3]

In January 1823, Robert Patterson read a paper to the Society entitled, 'Spurzheim's and Gall's System of Phrenology.'[4] Patterson, who was largely self-educated,[5] was probably exposed to Phrenology by Francis Archer, who in the early 1820s was studying Surgery in Edinburgh.[6] On 14th February 1827, Francis Archer wrote[7] to Robert James Tennent, a member of the prominent Belfast family,[8] concerning the purchase of busts for the fledgling Society. By then, Archer had qualified and was in Practice in Liverpool.[6] On Tennent's instructions he had been to Galleti's in Castle Street in that city, specifically to purchase phrenological busts made by O'Neil, of Edinburgh. Galletti's was one of five agencies which O'Neil had appointed to sell his busts.[9] Archer reported that, "… only Nos 20 (Napolian [sic]) and 23 New Phrenological Bust is available," but that Galletti has "the complete set of Phrenological busts, five in number." The letter finishes with this charming 'PS':[7]

> Bless your stars that you are not a Doctor. I have been obliged to go out three times since I sat down to write to you.

What this demonstrates is that the Belfast Phrenological Society was actively seeking to purchase O'Neil's series of busts. Plaster casts were a *sine qua non* for Phrenologists and represented the visible hardware of the movement. They consisted of casts of skulls, masks (of faces), and heads (or busts). These 'busts' were very often a head mounted on a square or round base (*socle*) rather than of the classical 'head and shoulders variety.'[10] In Phrenology the terms were used interchangeably. The range of casts in any collection represented the depth of the resource, and Phrenologists would practise on them and memorise the shapes. Hewett Watson advised the student to, "…keep a marked bust frequently before his eyes, so as to become quite familiar with the relevant position…of each organ."[10] Specimens which were highest in demand were those from 'the Great and the Bad' or 'the Famous and the Infamous': thus, those from celebrities, particularly with illustrious intellectual pedigrees or great moral worth (there is a Phrenological bust of James Wilson, the Belfast man who was blind from infancy, and who wrote the famous *Biography of the Blind*,[11] which is in the Anatomical Museum of Edinburgh University);[12] and from criminals, guilty of the most heinous crimes.

By the beginning of 1829, the Belfast Phrenological Society had acquired a wealth of material – as the Belfast Natural History Council minutes reveal. In 1829 the books and casts belonging to the newly fledged Phrenological Society were taken into charge by the Natural History Society. The entry in the Council Minute book for 14th January 1829 lists[13] as belonging to the Phrenological Society: around 15 books, 39 casts of skulls, 34 cast masks, 30 cast busts, and two pairs of steel compasses. In return the Natural History Society would have use of the material and the rent would be waived until the Phrenological Society's meetings were resumed.[13] The Centenary Volume states that there did not seem to be any

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record of further meetings.[1] What had actually happened was that the Phrenological Society had merged with the Natural History Society and was fully embraced by it.

Some weeks after receiving an honorary membership from the Royal Irish Academy, Johann Gaspar Spurzheim gave three 'lengthy lectures' in the Common Hall at Inst between 1st and 4th June 1830. By all accounts he was something of a showman, and his lectures were well-illustrated. *The Northern Whig*, however, was not impressed by his arguments, but in response to Spurzheim's requirement that "...we should not be afraid of truth, and that we should submit to facts" neatly conceded: "The former we readily promise, the latter we are not at liberty to refuse."[14] *The Belfast News-Letter* had a presence at the third lecture and concluded:[15]

> Phrenology as taught by Dr Spurzheim is far from deserving the senseless ridicule that ignorance has cast upon it, whatever may be its merits or demerits as a system; and of those we do not yet profess to be qualified judges.

In 1836, the botanist Hewett Cottrell Watson published[16] his *Statistics of Phrenology*. This was a survey of the state of the art in the British Isles. Watson was a protégé of George Combe, a lawyer, who was the main advocate for Phrenology in these islands.[17] Watson was less than impressed with the response rates to his questionnaire. The first phrenological society in the British Isles was formed in Edinburgh by Combe, his brothers and a few others, in 1820. London followed its example in 1824, and the Belfast Phrenological Society was the sixth to be formed. By 1836 there were 30 phrenological societies in the British Isles.[16]

There is a comprehensive entry for the Belfast Phrenological Society, furnished[18] by the Pharmaceutical Chemist, John Grattan.[19] It gave the date of the Phrenological Society's establishment as 15th January 1827. Its original membership was 44, of whom just seven were medical. From the number of doctors recorded in the membership lists of the day, almost all must have been members of both the Natural History and the Phrenological Societies. This proportion reflected the prevailing ratio of one medical to six non-medical members.

The British Phrenological Association, established in 1838, was short lived for in 1842, two London Members, John Elliotson and William Engledue, espoused an uncompromisingly materialistic view of Phrenology. This created a schism in the ranks from which, "…the institutional aspirations of phrenologists never recovered."[20] By 1850, 'Scientific' Phrenology in the United Kingdom was in terminal decline. In Belfast there seems to have been little further interest in Phrenology among the intelligentsia after the mid-1840s.

The Phrenological Collection

In his excellent account of the 'Anatomy Museum of The Queen's University of Belfast,' David Heylings states that in 1925 the Vice-Chancellor of Queen's reported a benefaction:[21]

> …the University has to thank the Belfast Natural History Society for the permanent loan to the Medical Museums of a series of about 100 casts of anthropometric interest.

It is not clear how much was lost in a fire in 1938 when the Museum was housed in the old building in the quadrangle at

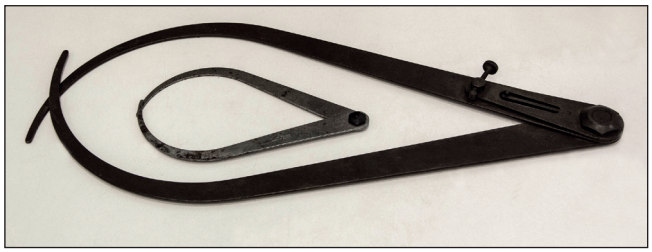

Figure 1:
The 'two pairs of steel compasses' (calipers), courtesy of the Centre for Biomedical Sciences/ Education, QUB

Queen's, as, sadly, the catalogue was lost in the fire. Despite Heylings' admirable efforts to upgrade the Museum, after his departure, constraints on space in the Medical Biology Centre, thanks to an ever-increasing intake of students, led to the remnants of the '100 casts of anthropometric interest' being jettisoned in the early 1990s.[22] The only survivors appear to have been the 'two pairs of steel compasses' (see Figure 1).

Figure 2: The Bust of James Cardinal by Luke O'Neil & Son of Edinburgh

There was, however, one 'Sleeper' in the shape of a bust of James Cardinal, the celebrated hydrocephalic. In 1968 the Museum was moved to the Medical Biology Centre on the Lisburn Road.[105] During the move the old building was 'ragged' by students and Cardinal's bust was borne off as a trophy. It had been 'liberated' by Art students who painted it bright purple and placed it on top of their television as a sort of totem. It was later restored, so all signs of its brush with psychedelia were expunged. It has since resurfaced (see Figure 2) and I can vouch for the bust as coming from the old Museum because I remember it as a particularly striking exhibit during my student days. It occupied part of a glass-fronted display cabinet to the left of the entrance to the main Anatomy lecture theatre, which I attended all too infrequently.

The Bust of James Cardinal

The bust is life-size, standing 14" high, with a head circumference of 35.5", and was made from life (see Figure 10). In the region of the inion is a plaque impressed with the

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legend: 'JAMES CARDINAL, BORN AT COGGESHALL, ESSEX, 27 YEARS OLD.' Across the forehead is a faint printed label which reads 'D 45 Cast of the head of an adult man, the subject of hydrocephalus' which almost certainly was his Queen's University of Belfast Anatomy Museum label. A considerable amount is known about James Cardinal thanks to copious clinical notes kept by the great English physician, Richard Bright, who described Non-suppurative Nephritis.[23]

The original notes (1827-32) and anatomical drawings and water-colours by Bright, with many drawings by Frederick Richard Say and CL Canton (1822-39), are held in the Library of The Royal College of London. Researchers may inspect them on appointment.[24] The earlier ones were published in 1831.[25] Two papers based on these documents have been published in recent years.[23, 26] Cardinal was born on 2nd March 1795 when his head was noted to be, "… a little larger than natural, and had a pulpy feel." His head expanded rapidly until the age of five years. He began to walk unaided by the age of six years but was never very steady and used to fall. He learned to read and write not long afterwards, but reading gave him a headache because he was forced to hold his head low because of near-sightedness.[26]

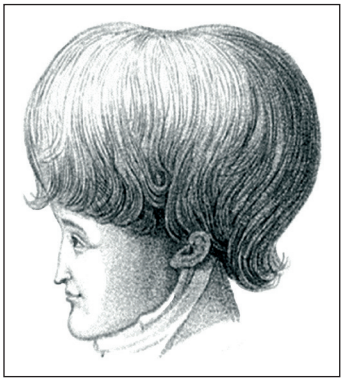

Figure 3: James Cardinal in 1814, aged 19 years, source Ref[31]

Until his fourteenth year a candle held behind his head caused his cranium to become semi-transparent, and Bright described Cardinal's head as "… translucent with the sun shining behind him."[26] This has been cited as the first example of trans-illumination in clinical practice.[27] He was seen by Spurzheim, who in 1815 published a drawing of him when aged 19 years with an abundant head of hair (see Figure 3),[28] which implies that the drawing was made in 1814. Spurzheim did not divulge Cardinal's identity in this publication but did so subsequently.[29] Cardinal began to suffer regular epileptic fits at the age of 23 and his health declined. In 1823 he survived an abscess over his ear which discharged for some time but resolved.

James Macartney, the great Anatomist at Trinity College Dublin, visited Cardinal in London in the summer of 1822. He recorded[30] in his diary that Cardinal was then aged 27 years and that "…the cast of whose head is in every museum." This may once have been true, but I have been unable to track down another example in the anatomy museums of the British Isles, apart from three in the Anatomical Museum of Edinburgh University, which plans to mount an online exhibition of Phrenology in 2021.[12] Macartney had also noted Cardinal's liveliness and intelligence.[30] This was something which Spurzheim had recorded in 1814 when Cardinal:[31]

> …manifested all the moral sentiments and intellectual faculties: he also read and wrote tolerably well.

At the age of 29, on 1st December 1824, Cardinal was admitted to Guy's Hospital under the care of Sir Astley Cooper, the famous Surgeon and Anatomist.[26] There was intense competition amongst Anatomists for the most interesting bodies to dissect and Cooper must have been drooling at the prospect of dissecting Cardinal. Indeed, Anatomists went to huge lengths to beat the opposition. In 1783, John Hunter had to stoop to the outrageous subterfuge of covertly plying Irishmen with drink to acquire the body of James Byrne, the Irish Giant, who was born near the border of Counties Tyrone and Derry in 1761. His skeleton is on exhibition in the Hunterian Museum at the Royal College of Surgeons, London.[32] There are currently calls for Byrne's skeleton to be repatriated.[33]

Cardinal had lately been in St Thomas' Hospital for several months. He "remained pretty" well for a while but then developed a fever and died on 24th February 1825.[26] Long before the advent of shunts, the outcome of progressive hydrocephalus was invariably death. John Holter's development of the first ventricular shunt in 1956, but not in time to save his son Casey, remains one of the most inspiring stories in modern Medicine.[34]

Spurzheim visited a few days after Surgeons Morgan and Keys, with Cooper not in sight, performed Cardinal's post mortem.[29] It showed that he was 5' 7" tall, and his cranium was enormously enlarged, at 33" in circumference (unchanged since 1814[28]), and completely ossified. "Nine pints of water" were found between the skull and the *dura mater*.

Spurzheim was permitted to carry out some further examination of Cardinal's head. In an account written in French a year later he stated:[35]

> I do not think that any case more remarkable than James Cardinal's has ever been the subject of observation. He had hydrocephalus to an enormous amount, and manifested the affective and intellectual faculties.

Figure 4: The Skull of James Cardinal, (Exhibit S28), courtesy of The Gordon Museum of Pathology, Guy's Hospital, London

He goes on to record that the brain was compressed against the base of the skull, and "between the membranes" there were five to six pints of fluid, while the ventricles also contained about a pint. Today Cardinal's skull is on display in the Gordon Medical Museum at Guy's Hospital (see Figure 4).[36]

There were two great, plaster cast makers working in Great Britain in the first half of the 19th century: James De Ville in

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London, and Luke O'Neil in Edinburgh.[10] De Ville, a statuary and lamp maker of The Strand published his first marked bust in 1821. He had been befriended by Spurzheim. From 1818 he began to make masks and then casts of heads. He was to become known as the 'arch-apostle' of Phrenology who amassed a collection of over 5,000 casts.[10]

It was undoubtedly De Ville who made the original of the bust of James Cardinal. Christies sold a bust of Cardinal in 2001 which was attributed to De Ville. It had been 'published' in 1828 but bore an 'A' suffix which De Ville was known to use in 1824.[37] The original cast was most probably made in 1822 because it bears the same inscription as the one described above. It is not surprising that De Ville would have known about Cardinal because he had become something of a celebrity. De Ville sought specimens avidly and once attempted to purchase the skull of another Cardinal, in this case Wolsey, for 200 Guineas.[38]

Luke O'Neil, despite his name, was of Italian extraction and is credited with publishing (producing) the first phrenological bust in 1821 for the newly formed Edinburgh Phrenological Society.[10] In the Transactions of the Edinburgh Phrenological Society, the *de facto* first edition of The Phrenological Journal in 1824, O'Neil and Son published a catalogue of the casts they offered for sale.[39] In the preface to this it is stated that the President, Sir George MacKenzie, had made his collection of casts available to O'Neil & Son "…for the purpose of enabling them to supply collections." Plagiarism seems to have been rife in those days so a strong suspicion[40] that the plaster casters copied one another's work seems to be confirmed by the statement above.

Intriguingly, No 6 in Luke O'Neil & Son's 1824 catalogue[39] is 'James Cardinal; an Illustration of Hydrocephalus.' It seems highly plausible that this bust was pirated from De Ville via Sir George MacKenzie's collection. It is identical to the De Ville bust except for a round *socle,* whereas De Villes's had a squarish one.

The clinching evidence that the bust of Cardinal under discussion is by O'Neil is that it bears a '6' on the *socle*, directly below the chin. Phrenologists were not only interested in the skulls of the 'Great and the Bad', but also in those affected by major pathological conditions, such as hydrocephalus.

CONCLUSION

As we have seen, Phrenology was often more avidly adopted by clergymen and lawyers, seeking to morally improve, or even to resolve criminality, than the medical profession. Even so, some of Belfast's leading physicians were keen devotees, most notably: James Drummond and James McDonnell. When Phrenology fell out of fashion, it was conveniently dropped and ignored as a movement which had strongly influenced Belfast Medicine. Later, The Natural History and Philosophical Society and Belfast Medicine may have wished to draw a veil over its dalliance with what the proto-socialist William Godwin, husband of the proto-feminist Mary Wollstonecroft,[41] dismissed as a 'shapeless science.'[42]

Never-the-less, Phrenology contributed to science in some momentous ways: it correctly identified the Brain as the seat of the Mind; and, did much, no matter how serendipitously, to unshackle Science from religious superstition, and prepare it for Evolutionary Theory. Moreover, it left a legacy of human measurement and a focus on individual differences.[43] If nothing else, it enriched[44] our language with words such as 'highbrow' and 'lowbrow.' Despite all this, a popular quip of the period was that, 'Fools and Phrenologists are terms… nearly synonymous.'[45] Yet, during the second quarter of the 19th century, the cream of Belfast Medicine was seduced by Phrenology, but in so doing, it was in excellent company.

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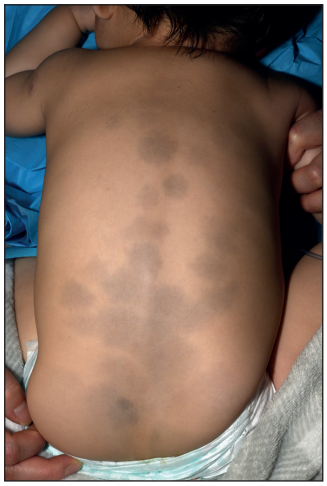
Ulster Med J 2021;**90(2):**117 - 118

Curiositas

UNDERGRADUATE QUIZ



Prior to an elective procedure, a paediatrician was asked to review this 14 month old patient after a consultant anaesthetist raised concerns about marks noted on their back.

1. What is the likely diagnosis?
2. Do you have any safeguarding concerns? What evidence could be reviewed to confirm the diagnosis?

Jonathan Callaghan (4th year medical student, Queen's University Belfast), Dr Melissa Mulholland (Paediatric trainee), Dr Thomas Bourke (Consultant Paediatrician), Dr Andrew Thompson (Consultant Paediatrician), Royal Belfast Hospital for Sick Children. The authors would like to thank the patient (and their parent) who gave consent for this image to be published.

POSTGRADUATE QUIZ

Platelets:	205 x 10^9/L (200-550)
PT:	11 s (9.3-11.8)
APTT:	60 s (23.4-32.4)
TT:	10 s (14-22)
Fibrinogen:	3 g/dL (1.9-4.0)
Factor (F) VIII:C:	0.1 IU/mL (0.6-1.3)

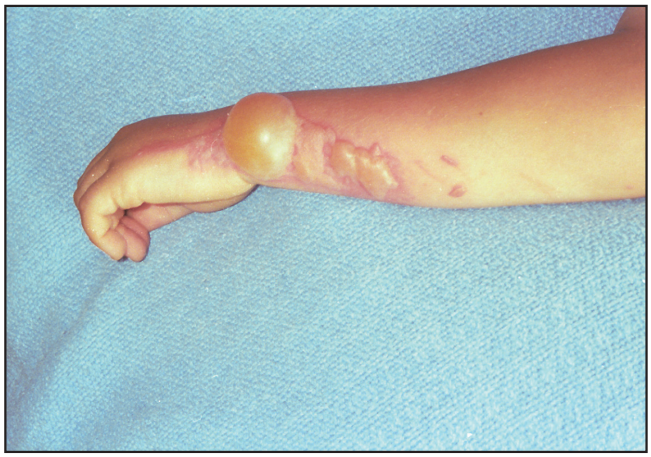
(PT Prothrombin time, APTT Activated Partial Thromboplastin Time, TT Thrombin time)

A 15 month old boy was referred for a safeguarding assessment by his health visitor after they had noticed significant bruising. On examination he had multiple bruises over bony prominences but also on his arms, buttocks and back. His mother reported frequent falling and had noticed that he tended to bruise easily. On a couple of occasions, she had noticed bleeding from his gums when brushing his teeth and commented on bruising following his vaccinations. There was no family history of bleeding disorders.

1. What are the indications to perform haematological investigations for a child presenting with bruising?
2. What first line haematological investigations would you request?
3. What does this extended coagulation screen suggest might be the cause of this child's bruising and what test is required to confirm the diagnosis?

Dr Simon McCracken (Paediatric trainee), Dr Melissa Mulholland (Paediatric trainee), Dr Andrew Thompson (Consultant Paediatrician), Royal Belfast Hospital for Sick Children.

HISTORICAL QUIZ

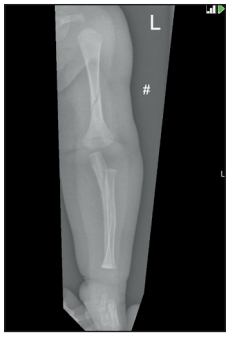


A 7 year old boy was referred with bullous lesions. The paediatrician was asked to review as they were thought to be inflicted burns. The boy had been out all day with his friends and his mother was unaware of any injury sustained.

What is the probable cause of these "scalds"?

Dr Melissa Mulholland (Paediatric trainee), Dr Thomas Bourke (Consultant Paediatrician), Dr Andrew Thompson (Consultant Paediatrician), Royal Belfast Hospital for Sick Children.

AND FINALLY…



A 3 year old attends the Emergency Department (ED) accompanied by his mother. He is not moving his arm and is very distressed. His mother reports catching her son by his arm as he fell from a swing in a playground. She heard an audible crack at the time and brought him to ED immediately.

1. What does this X ray show?
2. Does the explanation match the clinical finding?
3. What factors might heighten safeguarding concerns?

Dr Melissa Mulholland (Paediatric trainee), Dr Thomas Bourke (Consultant Paediatrician), Dr Andrew Thompson (Consultant Paediatrician), Royal Belfast Hospital for Sick Children.

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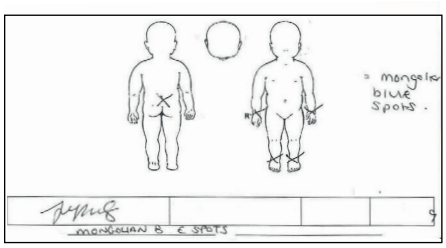
CURIOSITAS: Answers

UNDERGRADUATE QUIZ

1. These are Mongolian blue spots, also known as lumbosacral dermal melanocytosis. This is a congenital lesion (or "birthmark") where one or several blue/grey, homogenous macules or patches of up to several centimetres appear, usually in the lumbosacral region. Lesions may also be seen at other sites and can appear superimposed. They occur very commonly in South, East and Central Asian, Native American and other non-European babies and are seen infrequently in those of Caucasian descent. These spots are benign, non-tender and do not evolve over short time periods. Although they can persist, they usually regress over the first few years of life, with nearly all disappearing by puberty. The term "Mongolian blue spot" has an interesting history, with some calling for use of a more scientific term rather than one perceived to be based on racial generalisations[1].

2. The main differential diagnosis for this appearance is bruising from child abuse. This would prompt a thorough investigation and non-accidental injury work-up. It is important to always be vigilant for any safeguarding concerns. However, this was not an issue in this case. An important way to differentiate Mongolian blue spots from haematomas is review of the patient's medical notes. Although the distribution of the lesions and ethnic background of the patient could be useful pointers, previous documentation of the lesions is the most reassuring and definitive indication of this diagnosis. The Patient Care and Health Record or 'Red Book' contains a body map where these marks should be documented following examination shortly after birth.



[1]*Zhong, C., Huang, J. and Nambudiri, V. (2019) Revisiting the history of the "Mongolian spot": The background and implications of a medical term used today. Pediatric Dermatology, 36, 755-757.*

POSTGRADUATE QUIZ

1. It is important to consider haematological investigations in any child presenting with unusual bruising or bleeding out of proportion to the injury sustained. If there are any indicators from the history and/or examination that the child may have a bleeding disorder, haematological investigations should also be performed.

2. First line haematological investigations include a coagulation screen (PT, APTT, TT, fibrinogen), a full blood count and blood film, assays of factor VIII, IX, XIII and Von Willebrand factor (VWF antigen and VWF activity)[1].

3. The extended coagulation screen suggests a diagnosis of either Haemophilia A or Von Willebrand's disease (prolonged APPT, low levels of FVIII, normal platelets and normal PT). From the history, a diagnosis of VWD is more likely given the evidence of easy bruising and mucosal bleeding. Haemophilia tends to present with joint and soft tissue bleeding along with prolonged or excessive bleeding, common to both conditions. The first line investigation in this scenario is the ristocetin cofactor test[2]. The addition of ristocetin (an antibiotic) to a patient's plasma, causes VWF to bind to platelets, resulting in agglutination. This is diminished or absent in VWD but normal in Haemophilia A, hence allowing differentiation between the two conditions in most circumstances. A subtype of VWD (2N VWD) is challenging to discriminate from mild-moderate haemophilia A and therefore genetic testing is indicated to confirm the diagnosis.[3]

[1]*RCPCH Child Protection Companion (2019). Chapter 9: Recognition of Physical Abuse.*

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HISTORICAL QUIZ

These are chemical burns (phytophotodermatitis) inflicted by the sap of the phototoxic plant, giant hogweed. Treatment is the same as for any chemical burn, and post inflammatory hyperpigmentation may last months or even years. In Northern Ireland, these plants are often found in abundance at the water's edge of riverbanks or canals. Like so many ornamental invasive plant species introduced to British gardens in the early nineteenth century, it is now widespread in many regions of Europe and North America after its introduction from the Caucasus region of Eurasia.

AND FINALLY…

1. This is an AP film of the patient's left arm. The obvious finding is a spiral fracture of the mid shaft of the humerus.

2. Humeral fractures are particularly concerning for abuse in younger children. A meta-analysis showed that a child who is under the age of 3 years presenting with a humeral fracture has a 1 in 2 chance of having been physically abused.[1] Spiral and oblique fractures are the most common abusive humeral fracture types found in children but can occur accidentally. Spiral fractures occur due to a rotational force applied to the bone. The history given in this case would explain the clinical finding of a spiral fracture. Any explanation given by caregivers must be consistent with both the mechanism of injury and the child's developmental age.

3. Skeletal fractures are a common childhood injury. Approximately one third of children will experience a fracture before the age of 16. Fractures are also commonly found in up to one third of children who have suffered physical abuse.[2] It is therefore vital that clinicians are able to differentiate signs of intentional and unintentional injury. Younger age, an inconsistent or implausible history, multiple injuries and delayed presentation are factors that, when present in a child with a fracture, should trigger consideration of abuse.

[1]*Kemp AM, Dunstan F, Harrison S, Morris S, Mann M, Rolfe K et al. (2008) Patterns of skeletal fractures in child abuse: systematic review. BMJ 337: a1518*

[2]*RCPCH Child Protection Companion (2019) Chapter 9: Recognition of physical abuse.*

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Letters

INTRODUCING EXTENDED VENOUS THROMBOEMBOLISM PROPHYLAXIS FOR HIGH-RISK VASCULAR PATIENTS UNDERGOING LOWER LIMB AMPUTATION - A QUALITY IMPROVEMENT PROJECT

Editor,

Venous Thrombo-Embolism (VTE) is an established cause of morbidity and mortality amongst vascular surgery patients undergoing lower limb amputation[1,2]. All-cause mortality rates amongst this patient group are already substantial[3], thus VTE risk reduction may improve outcomes. However, best practice regarding post-operative VTE prophylaxis is unclear[4,5].

National Institute of Clinical Excellence guidelines suggest that vascular surgery patients should receive low-molecular-weight heparin until mobility is *no longer significantly reduced*[1]. However, for many amputees, the reduction in mobility from baseline is permanent, and the optimum duration of VTE prophylaxis is unclear.

The aims of this Quality Improvement Project (QIP) were: -

- to establish baseline practice within Northern Ireland's regional Vascular Surgery Unit regarding VTE risk-assessment and prophylaxis upon discharge
- introduction of a novel VTE risk-assessment proforma
- completion of two Plan-Do-Study-Act (PDSA) cycles to assess use of the proforma.

Prior to this QIP, VTE risk-assessment would be undertaken amongst all vascular patients upon admission, and prophylactic-dose enoxaparin prescribed during the inpatient stay (if indicated). However, there was typically no formal assessment of ongoing VTE risk upon discharge.

The VTE risk-assessment proforma was devised in conjunction with the local Haematology department and approved by the regional pharmacy group. The proforma was designed to facilitate assessment of the risk of VTE development versus the risk of bleeding should anticoagulation be prescribed. Where indicated, prophylactic-dose enoxaparin for thirty days post-operatively was recommended.

Information regarding VTE risk-assessment and prophylaxis upon discharge amongst patients undergoing lower limb amputation was obtained via review of inpatient records and electronic discharge prescriptions. Assessment of baseline practice was conducted throughout August - October 2016. Two subsequent PDSA cycles were conducted at one week and at two months following formal introduction of the proforma (April 2017). Interventions were made in the form of weekly educational seminars for junior doctors and empowerment of the ward pharmacist to encourage proforma use.

Results of the study are demonstrated in **Table 1**. At baseline, none of the patients underwent VTE risk-assessment upon discharge and none received new anticoagulation. One week following proforma introduction, 67% of patients underwent VTE risk-assessment +/- enoxaparin prescription. Two months following proforma introduction, compliance had risen to 80%.

Barriers to using the risk-assessment proforma include lack of staff awareness, which may reflect the rotation- and shift-based working patterns of junior doctors. Due to the single-centre nature of this study with small patient numbers, it has not been possible to determine statistical significance of our results.

In summary, patients undergoing lower limb amputation are generally at high risk for developing VTE due to pre-operative co-morbidities and post-operative immobility. With this QIP, we have introduced a novel VTE risk-assessment proforma and demonstrated acceptable and improving compliance levels at one-week and two-month intervals. We anticipate

Table 1.
Numbers of patients for whom Venous Thrombo-Embolism (VTE) risk-assessment was undertaken upon discharge, and VTE prophylaxis (enoxaparin for 30 days from date of lower limb amputation) prescribed where indicated, is shown.

	Total number of patients undergoing lower limb amputation	Number considered at risk for post-operative VTE	Number already receiving anticoagulation for pre-operative factors	Number receiving risk assessment +/- extended VTE prophylaxis upon discharge	Number managed in accordance with novel proforma
Baseline	17	15	3	0	3/15 (20%)
Cycle I	6	6	0	4	4/6 (67%)
Cycle II	20	20	4	16	16/20 (80%)

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that with increased familiarity of staff with the proforma, all patients will be risk-assessed upon discharge and will receive VTE prophylaxis if indicated. Further work should assess ongoing compliance with the proforma, and explore the impact of extended VTE prophylaxis on morbidity and mortality amongst vascular surgery patients.

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EVALUATION OF COMPUTED TOMOGRAPHY (CT) CHEST AS A SCREENING TOOL FOR COVID-19 IN SURGICAL PATIENTS PRESENTING TO THE ROYAL VICTORIA HOSPITAL EMERGENCY DEPARTMENT- A NORTHERN IRISH STUDY.

Editor,

Coronavirus disease (COVID-19) is an on-going pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. Undiagnosed COVID-19 infection can complicate peri-operative outcomes and increase transmission to staff via aerosol-generating anaesthetic procedures. In the absence of rapid reverse transcriptase-polymerase chain reaction (RT-PCR) testing, it had been recognised that CT chest could play a role in surgical emergencies where awaiting laboratory results would delay patients' management. On 25th March 2020, the British Society of Thoracic Imaging (BSTI) and the British Society of Gastrointestinal and Abdominal Radiology (BSGAR) recommended low-dose CT chest in addition to CT abdomen and pelvis in patients presenting as a surgical emergency[2].

We aimed to evaluate the use of additional CT chest in acute surgical patients presenting to the Emergency Department (ED) of the Royal Victoria Hospital, Belfast.

CT chest, abdomen and pelvis scans requested from ED where the indication was to identify acute surgical pathology were included. Chest x-ray (CXR) and CT images were obtained from Picture Archiving and Communication System (PACS) which were graded according to the BSTI guidelines; normal, indeterminate and classic/probable COVID-19[3]. Patient outcomes were verified from Northern Ireland Electronic Care Record (NIECR).

A total of 100 patients underwent CT chest as part of the national acute abdominal imaging pathway for COVID-19 from 1st March to 2nd May 2020.

Using BSTI CT reporting proforma, no CT chest scans were reported as classic/probable COVID-19. Three were reported as indeterminate, 78 scans were normal and 19 demonstrated other pathology. Interestingly, the only positive RT-PCR case had a normal CT chest.

Table 1.
CXR, CT and RT-PCR results in symptomatic cohort

Symptomatic patients	Report	%	n
CXR	Normal	35	6
	Abnormal	18	3
	Not performed	47	8
CT	Normal	82	14
	Indeterminate	6	1
	Classic/probable	0	0
	Other/non COVID	12	2
RT-PCR	Negative	76	13
	Positive	6	1
	Not performed	18	3

Table 2.
CXR, CT and RT-PCR results in asymptomatic cohort.

Asymptomatic	Report	%	n
CXR	Normal	41	29
	Abnormal	17	12
	Not performed	42	30
CT	Normal	75	53
	Indeterminate	2	2
	Classic/probable	0	0
	Other/non COVID	23	16
RT-PCR	Positive	0	0
	Negative	61	43
	Not performed	39	28

Of the three patients who had indeterminate findings on CT, results did not alter surgical management in any case. The first case was asymptomatic and RT-PCR negative. CT reported patchy areas of ground glass opacification (GGO). The patient was admitted to intensive care for the management of pancreatitis.

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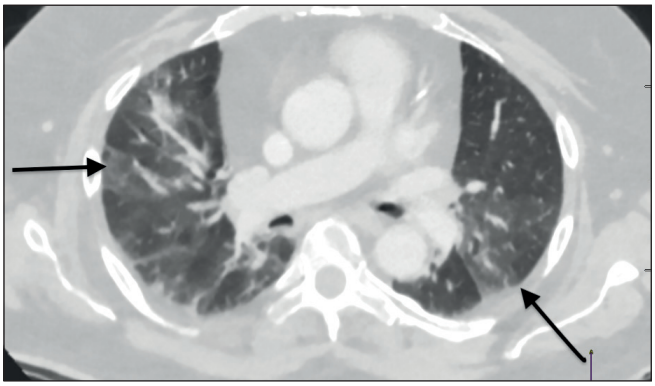
Figure 1.

Example of indeterminate findings on CT chest with ground glass opacification within basal aspects of both lower lobes (arrows).



The second patient was asymptomatic and RT-PCR negative. CT reported dependant lower GGO, equivocal for COVID-19. The patient proceeded to emergency laparotomy for intra-abdominal perforation. CT findings had no bearing on surgical management, however influenced bed management decisions.

The third case was a symptomatic patient with cough and fever, RT-PCR negative. CT reported GGO in the right upper lobe and multifocal consolidation in both lower lobes. The patient was managed conservatively for pancreatitis.

Additional CT chest screening had no impact on acute surgical management in our study. Due to increased radiation exposure, demand on radiology services and low diagnostic yield, BSTI/BSGAR advised that additional CT chest is no longer recommended[4]. Fortunately, we now have improved access to point-of-care testing e.g. LumiraDx SARS-CoV-2 Ag test which provides results within 20 minutes aiding timely surgical management[5].

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"WHY AM I SO YELLOW??" – LATE ONSET SEVERE HYPERBILIRUBINEMIA DUE TO CARBIMAZOLE THERAPY

Editor,

We present the case of a 38 year old male with late onset of severe hyperbilirubinemia 1 year after commencing carbimazole therapy. He had a history of hyperthyroidism, diagnosed in May 2019. His thyroid function tests (TFTs) were difficult to stabilize on carbimazole titration. Therefore, he was switched to block and replace treatment with carbimazole 40 mg and levothyroxine 100 micrograms daily after 3 months. TSH receptor antibodies were strongly positive in keeping with Graves' disease.

He presented to hospital in June 2020 with a 6 week history of jaundice, mild abdominal pain and feeling generally unwell. He had no prior history of liver disease and had a normal bilirubin in March 2020, with mildly cholestatic pattern of liver function tests. On admission, his bilirubin was 129 with a mixed cholestatic-hepatitic pattern of liver enzymes. Prothrombin time (PT) was raised at 15. Ultrasound imaging revealed normal liver structure with no biliary dilatation. Carbimazole was stopped and a full liver screen sent. He initially discharged himself against advice, however, he was re-admitted in July when his jaundice worsened and bilirubin had risen to 459 on repeat bloods with PT of 18.6. He did not have any other evidence of decompensated liver disease. MRCP showed no abnormalities within the biliary tree. Bilirubin continued to rise and liver biopsy was undertaken which revealed features of a mixed cholestatic-hepatitic liver injury, with the cholestatic injury significantly more prominent. It was considered most likely to represent a drug related liver injury. The patient had taken no other prescribed or over the counter medication and no illicit substances. Over time, liver function slowly improved and the jaundice resolved completely. Propylthiouracil was considered inappropriate for treatment given risk of hepatotoxicity and iodine was not practicable due to social circumstances. The patient went on to have a total thyroidectomy.

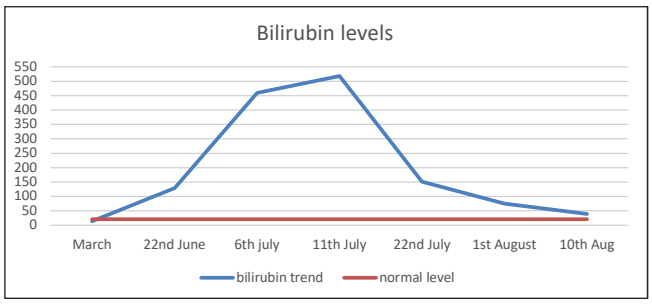

Fig 2: trend of bilirubin levels

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Fig 1: summary of LFTs

	Normal reference ranges	March 2020	June 22nd 2020 (1st admission)	July 6th 2020 (community bloods and readmission)	July 11th 2020 (bilirubin peak)	July 22nd 2020	August 1st 2020	August 10th 2020
Bilirubin (umol/L)	<21	14	129	459	518	151	75	39
ALP (u/L)	30-130	187	266	305	267	267	138	144
AST (u/L)	<40	27	119	123	84	84	35	27
GGT (u/L)	10-71	100	110	Not report-able	Not reportable	52	97	74
ALT (u/L)	<41	35	138	130	88	81	29	16

Discussion:

Methimazole (active metabolite of carbimazole) has been associated with transient, asymptomatic elevations in serum aminotransferase levels, typically during the first 3 months after starting high dose, induction therapy.[1]

It can also cause a clinically apparent, idiosyncratic liver injury. Onset is usually within 2 to 12 weeks of starting therapy and typically causes a cholestatic or mixed pattern of enzyme elevations, without evidence of hepatic necrosis on liver biopsy.[2] Most patients recover on drug discontinuation. There are, however, occasional reports of severe and fatal cases. The proposed mechanism of carbimazole□induced cholestasis is not fully understood.[1]

This patient developed severe hyperbilirubinemia 1 year after starting treatment with carbimazole. His bilirubin level peaked at 518, significantly higher than reported levels in the literature to date. It then began to slowly settle over a period of 4 weeks. Although hepatotoxicity is a rare side effect of antithyroid medication, it can be a significant one. It is important to remember to consider it as a cause of jaundice, with the potential to occur many months after starting treatment. Patient awareness is very important and they should be counselled about the potential side effect and to consult a doctor if they notice jaundice developing. This patient waited for 6 weeks before seeking medical attention, without realising that his medication could be causing this problem.

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FACTORS ASSOCIATED WITH IMPROVED CLINICAL CONTROL IN A DIFFICULT-TO-TREAT PAEDIATRIC ASTHMA COHORT THROUGH THE COVID-19 PANDEMIC LOCKDOWN PERIOD

It is recognised that fewer children attended Emergency Departments (ED) with asthma exacerbations during the COVID-19 pandemic.[1,2] However, it is unclear why. The common triggers of asthma attacks include viral infections, high pollen counts and air pollution. It would seem likely that significant changes in one of more of these would impact on asthma control. There have been no reports, to our knowledge, examining asthma control and medication adherence in a paediatric difficult to treat (DTA) asthma cohort over this period, and comparing it with air pollution and respiratory viral data. The clinical course of, and external influences upon, the Northern Irish paediatric DTA cohort through the pandemic can inform this discussion. The UK

Table 1. Comparison of factors associated with asthma control for the Northern Irish paediatric DTA cohort between corresponding epochs in 2019 and 2020. Air pollution and pollen levels refer to daily levels measured in Belfast over the specified epoch

	1st Feb- 31st May 2019	1st Feb-31st May 2020	p-value
PM_{10} (μg/m³)	16·4 (10·6)	13 (5·6)	<0·01
$PM_{2.5}$ (μg/m³)	52·5 (24)	31·1 (12·9)	<0·01
SO_2 (μg/m³)	4·3 (2·2)	1·3 (0·6)	<0·01
NO_2 (μg/m³)	11 (4·9)	10·9 (7·8)	0·9
Plane tree pollen (grains/m³)	0·4 (1·5)	0·01 (0·1)	0·01
Hazel tree pollen (grains/m³)	1·1 (2·2)	0·4 (1)	<0·01
Ash tree pollen (grains/m³)	2·2 (4·6)	10 (23·3)	<0·01
Grass pollen (grains/m³)	0·4 (1·4)	2·3 (6·8)	0·04
Unscheduled care attendances /per patient*	0 (0,1)	0 (0,0)	0·01
ACT score (out of 25) *	17 (12,19)	20 (15,24)	<0·01
Number of courses of oral steroids/ per patient *	0 (0,1)	0(0,0)	0·01
Adherence (% collections of ICS prescriptions) *	100 (60,100)	100 (50,100)	0·6

Data are presented as Mean (SD) unless indicated.

* Median (IQR). Statistical tests used: Student t-tests and Wilcoxon rank-sum tests for non-parametric data. A p-value ≤0.05 indicated statistical significance.

ICS: Inhaled corticosteroids; ACT: Asthma Control Test; NO_2: Nitrogen dioxide; PM_{10}: Particulate matter less than 10 μm in diameter; $PM_{2.5}$: Particulate matter less than 2·5 μm in diameter; SO_2: Sulphur Dioxide.

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Government recommended that children with severe asthma should 'shield' from COVID-19 infection.[3] To determine if there was evidence of a significant difference from the previous year, the clinical course of the DTA cohort of 51 patients through the epoch February-May 2020 was compared with the corresponding epoch in 2019. Unscheduled care attendances, courses of rescue oral corticosteroids (OCS), a marker of medication adherence (repeat prescriptions), and Asthma Control Test (ACT) scores for the DTA cohort were compared (Table 1). Levels of airborne aeroallergens, air pollution data and prevailing respiratory viruses over the two epochs were also compared.

Unscheduled care attendance data suggested that the cohort presented significantly less to emergency services and received fewer courses of rescue OCS during the pandemic than in 2019. ACT data was better for the 2020 epoch, suggesting that these differences may be on the basis of improved asthma control. No difference in inhaler adherence was observed. This may represent a 'ceiling effect', as sub-optimal adherence is improved and reinforced with remote monitoring at our DTA clinic.[4] Respiratory viral data showed that the number of samples of secretions positive for rhinovirus in 2020, as a percentage of the total number of positive samples, was less than half of that for 2019 [total positive samples: 9940 in 2019 and 12645 in 2020 - and rhinovirus positive samples: 428 (4·3%) v 234 (1·9%)]. There was no consistent pattern for tree pollen levels but there were greater levels of grass pollen in 2020. Air pollution data showed significantly lower levels of atmospheric $PM_{2.5}$, PM_{10} and SO_2 (but not NO_2) during the 2020 epoch.

This data suggests that shielding has been protective through the pandemic, leading to improved asthma control. The viral data may reflect the restricted movement of children, thereby limiting viral spread. Less air pollution is also likely a contributor to fewer exacerbations. Although there were greater airborne grass pollen levels in 2020, children may have been protected from outdoor exposure as a result of shielding indoors.

Once shielding stopped, children were mixing much more, resulting in greater exposure to respiratory viruses. However, schools have tried to implement measures to maintain social distancing and attenuate viral spread. It remains extremely important to optimise adherence, inhaler technique and the use of asthma plans over this period of uncertainty to help to minimise asthma morbidity.

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External data sources
Pollution data: The World Air Quality Index Project
Pollen data: The UK Meteorological office
Respiratory viral data- The Regional Virology Laboratory, Belfast

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PROTHROMBIN COMPLEX CONCENTRATE USE IN BELFAST HEALTH AND SOCIAL CARE TRUST

Dear Editor,

Prothrombin factor concentrate (PCC; Octaplex®), a combination of human coagulation factors II, VII, IX and X, protein C and protein S, is a potent reversal agent for vitamin K antagonists. Along with Vitamin K, it is used in emergency management of bleeding associated with warfarin and direct oral anticoagulants (DOACs).[1] Despite widespread use, there is a lack of consensus about optimal dosing,[2] with current guidelines specifying large ranges for dosing or, in the case of DOACs, no dosing recommendations at all.[3] Lack of clarity complicates development of clear local protocols, making accurate and timely administration more difficult, as highlighted by a serious adverse incident in which delayed administration led to a poor clinical outcome.[4]

This service evaluation aimed to assess current use of PCC in Belfast Health and Social Care Trust (BHSCT), to identify areas for improvement and improve alignment between local guidance and practice on-the-ground.

Two current BHSCT guidelines on management of bleeding while receiving anticoagulants provided audit standards. We sought records of all patients who received PCC within BHSCT between January and June 2016. We designed, piloted and adapted a pro-forma which was then used by Haemovigilance Specialist Nurses. Data were collated in Microsoft Excel and analysed using descriptive statistics to

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Table 1: Key findings

Audit standard	Finding
Patients on warfarin should receive 15 IU/kg PCC if INR<4, 30IU/kg if INR>4	Baseline INR <4: average dose 16.4 IU/kg (24 patients) Baseline INR >4: average dose 29.5IU/kg (9 patients)
Patients on DOACs should receive 40IU/kg PCC	Average dose in patients on apixaban or rivoroxiban (8 patients) 35.6 IU/kg
Patients on warfarin should receive 5mg IV Vitamin K in addition to PCC	Number of patients who received Vitamin K - 38 Dose of Vitamin K administered: 1mg - 1/38 (3%) 5mg - 31/38 (82%) 10mg - 6/38 (16%) No vitamin K administered - 10/48
Patients on warfarin presenting with head injury should receive PCC prior to neuroimaging	Prior to neuroimaging - 1/14 (7%) After neuroimaging - 13/14 (93%)

summarise patients' baseline characteristics, PCC dosing, coagulation assay results and clinical outcomes.

Records were available for 62 of 98 eligible patients. Twenty-nine were female (47%). Ages ranged from 34-95 years, with a mean of 71 years. At time of PCC administration, 44 patients were receiving warfarin (71%), 8 apixaban (13%) and 6 rivaroxaban (10%). One patient was not receiving any anticoagulant (2%); information was unavailable for 3 patients (5%). Average dose of PCC was 1739 IU (range 714-4000 IU). Only 34/62 (55%) patients received doses involving use of whole (500IU) vials. Weight was recorded for 49 patients (79%) but prior to administration in only 18 cases (29%). 18/62 (29%) of weights were estimated rather than measured. Administration of PCC was associated with an average reduction in International Normalised Ratio (INR) of 2.13. The average INR after administration was 1.36. Twelve patients (28%) were deceased by 60 days after administration. Table 1 summarises other key findings.

Most PCC dosing adhered to guidance, although many patients were not weighed prior to administration. Other areas of shortfall were identified, however. In patients with suspected intracranial bleeding, PCC was frequently administered after, rather than prior to, neuroimaging. Vitamin K was often inappropriately omitted during reversal of warfarin. We also found that it was common practice to use incomplete vials of PCC. While not precluded by current guidance, this practice could lead to PCC, at a cost of up to £21,560 per year, being discarded that could potentially improve clinical response if administered. Targeted quality improvement work is now needed to ensure that patients are weighed appropriately, PCC is given prior to neuroimaging in patients with head injury, and vitamin K is co-administered when reversing warfarin. Guidance should be updated to recommend that PCC doses involve use of complete vials. These interventions have the potential to maximise the efficacy and cost-effectiveness of PCC in the treatment of life-threatening haemorrhage.

Acknowledgements

We would like to thank the Haemovigilance Specialist Nurses for collecting the data used in this audit.

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REDEPLOYMENT IN A BELFAST COVID CENTRE: PLAYING IT SAFE OR PLAYING WITH FIRE

Editor

The COVID 19 pandemic has provoked the most significant re-purposing of services, capacity and staffing in NHS history,[1] with staff redeployed to unfamiliar roles to meet workforce demands.

In Belfast, the Mater Infirmorum Hospital was designated the COVID centre. Given the acuity of these COVID patients, high levels of non-invasive ventilation were utilised at ward level, most notably continuous positive airway pressure (CPAP). To assist with demand, staff from non-medical specialties (surgery, ophthalmology, psychiatry & OB GYN), were redeployed to the Mater. These staff remained for 7-21 days prior to an exchange of redeployed personnel. Ranging in grade from FY2 to ST4, redeployed staff reported varying experience regarding respiratory medicine and COVID.

Inadequate training of redeployed staff has the potential to generate patient safety issues and anxiety amongst those redeployed. We sought to ascertain the confidence levels of those redeployed to the Mater in January 2021 (3rd surge) in relation to COVID management and CPAP. We explored the level of training and induction these staff received, aiming to identify areas for improvement.

Methods

An anonymous survey was sent to all staff redeployed to the Mater in January 2021 (n=16). Initially this was sent to 8 medical staff deployed from the 1st – 14th January 2021, with a 100% response rate. Notably 50% of staff in this cohort had never previously managed a COVID patient. These staff received 'basic' site induction, with no formal education about COVID management or CPAP. Using this feedback, an improved induction program was formulated for future redeployed staff.

A further 8 staff were redeployed from 15 – 31st January, receiving an enhanced teaching at induction with a practical session on CPAP. They were also given a written guide, including information on pharmacological COVID management including VTE prophylaxis, when and how to initiate CPAP, managing the deteriorating COVID patient and parameters for ICU referral. The same anonymous questionnaire was then used to examine if greater education improved confidence levels in this cohort.

Results

The initial survey revealed none of those redeployed felt confident in managing CPAP. The intervention resulted in an increase in confidence, with 62.5% stating they felt confident/very confident in managing a COVID patient on CPAP, with 37.5% feeling neutral. Crucially, no one indicated they felt concern after the improved induction. Similarly, the enhanced training showed 75% of this cohort felt knowledgeable in the pharmacological management of COVID, an improvement from 25% previously.

Discussion

Redeployment is a time of great uncertainty, noted to generate higher levels of stress and anxiety in redeployed personel.[2] Doctors redeployed to the Mater had out-of-hours commitments admitting acutely unwell patients and were allocated to wards with patients on various forms of non-invasive ventilation. This data highlights the importance of a thorough induction for redeployed doctors to ensure confidence with their new duties. Due to the short duration of redeployment (1-3 weeks), a focused, time-efficient approach is required. Interventions such as written information and practical teaching sessions appear effective in improving the confidence of redeployed staff. We argue this helps mitigate against potential negative effects on wellbeing of those redeployed due to being overwhelmed, whilst allowing the additional workforce benefit to be effective.

One criticism proffered was that the improved training programme was overwhelming for one sitting. Acknowledging this, and appreciating the trade-off between providing a thorough induction and maximising the resource of redeployed staff, a solution may be to provide the written guide to doctors prior to redeployment. Similarly, recording the CPAP session and placing it on the hospital webpage would allow staff to view at their leisure. Lastly, we would like to take the opportunity to thank those staff who volunteered for redeployment to the Mater during the pandemic. You truly have been an invaluable asset.

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CASTING LIGHT ON THE CHALLENGES OF ILLUMINATING ENT EXAMINATIONS DURING THE COVID-19 PANDEMIC

Editor

Protecting healthcare staff from SARS-CoV-2 infection is a crucial element of the Covid-19 pandemic response and personal protective equipment (PPE) is vital in this respect. A high viral load of SARS-CoV-2 virus has been found in the nasal cavity and oropharynx of infected individuals, including patients with few or no symptoms[1]. Examinations of the ear, nose and throat (ENT) have the potential to release aerosols within close proximity of the clinician. Public Health England (PHE) recommend a full-face shield or visor or polycarbonate safety spectacles, as well as a filtering face piece class 3 (FFP3) respirator for aerosol generating procedures (AGP)[2]. ENT UK recommend full PPE for examinations and interventional procedures of the upper aerodigestive tract given that they are potential AGPs[3].

We have found that it is difficult, and not always possible, to use a full-face visor with a headlight for ENT examinations or procedures given that they both attach to the same area on the forehead. We have created protective goggles with an integrated LED light to overcome this problem (Figure 1). An LED light attached by cable to a rechargeable battery pack was sourced from an online retailer and the light was attached to protective goggles. A small hole was made on the top of the goggles to allow the LED light to slot into place and a screw on the light was pushed through the goggle material for a secure attachment. The goggles and LED light can be wiped down after use.

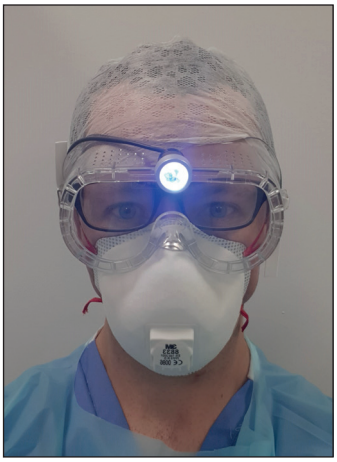

Figure 1:
protective goggles with integrated LED headlight worn with full PPE

Where these protective googles are unavailable, a peritonsillar abscess may be drained using a pen torch and tongue depressor. A tongue depressor is taped onto the end of a disposable pen torch. (Figure 2). This allows for tongue depression and targeted illumination of the peritonsillar area with one hand. We have devised a similar technique for nasal cautery. A silver nitrate stick taped to a disposable pen torch allows for targeted illumination of the nasal septum and simultaneous application of silver nitrate whilst using a nasal speculum in the other hand (Figure 3). Both techniques allow the clinician to use full PPE, including a visor or goggles, without the need for a headlight.

It is crucial that as clinicians we use adequate PPE to protect ourselves during ENT examinations and procedures. We must continue to do this as we return to elective practice whilst the SARS-CoV-2 virus is still in circulation within the community and a vaccine is not yet available. We must use adequate PPE for all patients in an elective setting because we know that people can be infected with SARS-CoV-2 and remain asymptomatic[4]. Current screening measures for detecting SARS-CoV-2 infection in patients are also not completely reliable. Reverse-transcriptase polymerase chain reaction (RT-PCR) performed on nasal and pharyngeal swabs has been reported to have a false negative rate of up to 29%[5].

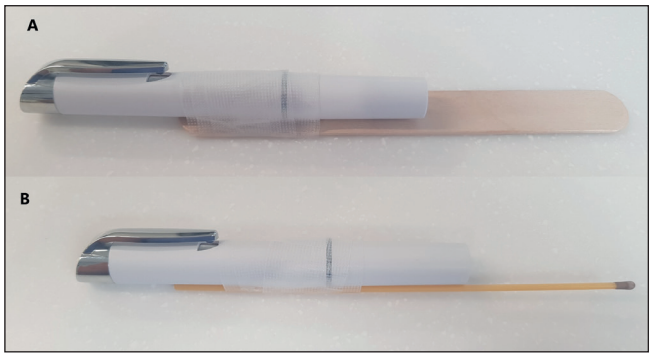

Figure 2:
(a) disposable pen torch attached to wooden tongue depressor for use in draining a peritonsillar abscess (b) disposable pen torch attached to 75% silver nitrate stick for use in nasal cautery

The two techniques that we describe above are inexpensive, easy to set up and allow for adequate use of PPE for ENT examinations and procedures. They are also a potential measure of preserving PPE supplies during a time of potential shortages of PPE for clinicians.

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Erratum:

A Short History of Occupational Disease:
1. Laboratory-acquired Infections. UMJ, 2021:90(1):28-31. Table 2 The risk figure for Brucellosis is 641/100,000 microbiologists NOT 64.1 as stated in the table.

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