Inside: The artificial womb: bridging the gap between embryo culture and the incubator

Watch this space: bringing medicine beyond Earth’s boundaries
Acknowledgements

Thank you to RCSI Alumni for their continued support to us as students – providing career advice, acting as mentors, enabling electives and research, and supporting the publication of the *RCSIsmj* since its inception in 2008.

We, as today's generation of students and tomorrow's generation of alumni, are very grateful for this ongoing support.

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Submissions to submissionsmj@rcsi.ie
Medicine: science or art?

As we wade through electronic journals, PowerPoint presentations, and modern mobile applications in the course of our medical education, the increased influence of modern science and technology makes it all too easy to think of medicine as a pure science. In this issue of the RCSIsmj, Vincent Healy’s review of the quest to build an ‘artificial womb’ and Jenna Geers’ discussion of incorporating whole genomic sequencing in the clinic exemplify how modern technology and science have changed the face of medicine. Reviews of relatively well-studied topics such as fibromyalgia by Ghalib Halaseh, diabetes by Samar Atteih, and antibiotics by Stephanie Tung highlight how our approach to diseases that are well understood continues to be moulded as our knowledge grows.

In addition to discussing advances in science, in this issue we also reflect the other side – that is, the art – of medicine. Travel briefs by Luke Gin and Amenah Dhanoo illustrate the true essence of medicine in nations dealing with difficult situations (such as Nepal and Syria, respectively), while Danielle Wuebbolt’s visit to Shanghai demonstrates how culture affects medicine. Jessica Suddaby examines the challenges and opportunities facing refugee and migrant healthcare in Europe, Katie Dunleavy et al. discuss the rotavirus burden and impact of vaccination in Uganda, and Naomi O’Sullivan takes us beyond our shrinking world to discuss medicine in space! The concepts of medicine as an art and science collide as Amelia Reid explores changing attitudes to communication, Michael Bravo argues for ‘sharing and caring’ in the world of scientific and medical literature, and Deirdre Harford, in her prize winning essay, deliberates on the ethics associated with the use of untested drugs in the treatment of the Ebola virus. Apart from reflecting how the world continues to evolve, they also serve as a reminder that humanity and the art of medicine are still very much alive and well, and not merely romantic rhetoric.

There is something to learn from every patient and every moment in medicine, and (we hope) in every page of this Journal. The pieces within exemplify the need to constantly evaluate our actions and motivations, particularly in how we balance science and art. Though our world continues to evolve, and science continues to advance, medicine desperately requires both and has since the time of Hippocrates. After all, “wherever the art of medicine is loved, there is also a love of humanity.”

Director’s welcome

“If we knew what it was we were doing, it would not be called research, would it?”

Attributed to Albert Einstein

I am delighted to welcome you to the ninth edition of the RCSIsmj. This year we received an unprecedented number of fabulous submissions from the RCSI student body, and as a result were able to fill a larger issue than ever before with high-quality pieces. I am confident that you will enjoy their work and learn a great deal from it. Our training has deeply instilled in us the concept of evidence-based decision-making, and we are introduced to research as an educational tool from the very beginning of medical school. Still, participation in the ‘publish or perish’ world of medical research can be extremely daunting for young scientists. The RCSIsmj aims to ease students at all levels of their training into the research and publication process in a collaborative, collegial environment. The result is the Journal you hold in your hands, but also (we hope) the initiation of several early physician-scientist careers. The RCSIsmj is a student-run organisation; all of the content published within is written, reviewed, selected, and edited by students, and our journal clubs are organised and presented by students for discussion with our peers. We are extraordinarily grateful for the support and assistance we receive from the Dean’s office in the RCSI, and from the faculty who take time out of their busy schedules to participate in journal activities. This publication would not be possible without any of them.

Though my involvement with the RCSIsmj has come to an end, I am excited to watch the Journal continue to grow and evolve under the guidance of the next generations of students. I hope that through their involvement they find, as I have, the confidence to dive head first into the challenging and rewarding world of medical research.

Mohit Butaney
Editor-in-Chief, RCSIsmj 2015-2016

Natalie Achemallah
Director, RCSIsmj 2015-2016
Gene editing allows sections of DNA from a genome to be precisely replaced or removed using ‘molecular scissors’. Techniques such as CRISPR-Cas9 can modify genomes of living organisms at precise locations in more specific and more cost-effective ways than were previously possible. In the future, these tools also hold the potential to be applied clinically to prevent or treat lethal and/or seriously debilitating genetic diseases. Gene editing of somatic cells is currently in clinical development for a variety of conditions, including HIV and leukaemia. Human germline editing, which involves altering genes in sperm, eggs or embryos, holds the possibility of not only correcting genes that cause disease, but also of passing those genetic fixes on to future generations. In April 2015, researchers in China announced that they had attempted to use CRISPR-Cas9 to edit non-viable human embryos with a debilitating disease. The experiment was partially successful, but the team concluded that there are still hurdles to overcome before CRISPR is safe for clinical use. The announcement was welcomed by some in the scientific community as a major step forward in eradicating debilitating human disease. Although these embryos were non-viable – they could not result in a pregnancy – a public outcry arose that the scientists had taken an alarming step towards the creation of ‘designer babies’. Then, in February 2016, the Human Fertilisation and Embryo Authority (HFEA) in the United Kingdom approved an application from Dr Kathy Niakan of the Francis Crick Institute to renew her laboratory’s research licence to include gene editing of embryos. In its approval, the HFEA stated that no research using gene editing could take place without research ethics approval, and that it is illegal to transfer any embryo used in research to a woman for treatment. Around the world, laws and guidelines vary widely about whether germline, or hereditary, research is allowed. Some ban any research; some allow only lab research but not pregnancies; and, some have no policies.

Questions

1. Should a temporary or permanent global ban on human germline editing be introduced and, if so, on what basis?
2. Is there an ethical difference between using gene editing for the avoidance of severe inherited diseases or for ‘enhancement’ of human capabilities?

References


This is the eighth instalment of the RCSIsmj Ethics Challenge. The editorial staff would like to congratulate Deirdre Harford on her winning essay in the 2015/2016 Ethics Challenge. Please see page 6 for her submission.

We invite students to submit an essay discussing the ethical questions raised in the scenario presented. Medical ethics is an essential aspect of the medical curriculum and we hope to encourage RCSI students to think critically about ethical situations that arise during their education and subsequent careers. All essays will be reviewed by a faculty panel of experts and the winning essay will be published in the 2017 print edition of the RCSIsmj. The deadline for submission of entries will be the same as the general submission deadline for the 2017 edition of the RCSIsmj. Please visit our website at www.rcsismj.com for specific dates. Please contact us at editorsmj@rcsi.ie with any questions or concerns.

Submission guidelines

Please construct a lucid, structured and well-presented discourse for the issues raised by this scenario. Please ensure that you have addressed all the questions highlighted and discuss these ethical issues academically, making sure to reference when necessary. Your paper should not exceed 2,000 words.

Your essay will be evaluated on three major criteria:

1. Ability to identify the ethical issues raised.
2. Fluency of your arguments.
3. Academic quality with regard to depth of research, appropriateness of references and quality of sources.

Good luck!
The winning entry will be presented with a prize at the launch of the next issue.
ETHICS CHALLENGE WINNER 2015/2016

The use of untested drugs in the treatment of the Ebola virus

Deirdre Harford
RCSI medical student

Introduction
The 2015/2016 RCSI smj Ethics Challenge presents the dilemma surrounding Ebola treatments and their distribution. Mapp Biopharmaceuticals, an American pharmaceutical company, has developed a number of promising but untested vaccines for treatment of the virus. With rising incidence and high mortality rates, the WHO decided to back the use of ZMapp, an untested Ebola intervention, in humans. Faced with this multi-faceted outbreak, we find ourselves placing under the microscope our principles with regard to clinical trials, intervention availability and duty of care beliefs. Further ethical questions arose following news that American missionaries who became infected while providing care to Ebola patients received ZMapp treatment and subsequently recovered, having been selected over Africans to receive the treatment. This article aims to examine the ethical grounds for providing patients with an untested drug for diseases such as Ebola, and the distribution, prioritisation and criteria for deciding the recipients of said treatment.

Providing Ebola patients with an untested drug
“Never mind that they haven’t been tested for safety. Believe me, I’d run for the freezer and ask for forgiveness instead of permission.”
Erica Ollmann Saphire, Scripps Research Institute, San Diego.

In the face of a crisis of this scale, parameters of right and wrong became less well defined and the magnitude of the disaster forced healthcare professionals to re-evaluate previously held values and principles. Traditionally, medical practice hangs on the four ethical principles from the work of Beauchamp and Childress, who believed that it is “legitimate and rewarding” to apply general ethical principles to medicine. This framework sets out the following:

Beneficence: providing benefits and balancing them with risks
High mortality rates, as high as 70%, fuelled the WHO’s decision to offer untested drugs, as conventional care failed to produce acceptable clinical outcomes.
As with all communicable diseases, containment is of the utmost importance, and therefore co-operation with health authorities, for instance regarding sanitation laws such as burial practices, is a top priority. Decisions about experimental treatments may damage the trust placed in a system and thereby jeopardise such protocols, should the experimental treatments prove to be harmful or of no benefit. However, some argue that on a public level, distribution of an experimental drug through a “transparent and equitable process” may rebuild and fortify the trust placed in health systems. It is also true that in return for any form of compliance or trust on the patient’s side, they expect the provision of respectable standards of care.

Writing for the *Journal of Medical Ethics*, Angus Dawson described the use of ZMapp as clearly following “directly from a physician’s general duty to do what is best for their patients, which is already explicitly endorsed by the Helsinki Declaration”.

**Respect for autonomy: respecting the capacity of autonomous persons to make decisions**

Ethical medicine recognises that a patient’s ability to think and act independently is what facilitates all other morals in life, and is therefore prioritised. It is questionable how informed a generally disadvantaged population – particularly with regard to education – can be about Ebola treatments. Indeed, one of the most contentious issues surrounding the Ebola outbreak is its geographical location. Many of the organisations tackling the outbreak believe that bringing an untested drug into a population that is already distrustful of the teams providing help is unfeasible.

In their report, the WHO recommended that the limited supply of ZMapp should generate as much data as possible, with a moral obligation being placed on the collection and free distribution of this data. In other words, as close as is possible to a clinical trial should be conducted given the circumstances. To fulfil these criteria while respecting autonomy, clear explanations of these trials and informed consent from patients is vital.

This outbreak has highlighted the need for trust, and for public understanding of treatment evaluation, and the necessity of conducting ethical research and subsequent interventions under crisis conditions.

**Non-maleficence: avoiding causation of harm**

Our duty of *primum non nocere* is in jeopardy when we experiment with untested drugs on patients, which is bad practice under usual circumstances. This potential harm not only threatens the patient, but also wider society. The consequences of unprecedented harm from use of an untested drug could jeopardise both the outbreak response (as the trust of patients and the public is lost) and efforts to develop future treatments. However, the lack of a definitive treatment equates to a limited incentive to present for medical help, which causes harm to patients who may nevertheless benefit from supportive care.

Many of the organisations tackling the outbreak believe that bringing an untested drug into a population that is already distrustful of the teams providing help is unfeasible.

**Justice: fairly distributing risks and benefits**

In the midst of an outbreak such as Ebola, there is still an obligation to ensure that all societies benefit equally. The development of stable, functional health systems offering a respectable level of care ensures that all communities obtain fair benefits from research during this epidemic, regardless of where this research is carried out. Offering an untested drug, under as close to clinical trial conditions as possible, challenges this principle.

In order for clinical research to be ethical, it requires equipoise – a state of genuine uncertainty regarding comparative therapeutic merits. However, if it becomes known that one treatment is of superior therapeutic merit (with conventional care proving to be of little benefit), there is an ethical obligation to offer the superior treatment. ZMapp is considered a more acceptable treatment than whole-blood transfusions from convalescent survivors. While ZMapp has not as yet proven superior therapeutic merit, one would be acting ethically to offer ZMapp as soon as such a conclusion could be drawn.

If an untested drug were solely used in the seriously ill, it might become more difficult to identify severe side effects associated with the drug. It has been argued that the experience in the first two people treated with ZMapp eliminated the possibility of a universally severe adverse response; however, as medics struggle to satisfy the principle of justice, one approach to investigating promising drugs for patients with Ebola would be to allow limited emergency use alongside studies in healthy volunteers to satisfy concerns about toxicity and adverse events. Under these circumstances, the provision of this untested drug is not unreasonable.

**Is it ethical to give an untested drug to healthcare professionals first?**

Perhaps the most controversial aspect of the current Ebola outbreak is the fact that the treatment, albeit untested, was first offered to white, western healthcare workers. A case in Germany in 2009 saw a researcher become exposed to Ebola following a needlestick injury. She remained asymptomatic after receiving immediate medical attention, with the vesicular stomatitis virus (VSV) vaccine rushed to Hamburg for her treatment. Whether the vaccine worked cannot be determined, as it is impossible to know whether she would have become infected otherwise. Such a response would not have been feasible in a developing country, demonstrating the inequitable risk distribution among healthcare workers and the general Ebola-affected population.
Reciprocity and consequentialism
The ZMapp debate draws upon many complex arguments as to why we treat first responders first. It is often argued that as health professionals place themselves in harm’s way to care for patients, and could help more once recovered, we have a duty of care to them. In three of the world’s poorest countries, with not only the lowest per capita gross national incomes, but also extremely low physician ratios: fewer than 0.1 physician per 10,000 persons. Therefore, many draw on the principles of reciprocity (receiving help from others, having provided help for others) and consequentialism (the consequences of actions provide the basis for their judgement) to justify the prioritisation of healthcare workers. In contrast, some believe that good medical ethics needs to focus on public health and societal perspectives, instead of allowing individualistic values to dominate the Ebola discussion. However, it is widely accepted that healthcare workers are financially comfortable and well connected within the medical field. Their prioritisation may be seen as a source of tension as we preferentially treat the privileged. This is an especially contentious issue when one considers those who provide care without being health professionals.

Populations who are terrified by Ebola, and who lack trust in healthcare workers and public authorities following civil wars, cannot be assumed to have the capacity to provide informed consent.

Informed consent
Despite this, to repeat what was done in Germany in 2009 for hundreds of people at a time in African countries is virtually impossible, not least due to issues of informed consent. Populations who are terrified by Ebola, and who lack trust in healthcare workers and public authorities following civil wars, cannot be assumed to have the capacity to provide informed consent. Therefore, it could be considered unethical to offer an untested treatment to these people. When recipients are healthcare workers, whose ability to understand risks is presumably high, the decision to prioritise them seems more ethically correct. There is still an influential school of thought which holds that the drug should be given on a first-come, first-served basis. According to this approach, prioritising access to experimental drugs in certain populations (healthcare workers) or countries (Western Hemisphere) promotes inequitable access to resources and is therefore unacceptable. In prioritising certain groups, we arguably negate the principles of distributive and social justice, which we previously achieved. This is of particular concern in places where human rights violations frequently occur, such as those countries affected by Ebola.

What ethical criteria should be used to decide which healthcare professionals receive the drug?
If one accepts that the limited, untested treatment should be offered to healthcare workers exclusively, another aspect of the Ebola ethics dilemma unfolds. The WHO report sets out criteria regarding which healthcare professionals should receive the limited ZMapp supplies. Such guidelines include transparency about all aspects of care – informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community. Nearly all of these guidelines focus on individualistic considerations. Indeed, one could consider the focus on autonomy of the patient inappropriate for those victims of Ebola who have limited capacity to provide consent. Arguably, one should prioritise those who can debate the risks and benefits of treatment and provide the most informed consent. The criteria provided also failed to address the ethical objectives of promoting patient benefits and protecting patients from harm. Perhaps those who are most likely to make a recovery should receive the drug.

Ethical Ebola research
If the use of ZMapp is limited to healthcare workers, expansion of its use without additional testing would be irresponsible. Moreover, it would be careless to use the small amount of experimental interventions possible without any collection of systematic data about its drug profile. Given this social backdrop, it is ethical for the treatment to be provided to those from whom we can generate the most data efficiently and under the safest experimental conditions. When untested drugs such as ZMapp are used in this Ebola emergency, it is important that research ethics are upheld to avoid exploitation of affected individuals and communities. The eight ethical principles for research as outlined by Emanuel et al. must be met to facilitate supply of the drug:

- informed consent;
- collaborative partnership;
- social value;
- scientific validity;
- fair selection of study population;
- favourable risk–benefit ratio;
- independent review; and,
- respect for recruited participants and study communities.

Any discussion regarding possible treatment programmes highlights that the identification of target groups may require improved viral transmission surveillance systems and a better understanding of Ebola transmission.
Conclusion

Despite there being compelling arguments for the immediate and widespread use of ZMapp in times of global crises, closer inspection of the situation indicates that this would be not only unfeasible but unethical. Any global epidemic with a 70% mortality rate poses momentous problems, but these were exacerbated further by the geographical and cultural setting of this virus. It would be reasonable to conclude that, given the circumstances of this illness, an untested drug may be ethically employed for compassionate use in conjunction with other trials. As soon as a proven treatment (such as ZMapp if proven efficacious), becomes available, global expansion of the treatment group is morally imperative. Regardless, the controversy surrounding the prioritisation of white healthcare workers and accessing Ebola interventions continues.

References

A rare case of post-gastric bypass hypoglycaemia

Abstract
A 46-year-old woman with a history of Roux-en-Y gastric bypass (RYGB) surgery in 2010 was referred to the hepatobiliary oncology clinic in the University of Colorado Hospital in May 2013 with frequent episodes of post-prandial hypoglycaemia with neurogenic and neuroglycopenic symptoms. Findings in her biochemical profile, a 72-hour fast, and a mixed meal test were all negative. Subsequent CT abdomen and endoscopic ultrasound did not identify pancreatic lesions. Interventional radiology (IR) hepatic venous sampling with calcium gluconate localised excess insulin production to the tail of the pancreas. Medical management with acarbose and octreotide was commenced, but due to progressive symptoms and life-threatening episodes of hypoglycaemia, the pancreas was surgically resected. Pathology failed to show neoplastic tissue; histology demonstrated mild hyperplasia and hypertrophy, although within normal limits. A diagnosis of nesidioblastosis – a rare disease that causes pancreatic hyperfunction in the absence of an insulinoma and with evidence of hyperplasia – was made. It is a leading cause of hyperinsulinaemic hypoglycaemia in childhood, but causes <5% of cases in adults. Although the exact pathogenesis is not understood, nesidioblastosis is increasingly recognised as a late complication of bariatric surgery, where it is termed “post-gastric bypass hypoglycaemia” to distinguish from other entities associated with nesidioblastosis.

Introduction
Patients experiencing episodes of hypoglycaemia may experience a broad range of symptoms. These can be either neurogenic or neuroglycopenic (Table 1). The presence of hypoglycaemic symptoms, low measured glucose levels, and relief of symptoms with glucose administration – Whipple’s triad – suggests true hypoglycaemia and is a diagnostic hallmark for insulin-secreting tumours (insulinomas). Differential diagnoses for true hypoglycaemia are categorised as endogenous or exogenous in origin (Table 2). The most common cause in non-diabetic and otherwise healthy adults is an insulinoma, a rare tumour with an incidence of four cases per million person-years.⁠¹ Approximately 90% of these are benign and 90% are solitary.² Diagnostic investigations include a 24-hour fast, 72-hour fast, and assay for insulin antibodies. C-peptide, proinsulin, and insulin levels can be measured to rule out factitious hypoglycaemia. Imaging includes CT abdomen and endoscopic ultrasound, with a combined sensitivity of >90%.³ An octreotide scan may show somatostatin receptor-positive tumours and interventional radiology (IR) hepatic venous sampling with calcium gluconate localises regions of pancreatic hyperfunction. Surgical resection of the affected pancreas is the gold standard, with a cure rate of 97.5%.⁴ Surgical options include enucleation, distal resection, total pancreatic resection and duodenumopancreatectomy (Whipple’s procedure).
Case report

A 46-year-old Caucasian woman with a history of Roux-en-Y gastric bypass (RYGB) surgery in 2010 was referred to the hepatobiliary oncology clinic in the University of Colorado Hospital in May 2013 with frequent episodes of post-prandial hypoglycaemia accompanied by neurogenic and neuroglycopenic symptoms. She reported sweating, tremors, palpitations, weakness, and dizziness, which came on approximately two hours after consuming simple sugars. The episodes had increased in frequency, requiring several emergency department visits. She denied pain, changes in appetite, or weight loss, but reported eating more frequently to prevent episodes from occurring. Her past medical history was significant for Graves’ disease, systemic lupus erythematosus, seizures, and asthma. Physical examination revealed no abnormalities. Blood investigations including insulin, proinsulin, C-peptide, and sulfonylurea were all within normal limits, ruling out exogenous causes of hypoglycaemia. She was negative for insulin antibodies. Both 24- and 72-hour fasts were conducted with negative results. Imaging with CT abdomen was unremarkable. The patient was managed conservatively with an α-glucosidase inhibitor (acarbose 25mg) and frequent low-carbohydrate meals, but intolerance of acarbose necessitated replacement with a somatostatin analogue (octreotide 100mcg three times daily). She responded well initially, but by March 2014 her octreotide dose was increased to 200mcg three times daily and she was still experiencing weekly episodes of hypoglycaemia. She reported a blood glucose of 1.44mmol/l with her latest episode, and had fallen on several occasions due to weakness or loss of consciousness. An octreotide scan failed to localise somatostatin receptor-positive tumour cells, but IR hepatic venous sampling with calcium gluconate showed over a six-fold rise in insulin levels localised to the pancreatic tail. A CT abdomen and endoscopic ultrasound in April and May 2015, respectively, were both unremarkable. Hepatic venous sampling was repeated and confirmed previous findings. It was then decided that due to the very low reported insulin levels with each episode, and the increasing risk of fall-related injury, the benefits of surgery outweighed the risks. The patient was scheduled for a distal pancreatectomy and splenectomy.

Table 1: Symptoms of hypoglycaemia.

<table>
<thead>
<tr>
<th>Neurogenic features</th>
<th>Neuroglycopenic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Double vision</td>
</tr>
<tr>
<td>Tremors</td>
<td>Blurry vision</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Coma</td>
</tr>
</tbody>
</table>

Outcome

In August 2015 the patient had her spleen and two-thirds of her pancreas removed. Pathological examination of pancreatic tissue ruled out neoplasm and all sampled lymph nodes were negative. Hyperplasia and hypertrophy in the pancreatic tissue were present but within normal limits. She was discharged on day six postoperatively after an uneventful recovery and reported no further episodes of hypoglycaemia, with all measured glucose levels above 4.4mmol/l.

Discussion

Nesidioblastosis is a rare disorder first described by George Laidlaw in 1938 as neof ormation of Langerhans islets in the pancreatic ductal epithelium. Initially observed in neonates and now recognised as the primary cause of hyperinsulinaemic hypoglycaemia in childhood, it is rare in adults and accounts for <5% of cases. RYGB surgery was first associated with adult onset nesidioblastosis in 2005; fewer than 100 cases of post-gastric bypass nesidioblastosis have been identified as of November 2014. Nesidioblastosis should be included as a differential diagnosis in hyperinsulinaemic hypoglycaemia, with a negative 72-hour fast and unremarkable findings on imaging. IR hepatic venous sampling with calcium stimulation test is a useful investigation when other imaging modalities fail to localise a pancreatic lesion. The technique involves placing a catheter in the right hepatic vein, and performing a pancreatic angiography via the femoral artery. Calcium gluconate is then injected into the selectively catheterised gastroduodenal, proximal splenic, and superior mesenteric arteries. Venous samples are collected at 0, 30, 60, and 120 seconds for each site. Five minutes are allowed between each injection. A greater than two-fold rise in insulin levels within 30-120 seconds is recorded as a positive result in the distribution of the relevant artery. This technique can thus indicate pancreatic hyperfunction and suggest either an insulinoma or (less commonly) nesidioblastosis, as well as guiding the surgical approach for resection.

Nesidioblastosis is diagnosed based on the absence of an insulinoma and the presence of islet cell hyperplasia on histological examination. It is

Table 2: Causes of hypoglycaemia in non-diabetic patients.

<table>
<thead>
<tr>
<th>Endogenous</th>
<th>Exogenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic β-cell tumour</td>
<td>Factitious hypoglycaemia</td>
</tr>
<tr>
<td>Post-gastric bypass dumping syndrome</td>
<td>Sulfonylurea induced</td>
</tr>
<tr>
<td>Noninsulinoma pancreateogenous hypoglycaemia (adult nesidioblastosis)</td>
<td></td>
</tr>
<tr>
<td>Post-gastric bypass hypoglycaemia (adult nesidioblastosis)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune insulin syndrome</td>
<td></td>
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</tbody>
</table>
important to note that the diagnostic criteria for hyperplasia are not universally agreed upon; Rindi et al. define hyperplasia in adults as an expansion of the endocrine cell mass to more than 2% of total pancreas mass. Due to the impracticalities of conducting detailed pancreatic morphometry of a sample, the diagnosis may often be subjective. However, most would regard an increase in islet numbers as evidence of hyperplasia. Four major criteria have been proposed to diagnose nesidioblastosis:

1. Exclusion of insulinoma by macroscopic, microscopic and immunohistochemical examinations.
2. Multiple β-cells with enlarged, hyperchromatic nuclei and abundant clear cytoplasm (β-cell hyperplasia and hypertrophy).
3. Islets with normal spatial distribution of various cell types.
4. No proliferative activity of endocrine cells.

Utilisation of this criterion may help to improve diagnostic consistency. The recommended management of post-gastric bypass surgery hypoglycaemia is with frequent, low-carbohydrate diet or medical management (α-glucosidase inhibitors, diazoxide, octreotide). If these fail, reversal of gastric bypass can be performed. Often symptoms persist, in an attempt to preserve pancreatic function, a partial pancreatectomy may be performed, but symptoms often return and necessitate further surgery.

**Conclusion**

Nesidioblastosis is a rare cause of hyperinsulinaemic hypoglycaemia in adults and can occur as a late complication of RYGB surgery. Diagnosis must be suspected when 72-hour fast is negative and imaging fails to identify insulinoma, and is established when pathological assessment confirms absence of insulinoma and presence of pancreatic hyperplasia. A multidisciplinary approach becomes necessary when the diagnosis is unclear and investigations suggest a rare pathology; as in this case, involvement of endocrinologists, general surgeons, interventional radiologists and pathologists can ensure that an adequate management plan is put in place to bring about the best possible patient outcomes. Typically, management is dietary and medical, but surgery may be considered in refractory cases such as this one. Where surgery is deemed necessary, IR hepatic venous sampling may localise the site of pancreatic hyperfunction to determine the extent of surgical resection. As our case demonstrates, the subjective and impractical nature of pathological assessment can show hyperplasia and hypertrophy to be within normal limits, thus making definitive diagnosis of nesidioblastosis a technical difficulty. Implementation of established diagnostic criteria can help to resolve this issue and improve inter-observer consistency. Further research and long-term studies are needed to understand the pathogenesis of post-gastric bypass hypoglycaemia and the therapeutic outcome, as this has implications for the future of gastric bypass surgery as an option for weight loss.

**References**

Kicking up a cytokine storm: an unusual presentation of Castleman’s disease

Abstract

Castleman’s disease (CD), or giant lymph node hyperplasia, is a rare disorder first described by Castleman et al. in 1956. CD is separated into localised disease and multicentric Castleman’s disease (MCD). Kaposi’s sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus-8 (HHV-8) is the causal agent for Kaposi’s sarcoma (KS) and MCD in human immunodeficiency virus (HIV)-infected patients. This virus encodes a homologue of interleukin 6 (vIL-6), which may mediate some systemic features of MCD. A 58-year-old man presented to the infectious disease department with a three-day history of dyspnoea, fever, and cough. He had a history of HIV and had been on antiretroviral treatment for the previous year. Despite compliance, his CD4 count had dropped and he was found to have widespread lymphadenopathy and pancytopenia on admission. Biopsy showed the presence of KS and it was decided to treat him for an ‘MCD-like’ syndrome based on his clinical presentation. The patient responded well to treatment with rituximab, an agent used for MCD, and his haematological profile improved. This case lends support to the theory that some patients with HIV and HHV-8 co-infection, but without MCD, can develop severe systemic inflammatory symptoms associated with elevated levels of HHV-8 vIL-6, IL-6 and HHV-8 viral loads. It additionally illustrates the challenges faced in the diagnosis of this unusual form of MCD in patients with HIV. Most importantly, this case highlights the importance of a thorough history and examination in eliciting the clues to diagnosis in the face of these challenges.

Introduction

Castleman’s disease (CD), or giant lymph node hyperplasia, is a rare disorder first described by Castleman et al. in 1956. CD is separated into localised unicentric disease, with solitary hyperplastic mediastinal lymph nodes, or multicentric disease (MCD). Histologically, CD is divided into the hyalinated vascular form and a plasma cell variant, the former being more common in localised disease, and the latter more common in MCD. Mixed forms of CD have also been documented.

MCD is characterised by polylymphadenopathy and inflammatory manifestations including fevers, malaise, wasting, hypoalbuminaemia, cytopenias, and hyponatraemia. These symptoms are a result of inflammatory cytokine overproduction, especially IL-6 (Figure 1). The diagnosis of MCD requires the clinical features of active disease described above plus pathologic confirmation on biopsy.

In HIV-infected patients, MCD is usually caused by Kaposi’s sarcoma-associated herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8). This virus encodes a homologue of interleukin 6 (vIL-6), which may mediate the systemic features of MCD. Symptomatic patients with HHV-8-positive MCD have HHV-8 viral loads that are exponentially greater than asymptomatic HHV-8-positive patients (Table 1). In accordance with this, the increased viral load correlates with increased serum levels of IL-6. This virus predisposes patients to much higher risk of other malignancies, including Kaposi’s sarcoma (KS) (13% increased risk) and primary effusion lymphoma.
There is evidence that MCD has become more common since the advent of combination antiretroviral therapy, affirming the theory that immune-overactivation rather than immunosuppression leads to MCD. Like MCD that is unrelated to HHV-8, the clinical presentation of HHV-8-associated MCD is dominated by systemic inflammatory symptoms and polylymphadenopathy. It is diagnosed upon lymph node biopsy and has a fluctuating course, which, if untreated, proves fatal. This report discusses the presentation of a new variant of HHV-8-associated MCD and the difficulties faced in diagnosis and management.

The case

A 58-year-old Caucasian gentleman presented to St George’s Hospital in London with a three-day history of dyspnoea, fever, and cough. This was on a background history of community-acquired pneumonia five weeks previously, for which he had been successfully treated at the same hospital.

Past medical history was significant for HIV, diagnosed 13 months previously, and he was being treated with antiretroviral medications – specifically, oral combined tenofovir and emtricitabine (Truvada®; Gilead Sciences, Foster City, CA, USA), and darunavir. However, his CD4 count had decreased over the previous year from 800 to 285 cells/mm³, despite compliance with his medications. Other medical history included a parietal skull fracture three years previously following a fall, hypothyroidism, for which he took 100mcg levothyroxine once daily, and depression, for which he took 37.5mg venlafaxine once daily. His father passed away from lung cancer at the age of 83 and his mother passed away from a cerebral sarcoma aged 50. He was a non-smoker and non-drinker, who lived alone and worked as an optometrist.

On examination, he appeared pale and dyspnoeic. Auscultation of the lungs elicited increased vocal fremitus and crackles of the right lower zone. A full blood count revealed low neutrophil and platelet counts, and C-reactive protein (CRP) was elevated. X-ray findings were consistent with right lower lobe pneumonia. He was commenced on an amoxicillin and doxycycline antibiotic regimen

<table>
<thead>
<tr>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least three of the following symptoms:</td>
</tr>
<tr>
<td>Peripheral lymphadenopathy</td>
</tr>
<tr>
<td>Enlarged spleen</td>
</tr>
<tr>
<td>Oedema</td>
</tr>
<tr>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Nasal obstruction</td>
</tr>
<tr>
<td>Xerostomia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Central neurologic symptoms</td>
</tr>
<tr>
<td>Jaundice</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
</tr>
</tbody>
</table>

Increased serum C-reactive protein level >20mg/L in the absence of any other aetiology

HIV = human immunodeficiency virus; MCD = multicentric Castleman’s disease.
with 30mg prednisolone. Upon completion of his treatment course, his chest symptoms resolved but his platelets remained remarkably low and CRP remained elevated. He became progressively fatigued and his blood profile failed to improve despite medical treatment, prompting a re-evaluation of his initial diagnosis. Further questioning uncovered a four-month history of fatigue, night sweats, and weight loss. Repeat bloods revealed worsening pancytopenia in addition to persistently elevated CRP, lactate dehydrogenase (LDH) and hyponatraemia. CT showed widespread lymphadenopathy and splenomegaly. Based on these findings, and as a result of immunosuppression because of his low CD4 count, a diagnosis of immune thrombocytopenia (ITP) was made. He was commenced on ITP-specific therapy, which consisted of platelet transfusion, intravenous immunoglobulin (IVIG) and glucocorticoids (prednisolone 30mg once daily) in an effort to raise his platelet count. His antiretroviral medication was switched from a darunavir-based regimen to raltegravir 400mg twice daily in an effort to improve his CD4 count.

Two weeks after his admission, the patient developed a palpable light brown lesion on his right forearm measuring 6cm by 7cm in diameter. Following a cervical lymph node biopsy, a histological diagnosis of HHV-8-positive KS was made (Figure 2). A plan was made to commence chemotherapy treatment once his platelet levels could be raised to a level above 50 x 10^9/L with his ITP-specific therapy. However, following a five-day treatment course, his platelet levels failed to respond. As a result, he was initiated on a weekly romiplostim regimen with continuation of prednisolone.

This also failed to improve his condition, so a discussion between the departments of haematology, infectious diseases, and oncology was held. This patient's clinical and haematological presentation fit the diagnosis of MCD, yet the tissues obtained for histological diagnosis were only positive for HHV-8 and not for MCD (Figure 3). It was

**FIGURE 2**: Cervical lymph node biopsy from patient with a CD31 positive stain showing: a) lymph node follicle with KS x20 magnification; b) KS with HHV-8 x20 magnification; c) lymph node follicle with KS x200 magnification; and, d) KS cell with HHV-8 x200 magnification. Typical histologic findings in KS include: proliferation of spindle cells; prominent, slit-like vascular spaces; and, extravasated red blood cells. KS = Kaposi’s sarcoma.
RCSI Smj Case Report

hypothesised that the patient’s symptoms of lymphadenopathy and inflammation might not be caused by HHV-8-MCD, but might instead result from HHV-8 lytic activation and consequent cytokine production. The patient was found to have a substantial elevation of vIL-6 and hIL-6, and so he was proposed to have a rare and newly described syndrome called ‘KSHV inflammatory cytokine syndrome’ (KICS) (Table 2).4 Due to its relatively new classification, the treatment approach for KICS is still largely theoretical and based on MCD treatment. Our patient was started on a trial of rituximab 375mg/m² once weekly for four weeks. His first dose was well tolerated and his platelets increased from 22 x

Table 2: Working case definition of KSHV (HHV-8) inflammatory cytokine syndrome.5

<table>
<thead>
<tr>
<th>1. Clinical manifestations</th>
<th>b. Laboratory abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Symptoms</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Fever</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Hypoalbuminaemia</td>
</tr>
<tr>
<td>Oedema</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Cachexia</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms (including cough, dyspnoea, airway hyperreactivity)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disturbance (including nausea, anorexia, abdominal discomfort, altered bowel habit)</td>
<td></td>
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<tr>
<td>Arthralgia and myalgia</td>
<td></td>
</tr>
<tr>
<td>Altered mental state</td>
<td></td>
</tr>
<tr>
<td>Neuropathy with or without pain</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Evidence of systemic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated C-reactive protein (≥3g/dL)</td>
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</tbody>
</table>

<table>
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<tr>
<th>3. Evidence of KSHV lytic activity</th>
</tr>
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<tbody>
<tr>
<td>Elevated KSHV viral load in peripheral blood mononuclear cells (≥100 copies/10⁶ cells)</td>
</tr>
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<tr>
<th>4. No evidence of KSHV-associated Castleman’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion of MCD requires pathologic assessment of lymph node, bone marrow, or spleen</td>
</tr>
</tbody>
</table>

FIGURE 3: Lymph node biopsy demonstrating the histological appearance of MCD: a) haematoxylin and eosin-stained section of lymph node (100× magnification) showing the concentric layering of lymphocytes in the mantle zone of the lymphoid follicle – ‘onion-ring’ appearance; and, b) HHV-8 immunohistochemical stain showing mantle zone concentricity and distinct HHV-8 positive nuclear staining of lymphoid cells in the mantle zone (100× magnification). MCD = multicentric Castleman’s disease.7
been described. Its clinical manifestations resemble those of lymphadenopathy, severe inflammatory symptoms, KS and pancytopenia, but in whom a histological diagnosis of MCD could not be made. Recently, another HHV-8-associated condition, KICS, has been described. Its clinical manifestations resemble those of HHV-8–MCD but, as seen in this case, the histological changes of HHV-8–MCD are absent. Patients with KICS exhibit elevated HHV-8 viral loads and elevation of vIL-6, a homologue of human interleukin-6 and IL-10 comparable to those seen in HHV-8–MCD. The pathological evolution of this syndrome and its relationship with HHV-8–MCD remains to be elucidated. No standardised therapy exists for MCD, and only one RCT has been conducted for MCD treatment. Management thus far has been guided by case reports or observational studies, and usually involves a combination of immunotherapy, chemotherapy and antiviral agents. Treatment selection depends upon whether the patient is HIV/HHV-8 positive, and on the clinical aggressiveness of the disease. Concurrent combination antiretroviral therapy (HAART) is generally used in HIV-infected patients. Prompt therapy must be instituted to avoid potentially fatal complications from organ failure and infections. Rituximab, a humanised monoclonal antibody against the B-cell antigen CD20, has been shown to be effective in MCD treatment. Two prospective phase II studies have shown a significant reduction in symptoms and decreased HHV-8 viral load. Other case reports have used a successful combination of rituximab and liposomal doxorubicin to kill KS spindle cells. It is on the basis of these studies and previous case reports that this therapy was commenced with this patient. Furthermore, the patient's positive response to his rituximab treatment strengthens the theory of a KICS diagnosis for our patient.

Discussion

The differential diagnosis of fever and adenopathy in HIV-infected patients, even with other laboratory abnormalities, is broad. As a result, HHV-8–MCD can be difficult to diagnose and is often missed. This is an unusual case of a HIV-infected patient who had lymphadenopathy, severe inflammatory symptoms, KS and pancytopenia, but in whom a histological diagnosis of MCD could not be made. Recently, another HHV-8-associated condition, KICS, has been described. Its clinical manifestations resemble those of HHV-8–MCD but, as seen in this case, the histological changes of HHV-8–MCD are absent. Patients with KICS exhibit elevated HHV-8 viral loads and elevation of vIL-6, a homologue of human interleukin-6 and IL-10 comparable to those seen in HHV-8–MCD. The pathological evolution of this syndrome and its relationship with HHV-8–MCD remains to be elucidated. No standardised therapy exists for MCD, and only one RCT has been conducted for MCD treatment. Management thus far has been guided by case reports or observational studies, and usually involves a combination of immunotherapy, chemotherapy and antiviral agents. Treatment selection depends upon whether the patient is HIV/HHV-8 positive, and on the clinical aggressiveness of the disease. Concurrent combination antiretroviral therapy (HAART) is generally used in HIV-infected patients. Prompt therapy must be instituted to avoid potentially fatal complications from organ failure and infections. Rituximab, a humanised monoclonal antibody against the B-cell antigen CD20, has been shown to be effective in MCD treatment. Two prospective phase II studies have shown a significant reduction in symptoms and decreased HHV-8 viral load. Other case reports have used a successful combination of rituximab and liposomal doxorubicin to kill KS spindle cells. It is on the basis of these studies and previous case reports that this therapy was commenced with this patient. Furthermore, the patient's positive response to his rituximab treatment strengthens the theory of a KICS diagnosis for our patient.

Conclusion

CD and its associations are broad and complex in their presentation and diagnosis. KICS demonstrates that the clinical manifestations of HHV-8 infection may vary and sometimes overlap. Future work to establish the incidence of this syndrome and its ideal treatment, and to clarify how it differs from MCD or KS, is crucial. Additionally, this case reminds us to consider an IL-6-related inflammatory syndrome in critically ill patients with HIV and KSHV co-infection.
Toxic shock syndrome complicated by necrotising fasciitis: back to basics

Abstract
Necrotising soft tissue infections (NSTIs) are uncommon but potentially fatal, and both their recognition and management represent significant challenges for clinicians. A 68-year-old male presented to the emergency department complaining of pain in his left lower limb following abrasion injuries sustained from a fall off a wooden ladder the previous evening. His injuries extended from the left anterior tibia up along the medial aspect of the left knee and thigh, and showed erythema, induration, and vesiculation. The patient had a history of hypertension and hypercholesterolaemia. On examination, he was hypotensive, tachycardic, and hypothermic. He rapidly deteriorated and developed acute kidney injury secondary to septic hypovolaemia, requiring haemodynamic support, long-term intravenous antibiotics, several surgical debridements, dialysis, and skin grafts, but he subsequently made a full recovery. The clinical, laboratory, and radiological findings in NSTIs can vary significantly, and definitive diagnosis is made by surgical exploration. Pain out of proportion to clinical findings, rapid clinical deterioration, and signs of systemic involvement are important clues for the clinician. This case demonstrates how rapid diagnosis and multidisciplinary management (in which surgery is the cornerstone) can lead to the most favourable outcome for patients.

Background
Necrotising soft tissue infections (NSTIs) encompass a relatively broad spectrum of potentially life-threatening infections, including necrotising forms of cellulitis, fasciitis, and myositis. NSTIs can be classified according to the depth of tissue involvement, severity of infection, and causative organism. The most commonly used classification describes type I polymicrobial infections (especially anaerobes), type II monomicrobial infections (most commonly group A β-haemolytic streptococci such as S. pyogenes and, increasingly, Staphylococcus aureus), and type III infections (gram-negative aquatic organisms). NSTIs are uncommon, with recent reports estimating up to 1,500 cases in the United States annually. Predisposing factors include diabetes and other chronic diseases, traumatic injuries (with or without skin injury), and intravenous (IV) drug use. An association with non-steroidal anti-inflammatory drug (NSAID) use has been described, but remains controversial. Virtually all untreated cases are fatal, and mortality with treatment approaches 35%.

Case
We describe a 68-year-old male who self-presented to the emergency department with abrasions and pain in his left leg along the anterior tibia, medial knee and medial thigh, from a three-foot fall from a wooden ladder the previous evening. Following the injury, the patient self-administered povidone iodine ointment, cetrimide 0.5% (w/w) cream, chlorhexidine gluconate 0.1% (w/w), and mentholatum to the wound. He complained that he had been awakened from sleep with severe pain and swelling in the leg, and that he “felt unwell”.

The patient had a high BMI, but past medical history was significant only for alcohol use (approximately 50 units of alcohol weekly) and ongoing hypertension and hypercholesterolaemia. On examination, the patient was profoundly hypotensive (66/43 mmHg), tachycardic (95 bpm), and hypothermic (34.6°C). He appeared pale and clammy, but was oriented to person, place, and time with a GCS of 15/15. Examination of the left lower limb revealed leg weakness, well-demarcated pretibial erythema with warmth and tenderness distally, and a hemi-circumferential area of yellow discoloration, overlying vesiculation, and induration on the medial thigh. This region was exceptionally tender. Clinically, necrotising fasciitis was suspected and initial management involved IV fluid resuscitation, analgesics, and clindamycin. Laboratory results (Table 1) indicated a non-oliguric acute kidney injury (AKI) secondary to hypoperfusion caused by septic shock and a likely hypovolaemic hyponatraemia. The patient remained hypotensive despite ongoing fluid resuscitation. Blood, urine, and vesicular fluid samples were sent to the laboratory for culture. Piperacillin-tazobactam, vancomycin, and gentamicin were commenced, and the patient was transferred to the intensive therapy unit (ITU), where he was intubated and mechanically ventilated. A CT scan showed evidence of infection but no direct evidence of necrotising fasciitis (Figure 1). With this diagnosis unconfirmed, antibiotic treatment was escalated to a combination of clindamycin, piperacillin-tazobactam, linezolid, and ciprofloxacin to provide broad-spectrum cover for group A β-haemolytic streptococci (GAS), Panton-Valentin leukocidin-positive methicillin-resistant *Staphylococcus aureus*, gram-negative bacilli, and anaerobes. Due to ongoing hypotension and the associated AKI, the patient was started on inotropes and placed on continuous veno-venous haemodialysis (CVVH). He received prophylaxis for venous thromboembolism with unfractionated heparin, and was taken to theatre for a decompressive fasciotomy; no evidence of

---

**Table 1: Relevant laboratory results.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Flag</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>123mmol/L</td>
<td>L</td>
<td>133-146mmol/L</td>
</tr>
<tr>
<td>Lactate, serum</td>
<td>6.4mmol/L</td>
<td>H</td>
<td>0-1.8mmol/L</td>
</tr>
<tr>
<td>Urea, serum</td>
<td>14.2mmol/L</td>
<td>H</td>
<td>2.5-8.5mmol/L</td>
</tr>
<tr>
<td>Creatinine, serum</td>
<td>188µmol/L</td>
<td>H</td>
<td>64-104µmol/L</td>
</tr>
<tr>
<td>WCC</td>
<td>20.1x10⁹/L</td>
<td>H</td>
<td>4.0-11.0x10⁹/L</td>
</tr>
<tr>
<td>CRP</td>
<td>378mg/L</td>
<td>H</td>
<td>0-5mg/L</td>
</tr>
</tbody>
</table>

WCC: White cell count; CRP: C-reactive protein.

---

**FIGURE 1:** CT femur. Marked oedema and stranding within the subcutaneous tissues of the left lower extremity, with fluid tracking along the intermuscular planes of the medial and posterior compartments. No dominant focal fluid collection to suggest a discrete abscess. No air within the soft tissues.

**FIGURE 2:** CT femur. Views of the legs demonstrate left thigh medial fasciotomy. No evidence of subcutaneous emphysema or collection visualised within the scan range (to mid calf). There is a vacuum dressing in situ.
necrotising fasciitis was found intraoperatively. However, theatre samples grew GAS and vesicular fluid cultured *Staphylococcus aureus*. A diagnosis of toxic shock syndrome (TSS) was made on the basis of his clinical picture and microbiology results.

In the following days, the patient’s blood pressure and renal function proved too unstable to reduce CVVH. He developed profuse diarrhoea (*Clostridium difficile* negative), and wound appearance continued to worsen. Questions arose concerning the patient’s immunological status, due to the extent and severity of the infection. HbA1c levels proved normal, and HIV tests were negative. Given the lack of a history of recurrent soft tissue or respiratory tract infections, normal immunoglobulin levels and serum protein electrophoresis results, hypogammaglobulinaemia was outruled. However, a positive GAS culture, without an associated rise in the antistreptolysin O titre (ASOT), indicated a possible functional humoral defect. In the context of a worrying clinical picture and suspected GAS-induced sepsis, the patient was given high-dose IV immunoglobulin (IVIG) with pre-administration of antihistamines, hydrocortisone, and anti-inflammatories. CT imaging of the abdomen and left leg remained unremarkable (Figure 2).

By day seven, increasing urine output indicated improving renal function, and the patient was able to maintain blood pressure without inotropic support. However, he developed bilateral pleural effusions with significant peripheral oedema, likely from fluid loading, and evidence of cholestasis (elevated alkaline phosphatase (ALP) and bilirubin), likely secondary to antibiotic treatment; no liver or biliary abnormalities were noted on ultrasound. As a result, linezolid and piperacillin-tazobactam were discontinued, daptomycin was commenced and the patient continued on clindamycin.

The patient continued to improve, and was successfully extubated on day nine. However, blood cultures grew *Klebsiella pneumoniae*, while *Candida spp.* was cultured from the tip of a
right jugular line. Aztreonam and caspofungin were added to the antimicrobial regimen.

Over the following ten days the patient deteriorated, became pyrexic, required re-intubation and a further dose of IVIG. His wounds began to show evidence of necrotic tissue. Surgical exploration confirmed the presence of necrotic change of the subcutaneous tissues and fascia, and a diagnosis of necrotising fasciitis was made. The patient underwent a total of four debridements over the next few days before it could be confirmed that no involved tissue remained (Figure 3). While at times agitated, the patient began to show significant clinical improvement, and was systemically stable and suitable for surgical skin grafting by day 26 of hospital stay; extensive skin grafts were required along his upper medial thigh (Figure 4). The patient was transferred out of the ITU on day 27 and recovered on the ward, completing three weeks of physiotherapy before being discharged home.

**Discussion**

This patient presents a classic example of TSS complicated by necrotising fasciitis. The microbial aetiology – GAS with synergistic *Staphylococcus aureus* – and the previously healthy patient’s history of a minor injury with skin breach were consistent with that of most type II NSTIs described in the literature. While most infections evolve over a period of two or three days, GAS has been shown to be particularly aggressive; in this case, the patient was in septic shock less than 12 hours following the initial injury. Many factors, including advanced age and comorbidities, have been shown to adversely affect patient outcome, but delayed surgical intervention is the most important factor leading to increased mortality. However, neither surgery nor antimicrobial therapy alone are sufficient in patient management. It has been well documented that early and complete surgical debridement, appropriate antimicrobial therapy, and physiological support and monitoring provide the best chance for patient recovery.

**Table 2: Common features of necrotising fasciitis.**

<table>
<thead>
<tr>
<th>Symptoms3,7</th>
<th>Clinical findings3,7</th>
<th>Laboratory studies2</th>
<th>Radiological imaging10</th>
<th>Surgical exploration2,7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme pain, disproportional to clinical findings</td>
<td>Rapid progression of clinical manifestations</td>
<td>Evidence of sepsis (elevated lactate, WCC, CRP, altered electrolytes, abnormal renal or liver profiles)</td>
<td>Early changes are similar to those in cellulitis: soft tissue thickening, increased opacity</td>
<td>Easy blunt dissection of the subcutaneous tissues from deep fascia ('finger test')</td>
</tr>
<tr>
<td>Rapid progression and spread of lesions, erythema, and tenderness</td>
<td>Tenderness and oedema past the apparent area of erythema</td>
<td>WCC &gt;15.4*10^9/L and serum sodium &lt;135mmol/L</td>
<td>Subcutaneous emphysema, may track along fascial plains</td>
<td>Gray, swollen tissue/fascia</td>
</tr>
<tr>
<td>Systemic symptoms of infection/toxicity: fever, fatigue</td>
<td>Supralesional vesiculation, bullous formation</td>
<td>LRINEC score &gt;8 suggests high risk of NSTI</td>
<td>Fluid or air collections in subfascial planes</td>
<td>Lack of bleeding, thrombosis of vessels</td>
</tr>
<tr>
<td></td>
<td>Indurated, hard, wooden feeling of subcutaneous tissue; inability to feel underlying muscle groups</td>
<td>Dermal thickening</td>
<td>Thin exudate, lack of excessive pus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Signs of sepsis: tachycardia, hypotension, hypothermia or fever, end organ dysfunction</td>
<td>Inflammatory fat stranding</td>
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<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** WCC – white cell count; CRP – C-reactive protein; LRINEC score – laboratory risk indicator for necrotising fasciitis score (variables include WCC, haemoglobin, sodium, glucose, serum creatinine and C-reactive protein); NSTI – necrotising soft tissue infection.
but controversial therapies include IVIG and hyperbaric oxygen. IVIG was used in this patient based on evidence that suggests its usefulness in GAS-induced sepsis. Importantly, this case shows excellent patient management by the multidisciplinary clinicians involved and demonstrates the benefit of early senior clinical input. Emergency physicians recognised sepsis, suspected necrotising fasciitis, provided appropriate resuscitation, and referred to ITU when septic shock developed. From the outset, the patient received input from emergency, surgery, microbiology, critical care, renal, radiology and immunology experts, demonstrating a co-ordinated multidisciplinary approach to patient management. Early diagnosis, while of paramount importance, can be challenging even for experienced physicians. NSTIs can resemble simple cellulitis in the early stages, and overlying skin changes may not necessarily reflect the ongoing extensive subcutaneous disease process. Clinical presentation may vary depending on various factors, including time of presentation within the natural history of infection, and microbial aetiology. Scoring systems to aid in diagnosis are typically more useful for ruling out an NSTI, or discriminating between necrotising and non-necrotising forms, than for confirming it. Additionally, radiological signs may be absent or non-specific; for example, gas in the fascial planes (while highly specific) is not a sensitive finding. The direct visualisation of the subcutaneous tissues and fascial planes during surgical exploration remains the most important feature of an NSTI, and is the only way to make a definitive diagnosis. Thus, maintaining a high index of clinical suspicion is crucial, and in suspected cases, surgical intervention should not be delayed while awaiting laboratory, microbiological, or radiological studies. Some of the important surgical findings and supporting clinical, laboratory and radiological evidence are summarised in Table 2.

Conclusion

While uncommon, NSTIs can affect healthy individuals as well as at-risk groups, and are rapidly fatal if not promptly diagnosed and treated. Appropriate patient management requires multidisciplinary care, and core principles are early surgical debridement, broad-spectrum antibiotic therapy, and organ and haemodynamic support. These interventions crucially depend on high clinical suspicion and early diagnosis.

Acknowledgements

I would like to express my gratitude and appreciation to the patient for his help and co-operation throughout the development of this case study. Many thanks also to Dr Mark Sheehan and Dr Mohammad Alakkad for helping to procure and interpret patient images.

References

A missed coarctation

Abstract
Coarctation of the aorta (CoA) is a very dangerous congenital heart defect, with many patients presenting in the neonatal period with heart failure. This defect is especially serious since many cases are missed at birth due to inaccurate examination or lack of screening. Recommended pulse oximetry and blood pressure screening is currently not a mandatory screen in the HSE guidelines for newborn checks, but provides a much-needed support to clinical skills in detecting a CoA defect. This is the case describing a nine-day-old boy whose cardiac condition was misdiagnosed, leading to preventable and potentially fatal consequences. His defect was missed at both a newborn assessment and his presentation to Cavan General Hospital. He presented to Cavan General Hospital with upper extremity cyanosis and discoloration, pale trunk and legs, and tachypnoea. After clinical assessment, the impression was septicaemia on underlying congenital heart disease (CHD), and he was then transferred to Our Lady’s Children’s Hospital Crumlin (OLCHC). Upon examination and screening, he was determined to have CoA, which was successfully repaired surgically with end-to-end anastomosis with patent ductus arteriosus (PDA) ligation. This case highlights the importance of complete paediatric examinations and the necessity for pulse oximetry and blood pressure screening for CoA to prevent future complications.

Introduction
Coarctation of the aorta (CoA) is a common condition, accounting for 5-8% of all congenital heart conditions, and can be one of the most fatal congenital heart defects depending on its classification. The danger of CoA is further emphasised by its subtlety, as it can easily be missed; a Swedish study showed that of 104 missed diagnoses of duct-dependent cardiac defects, CoA was the most common at 64/104 (62%). The pathogenesis of CoA is currently unknown, but it is known to be associated with aortic valvular defects and, most commonly, Turner’s syndrome, among many other syndromes. The main pathology underlying this condition is the narrowing of the aorta either proximal to or at
the juncture with the ductus arteriosus (pre-ductal/ductal) or distal to the ductus arteriosus (post-ductal), as shown in Figure 1. Pre-ductal and ductal coarctations are duct dependent and have a worse prognosis due to ductus arteriosus closure at about seven days postnatally, leading to cardiac decompensation. Postnatally diagnosed pre-ductal CoA typically presents at approximately seven days postnatally with cardiogenic shock or signs of heart failure, typically central cyanosis, breathlessness, and systemic oedema.

This presentation is associated with a mortality rate of approximately 13.6%. Post-ductal CoA patients typically have the classic sign of rib notching and pulsations due to intercostal collateral circulation. Non-duct-dependent children may never experience symptoms until adulthood due to collateral circulation through intercostal arteries, but eventually experience cardiac decompensation. Management of a duct-dependent coarctation requires immediate administration of prostaglandin E1 to maintain the ductus arteriosus. The ductus arteriosus is the primary means of perfusion to the lower extremities, especially in very narrow coarctations. If prostaglandin E1 is not administered, death is nearly certain from cardiogenic shock. Dobutamine must also be given to maintain cardiac output in heart failure. Management of post-ductal coarctation presentation is dependent on the severity of narrowing and symptoms. Surgery is always required for pre-ductal CoA, while patients with post-ductal CoA should have surgery prior to decompensation to increase life expectancy. The common types of surgical intervention in pre-ductal and post-ductal CoA repair include stent placement, end-to-end anastomosis, and catheter balloon aortoplasty with concurrent patent ductus arteriosus (PDA) ligation. A comparison of both classifications based on presentation age, signs and

Table 1: Comparison of pre-ductal and post-ductal CoA.

<table>
<thead>
<tr>
<th>Comparative qualities</th>
<th>Pre-ductal/ductal CoA</th>
<th>Post-ductal CoA</th>
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<tr>
<td>Age</td>
<td>Neonatal presentation</td>
<td>Adolescent/adult presentation</td>
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<tr>
<td>Symptoms/signs</td>
<td>Cyanosis when DA closes</td>
<td>Cyanosis during exercise/stress</td>
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<tr>
<td></td>
<td>Dyspnoea, tachypnoea</td>
<td>Dyspnoea, tachypnoea</td>
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<td></td>
<td>Loss of consciousness</td>
<td>Loss of consciousness</td>
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<td></td>
<td>Absent femoral pulses</td>
<td>Rib notching and pulsations</td>
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<td></td>
<td>Plethora of upper extremity</td>
<td>Upper extremity hypertension</td>
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<td></td>
<td>Upper extremity hypertension</td>
<td>Possible cardiogenic shock</td>
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<td></td>
<td>Decreased lower extremity perfusion</td>
<td></td>
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<tr>
<td></td>
<td>Cardiogenic shock</td>
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<tr>
<td>Investigations</td>
<td>Pulse oximetry of four limbs</td>
<td>Pulse oximetry of four limbs</td>
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<td>Blood pressure of four limbs</td>
<td>Blood pressure of four limbs</td>
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<tr>
<td></td>
<td>VBG – metabolic acidosis</td>
<td>ABG – metabolic acidosis</td>
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<td></td>
<td>CXR – cardiomegaly</td>
<td>CXR – cardiomegaly</td>
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<td></td>
<td>ECG – arrhythmia</td>
<td>ECG – arrhythmia and RVH/LVH</td>
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<td></td>
<td>ECHO – RVH</td>
<td>ECHO – RVH and LVH</td>
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<td></td>
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<td>CT or MRI angiography</td>
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<tr>
<td>Management</td>
<td>Alprostadil/Prostin</td>
<td>Dobutamine</td>
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<td>Dobutamine</td>
<td>High flow oxygen</td>
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<td></td>
<td>CPAP and intubation (if needed)</td>
<td>Diuretics – if fluid overloaded</td>
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<td>Diuretics – if fluid overloaded</td>
<td>NPO prep. for surgery</td>
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<td>NPO prep. for surgery</td>
<td>Anti-hypertensive medication</td>
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<td></td>
<td>Anti-hypertensive medication</td>
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Abbreviations: CoA – coarctation of the aorta; DA – ductus arteriosus; VBG – venous blood gas; ABG – arterial blood gas; CXR – chest x-ray; ECG – electrocardiogram; ECHO – echocardiogram; RVH – right ventricular hypertrophy; LVH – left ventricular hypertrophy; CPAP – continuous positive airway pressure; NPO – nil per os.
management can be seen in Table 1. Failure to operate on CoA in both pre- and post-ductal cases has been shown to result in 75% mortality by the age of 46 years, with an average life expectancy of 35 years. These statistics emphasise the need for early detection and intervention. The purpose of this article is to present a rare case of missed CoA, and emphasise the importance of complete examinations, maintaining suspicion of CoA, and screening, both at neonatal check-ups and upon presentation to hospital.

The case
A nine-day-old baby boy presented to Cavan General Hospital in Cavan, Ireland, with a one-hour history of blue/purple facial and upper extremity colour and pallor of the trunk and lower extremities associated with fast, deep breathing. On the previous night, he had been normally active and feeding, with his last feed at 6.00pm, but the parents noted fatigue and irritability with feeding. At about 4.00am, he was noted to have a purplish blue face and upper chest, with pale trunk and legs. He was tired, floppy, cold, sweating, and taking fast, deep breaths. He was immediately brought by ambulance to Cavan General Hospital and admitted to the neonatal ICU. He spent one day there, initiated on antibiotics and intubated due to continuous positive airway pressure (CPAP) intolerance. He had multiple cyanotic episodes lasting 15-20 minutes every three hours while at Cavan General Hospital. He was noted to have passed bowel motions and to have urinated at normal frequency and colour with no pain. He had no past medical history of any illness or medication use. Birth weight was 3.78kg at 40+2 gestation without complications pre- or postnatally.

Initial examination only revealed cyanotic features in the upper extremity, pale and cold lower extremities, with weak peripheral pulses and a continuous systolic murmur. There was noted increased work of breathing but no wheeze, consolidation, or crepitations in both lung fields. Temperature was recorded at 38.2°C. Full blood count revealed WBC of 14.2 x 10^9/L (ref. 4.0-11.0), which is slightly raised, but not entirely suggestive of severe infection. Arterial blood gases revealed combined metabolic and respiratory acidosis with severe deoxygenation: pH 7.22; PaCO₂ 6.3kPa; PaO₂ 4.2kPa; and, HCO₃ 19.2mEq/L. Chest x-ray revealed cardiomegaly.

Initial impression led to a diagnosis of sepsis compounded by underlying decompensated congenital heart disease, with triple antibiotics implemented but with no relief. He also received prostaglandin E1 and dobutamine to maintain perfusion and cardiac output, but remained cyanotic with low oxygen saturations. He received morphine for pain relief and eventually required nasogastric (NG) tube feed and ventilated intubation at FiO₂ 30% due to CPAP intolerance. After hours of no improvement, he was urgently transferred to Our Lady’s Children’s Hospital Crumlin (OLCHC) for tertiary care. This diagnosis of pre-ductal coarctation of the aorta was due to his classical findings of breathlessness and cyanosis. A successful urgent end-to-end anastomosis repair of the coarctation and PDA ligation was performed. Postoperative echocardiogram revealed left and right ventricular hypertrophy and postoperative gradient of 19mmHg, much decreased from its previous coarcted state. He was also initiated on morphine for pain relief, paracetamol to continue closure of the PDA, furosemide with spironolactone to decrease fluid overload, and clonidine for hypertension. He began to improve with no cyanotic episodes on close observation, and was then discharged with daily medication to combat further ventricular hypertrophy and prevent heart failure.

Discussion
While this case’s end results were good, with no immediately noticeable neurological or pulmonary damage, this missed diagnosis is a failure from the physician’s point of view. Palpating femoral pulses is a necessary part of the paediatric exam and may appear to be relatively simple, but children may be irritated by finger pressure into the sensitive inguinal area, making it difficult to appreciate. Due to either lack of clinical experience or circumstances, many physicians have missed congenital heart abnormalities, specifically CoA. One study showed that 21/22 infants presenting and diagnosed with CoA had weak or absent femoral pulses. However, femoral pulse palpation should not be the only screening tool for CoA, as a PDA can possibly provide enough blood volume from the right ventricle to create a palpable pulse. While a normal femoral pulse may appear to be a good sign of perfusion, it also masks the hidden danger of a coarctation. One study showed that 22/83 misdiagnosed infants were readmitted with circulatory failure and 3/83 died from CoA. If CoA does not present in earlier life, adults may go untreated for hypertension, resulting in stroke or cardiac failure, with most patients dying before the age of 46 years. This emphasises the importance of diagnosing CoA at birth and not waiting for hospital admission with cardiogenic shock. Simply put, doctors are fallible and can miss diagnoses. This does not mean that the physicians involved in the missed diagnoses are necessarily poor or lazy; other investigations supporting clinical skills may be necessary to diagnose CoA. It is also difficult to assess the sensitivity of palpating femoral pulses for CoA versus lack of experience, given the
expertise required for confidence at this examination. A secondary assessment for CoA is to use pulse oximetry and measure blood pressure on all four limbs to find CoA, and this has been a recommended evidence-based screening method in previous studies.5,6 A noticeably diminished blood oxygen saturation of the lower versus upper limbs should trigger a diagnostic echocardiography or CT scan.5 Pulse oximetry screening (POS) and four-limb blood pressure measurements are easy to perform, non-invasive, and require little economic input due to the use of previously stocked equipment for which little training is required. Neither femoral pulse palpation nor POS are sensitive enough to rule out CoA, but together this combination provides the best screening tool for CoA in the newborn. The largest expense and greatest barrier to using both POS and femoral pulse palpation is extra time spent by the physician or nurse to perform these screening procedures. A POS and blood pressure screen algorithm is provided by the Health Service Executive, but is not a mandatory part of newborn testing.5 Currently, the only required newborn screens are bloodspot and hearing test,9 but CoA screening should be done to prevent fatal complications in the young infant as it is both non-invasive and potentially life saving. Pulse oximetry and blood pressure screening of newborns appears to satisfy each of the Wilson and Jungner Screening Criteria from the evidence listed above.10 Other investigations to diagnose CoA have been explored, but with little success.

Antenatal echocardiogram screening for CoA has been shown to have modest results in improving outcome, but is not sensitive enough to stand alone as a diagnostic tool.1

A major limitation to antenatal echocardiogram screening is also the heavy expense on the healthcare system. Pulse oximetry and blood pressure screening, in addition to femoral pulse palpation, require a commitment of a great deal of time on already time-pressured physicians, but should be used like the standardised heel-prick test to recognise this potentially fatal condition.

Conclusion

This is a lesson in the importance of paediatric physical examinations and investigations, both at the first neonatal check and at subsequent checks. This case also shows the necessity of detecting CoA as early as possible, and the importance of pulse oximetry and blood pressure screening in early life. While CoA patient signs may be missed by multiple physicians, this does not excuse the use of simple, non-invasive screening in addition to femoral pulse palpation to identify CoA in the newborn stage.

References

Exploring the views of healthcare professionals on increasing smoking cessation advice for patients

Abstract

Background: Smoking cessation advice provided by healthcare professionals can be effective in increasing smoking cessation among patients. Any successful intervention will require staff knowledge of local barriers to implementation. However, the views of Irish healthcare professionals on increasing the provision of smoking cessation advice and the associated barriers remain unexplored.

Aims: To explore the views of Irish healthcare professionals on barriers to increasing smoking cessation advice for patients in a large Irish university teaching hospital.

Method: Semi-structured interviews were conducted separately with 16 healthcare professionals in a large Irish university teaching hospital.

Results: The main barriers identified were patient and staff attitudes, time and service constraints, information not readily available, and issues and opinions on a smoke-free campus policy in a hospital setting.

Conclusion: Our results revealed several barriers, expressed by Irish healthcare professionals, to providing smoking cessation advice to patients. This supports the need to implement a multi-component intervention in a hospital setting to improve the rate of provision of smoking cessation advice in patients by healthcare professionals.

Introduction

Smoking is the single most important preventable cause of illness, chronic disability, and death in Ireland. According to the Health Survey Ireland 2015, 23% of the Irish population are smokers. Smokers lose an average of 10-15 years from their life expectancy, according to the HSE website on smoking cessation, “one in every two smokers will die of tobacco-related disease”. Every year, there are over 5,000 deaths due to tobacco in Ireland. To combat this problem, healthcare professionals (HCPs) are encouraged to provide cessation advice to patients who are smokers. Based on a Cochrane review in 2008, brief cessation advice provided by doctors increases the possibility of smokers being successful in quitting. The Health Survey Ireland 2015 reported that a “majority (63%) of smokers are trying to, planning to or considering quitting”. However, there is a low prevalence of provision of cessation advice by HCPs, in Ireland and more widely. An Irish study (2012) found that 61% of hospitalised patients were asked about smoking status, and only 44% of current smokers received advice from HCPs. This was also recently explored in another Irish study (2014) carried out in two large Irish university teaching hospitals, which reported that 62% of inpatients did not receive smoking cessation advice, despite 55% being interested in quitting when asked. In a German study, only 39% of patients who smoked recalled being counselled to quit, while only 10.5% of general practitioners in Montreal and 22.6% of university hospital physicians in Turkey offered smoking cessation advice. Use of the Ottawa Model for Smoking Cessation (OMSC) has been proposed to accomplish a systematic approach to the delivery of cessation advice by HCPs to patients.
in an Irish hospital setting. A study evaluating the OMSC showed that 69% of smokers receiving the OMSC intervention achieved six-month continuous abstinence, suggesting that it is a successful cessation model. A cross-sectional study in Japan reported HCPs lacking knowledge and training, and patients’ unwillingness to quit, as potential barriers to smoking cessation care. In the UK, a qualitative study showed that patients were more likely to consider cessation when referred to a separate specialist smoking cessation centre, and this service was favoured by HCPs because they felt that they lacked the time and expertise to intervene during daily practice. The views of HCPs on increasing the provision of smoking cessation advice in Ireland are not well elucidated. This study aims to explore the views of HCPs on current barriers to the provision of cessation advice to patients, and their recommendations on how to increase such advice, in a large university teaching hospital.

Methods

Participants and setting

Venue-based and snowball sampling methods were employed, whereby 16 HCPs were recruited from Beaumont Hospital. Once a HCP was interviewed, they then recommended two to three others who might consider participating in the project. Each HCP was contacted in turn, and the researcher (SYH) met those who agreed to participate, and conducted the interviews within the allocated timeframe. Participants were selected and interviewed if they fulfilled the criteria: a healthcare professional working in an environment where they would have daily contact with patients. Interview appointments were arranged from July 4-11, 2012. HCPs were categorised as doctors, surgeons, nurses and allied HCPs to ensure anonymity.

Procedure

Ethical approval was given by the Beaumont Hospital Ethics (Medical Research) Committee. Each participant was given a leaflet about the study and its purpose, and a consent form to sign prior to the interview. A set list of open-ended questions was used to maintain consistency (Figure 1). All participants were interviewed by the same interviewer. Each session lasted 15-30 minutes, and was recorded with the respondent’s permission. Participants were questioned on their smoking status, whether they routinely provide cessation advice, barriers to delivering such advice to patients, and recommendations.

Analysis

Digital recordings were analysed and fully transcribed. A thematic

Do you smoke?

Do you routinely record patients’ smoking status?

Do you routinely provide patients who are smokers with smoking cessation advice?

Do you follow up on all these patients that you provide with smoking cessation advice?

On average, how many years of life would you estimate for smokers to lose in comparison to non-smokers?

Do you refer patients to a community smoking cessation programme or any other that is similar?

Are you familiar with the SAs model, 5Rs model or the Ottawa model?

If the SAs model were implemented in this hospital, do you think it would be effective?

If the 5Rs model were implemented in this hospital, do you think it would be effective?

What do you think about the Ottawa model, if it were to be implemented in this hospital?

Do you think practice-based supports such as stickers on a patient’s chart, or posters or emails, would increase the rate of delivery of smoking cessation advice to patients?

Do you think brief smoking cessation advice from a healthcare professional is effective in increasing quit rates?

How long do you think brief smoking cessation advice should take?

Present results suggest that 10-15 minutes is the optimal length for provision of smoking cessation advice. How realistic do you think this is? What do you think of this?

Do you have any other recommendations for improving the rate of recording patients’ smoking status and providing smoking cessation advice?

What do you think about this hospital as a smoke-free campus? Would that help patients?

In this hospital, what systematic barriers do you and your staff experience in terms of recording patients’ smoking status and providing smoking cessation advice?

FIGURE 1: List of interview questions.
analysis was done to identify the main themes (barriers and recommendations) relating to smoking cessation from interview transcripts. Significant key words, phrases and quotes from transcripts were identified and marked with ‘descriptive tags’ or codes by a researcher (SYH). Coded transcripts were then reviewed by another researcher (MB) to ensure the reliability of the first author’s (SYH) codings and to see if any further themes could be detected in the transcripts. Once both researchers (SYH, MB) agreed on the codings, all codes that were thematically similar were grouped together and labelled as a category, which became the organising themes of our analysis.

Results

HCP recruitment and participation

Of the 26 HCPs approached, 16 agreed to participate. Of the 10 that declined to participate, eight stated that they were busy and two did not respond to the emails. The HCPs who participated were doctors (n=6), surgeons (n=2), nurses (n=5) and allied HCPs (n=3), none of whom currently smoked. One nurse had stopped smoking 11 years previously (Figure 2).

Current practice

Most HCPs (75%; 12/16) routinely recorded patients’ smoking status on admission, 18.75% (3/16) did not do this routinely, and 6.25% (1/16) did not record patients’ smoking status at all. The 18.75% (3/16) of participants recorded smoking status when reminded to do so (i.e., on admission note or social history), or when it was relevant to the patient’s medical condition (i.e., if the patient had a respiratory condition).

Only 43.75% (7/16) of the interviewed participants provided smoking cessation advice to patients routinely, 37.5% (6/16) did not routinely provide it, and 18.75% (3/16) did not provide it at all. The time spent for provision of cessation advice was less than five minutes.

“We would contact the smoking cessation officer, but we don’t offer advice for patients who come in.” (Interview 3 – nurse)

“We would [provide cessation advice] in young breast cancer patients who are getting better and will live a long life, but if it’s somebody who is quite sick and palliative, it’s not really considered important to do that.” (Interview 10 – allied healthcare professional)

“I am not sure whether everyone does anything other than record [smoking status] as part of the history that they take.” (Interview 6 – doctor)

There was also lack of routine documentation of patients’ smoking history by staff. According to one nurse, patients’ smoking history was not “written in black and white” and there was no “specific column for it”.

“Sometimes it’s pack years, sometimes it’s ‘ex-smoker gave up 15 years ago’, but not the amount. Maybe [it would be documented more] if there was a routine hospital policy on how you document and to always document it.” (Interview 10 – allied HCP)

Barriers to delivering smoking cessation advice

All HCPs interviewed viewed the provision of smoking cessation advice as effective in increasing quit rates among patients. However, several barriers were reported when providing patients with such advice.

1. Patient and staff attitudes

Participants said that it can be difficult to encourage patients to quit smoking when they have no intentions of quitting at all.

“When you start talking to a patient about smoking, you can see them shut off. Most patients when asked, they smile and, it’s like, ‘I suppose
you are going to give me a lecture now’...” (Interview 6 – doctor)

It was also voiced that patients come to the hospital for specific medical problems and not smoking cessation, making it difficult for HCPs to initiate.

“The patient didn’t come to quit smoking, they came for [a different] problem, so it won’t have an impact.” (Interview 1 – surgeon)

One noted that there was no routine management for smoking cessation.

“It was maybe done once or twice during a patient’s stay. I haven’t seen it done any more.” (Interview 13 – doctor)

With regard to staff attitudes, participants felt that there was a “huge lack of awareness”, as most doctors “don’t know the actual process of referring someone for smoking cessation”. Furthermore, most HCPs do not think that this is their primary goal, and believe that they are not the “primary people” to give cessation advice. Both of these factors contributed greatly to the lack of provision of cessation advice to patients.

“They are not coming to me actually to see that [smoking cessation], they are coming to me to diagnose a tumour, or treat their COPD with whatever medication. That is what I’m supposed to do as a doctor.” (Interview 15 – doctor)

The lack of knowledge among junior staff also contributed to a lack of provision of smoking cessation advice. This resulted in HCPs not providing cessation advice routinely or intensively in the hospital. Another doctor suggested that staff should be educated on “actual smoking-related illnesses and the latest figures on how smoking impacts on patients” in addition to cessation advice.

“I think [smoking cessation advice] needs to come from all members of the teams, because I think just one advising them to stop smoking is not helpful.” (Interview 11 – allied HCP)

2. Time and service constraints

Most respondents viewed time as a major factor in providing brief cessation advice to patients.

“We just lack time to talk to patients.” (Interview 14 – doctor)

“You have to do so much work. There is no time to spend per patient to give cessation advice.” (Interview 1 – surgeon)

Having a part-time smoking cessation officer (three days per week) was among the barriers faced by HCPs, as referrals made were “not always consistent” (Interview 15 – doctor).

One nurse voiced the opinion that there should be immediate access to a cessation officer at all times.

“You can’t send people over and say ‘we will have them talk to you tomorrow’.” (Interview 3 – nurse)

One surgeon suggested that a smoking cessation clinic should be available in the hospital for patients willing to quit (Interview 1 – surgeon). With the heavy workload and the time constraints every HCP has, having a smoking cessation clinic where patients could be followed up consistently and seen primarily for cessation would be a great improvement. Facilities such as community smoking cessation programmes, support groups and follow-up services for patients on pharmacotherapy for cessation are unavailable, affecting the quit rates among patients.

“I think it’s important when a patient avails of a service, they should be followed up within six months.” (Interview 16 – allied HCP)

“There are no community cessation programmes and facilities available.” (Interview 15 – doctor)

Staff shortages in the hospital contributed to inconsistent provision of cessation advice. One nurse suggested that having a cessation nurse assigned to wards to follow up on patients would improve the rate of delivering cessation advice.

“I think if someone was assigned specifically, a nurse to go around and check what patients are smokers and sit down [with them], maybe that will help.” (Interview 5 – nurse)

3. Information not readily available

One practical barrier expressed by participants was a lack of availability of information on smoking cessation. Without information leaflets and posters readily available throughout the hospital, HCPs can only provide cessation advice verbally.

“There aren’t any information leaflets and things like that. So maybe if there were leaflets on the wards, it might help inpatients as well.” (Interview 8 – doctor)

“...you always ask about smoking history and it’s at the forefront of your mind ... By the time they make it to the wards, it’s forgotten, and you deal with their acute problems.” (Interview 8 – doctor)

4. Smoke-free campus

During the study period, the hospital had just implemented a smoke-free campus policy and experienced several issues. Patients
smoking in a hospital affects not only their health, but also subjects non-smoking parties to passive smoking, so with the hospital being designated a smoke-free campus, there would have to be an increase in the rate of provision of cessation advice and encouraging patients to quit smoking. Hospital staff would also theoretically be motivated and encouraged to quit smoking, as there is a “restriction they have to respect” (Interview 1 – surgeon). However, the idea of the smoke-free campus was not supported by all. One doctor said it “is not fair for the palliative patients”, despite helping other patients with smoking cessation, and suggested that exceptions should be made for these patients (Interview 9 – doctor).

Discussion
This is the first qualitative study to explore the views of HCPs in Ireland on the barriers to increasing smoking cessation advice for patients. The main barriers identified from our study were time and service constraints, patient and staff attitudes, information not readily available, and issues with the smoke-free campus policy. Time constraint was viewed as the major barrier to the provision of smoking cessation advice to patients by HCPs. In an Irish study, 74% of nurses had no time to provide cessation advice to patients. In another study, smoking cessation counselling was perceived as too time-consuming by physicians. According to Duffy et al., having trained nurses to deliver cessation care to patients is ideal, as nurses are well informed on patients’ medical conditions, nursing time is more cost-effective compared to physician time, and nurses have access to and immediate rapport with patients. Future research should investigate the suitability of nurses to deliver cessation care. Another barrier perceived was that HCPs underestimate the relevance of cessation advice to the patients and do not regard it as their primary goal and priority. This was reflected in other research: 76.3% of physical therapists asked patients’ smoking status but only 21.6% reported assisting patients to quit smoking (due to lack of training). Despite HCPs being aware of the importance of smoking cessation, there is a lack of knowledge as regards counselling patients. Desalu et al. found that 67% of physicians were aware of smoking cessation but only 30.3% had knowledge on cessation counselling and 66.3% had poor knowledge of interventions. An Irish study reported that 65% of nurses lacked training in delivering cessation advice. Smoking patients who received cessation advice from two or more types of HCP had an almost three-fold increase in quit attempts and readiness to quit in the next six months.

With regard to patient attitudes, patient resistance or unwillingness to quit smoking was also among the barriers. Dentists and general practitioners in the UK reported patient resistance as a barrier. However, Duffy et al. reported that only 17% of inpatient veteran smokers received advice, despite more than two-thirds being motivated to quit. In Ireland, Bartels et al. reported that 40% of smokers would like to receive cessation advice. A further barrier identified was the lack of a facility to follow up patients who had received smoking cessation advice from HCPs. It has been demonstrated previously that cessation rates were higher in groups receiving extended counselling (22% versus 20% in the control group) and follow-up (28% versus 24% in the control group) compared with those receiving brief advice. Training residents and labelling medical records with reminders has more than doubled the percentage (from 9% to 23%) of patients receiving advice. Intervention, including a follow-up call, showed a rise in the six-month continuous abstinence rate (29.4% vs. 18.3%). Rigotti et al. confirmed that intensive intervention with follow-up support increased cessation rates. Multi-component interventions that increase provision of cessation advice have demonstrated some success. Freund et al. implemented a multi-strategic approach, which involved seven broad intervention strategy areas, and this was effective in increasing hospital smoking care delivery and provision of nicotine replacement therapy. A further multi-strategic intervention trial showed that improving the routine provision of cessation care practices in a hospital setting is achievable. This confirms the need for multi-component intervention to increase the efficiency of provision of cessation advice in a hospital setting. This study has several limitations. Results were based on interview sessions with HCPs, leading to recollections and biases of individuals affecting the data’s accuracy. The sample size was 16 HCPs from a single large university teaching hospital, suggesting that the sample may not be representative of the entire HCP population. However, the HCPs interviewed are involved with patients directly in their clinical practice and would be the ones providing cessation advice directly.

Conclusion
This study investigated the views of HCPs on increasing smoking cessation advice for patients. We identified several barriers expressed by HCPs to providing cessation advice to patients. With the knowledge of these barriers, we are able to understand and overcome them, and to personalise and improve the provision of smoking cessation advice to patients, thus increasing smoking cessation rates. Overall, this supports the need to implement a multi-component, hospital-based intervention, or specialist cessation care, to promote and increase the rate of provision of smoking cessation advice to patients by HCPs.
References


An investigation of responsiveness to PI3K inhibition in breast cancer cells expressing high levels of androgen receptor

Abstract

Introduction: Approximately 75% of breast cancers express androgen receptor (AR). There is conflicting evidence regarding the role of androgen signalling and breast cancer survival; a number of studies suggest a protective function but, more recently, AR has been shown to drive oestrogen receptor (ER) gene expression in ER-negative apocrine (AR positive, triple negative) breast cancer. This concept is echoed by a number of studies that have focused on the oncogenic potential of the AR. In this study, we evaluated responsiveness to PI3K inhibition in a series of breast cancer cell lines expressing varying levels of AR.

Methods: IC50 values for the pan-class I PI3K inhibitor BEZ235 were established in a range of breast cancer cells in vitro. BEZ235 inhibits phosphorylation of Akt and also blocks the mTOR pathway. MTS assays were optimised and suitable drug concentrations were then evaluated. Endocrine-sensitive (MCF7) and -resistant (LetR, ZR75.1) cell lines were assessed.

Results: MCF7 cells had an IC50 of 0.01031M, ZR75.1 cells had an IC50 of 0.001064M, and LetR cells had an IC50 of 0.001826M.

Conclusion: Low-AR expression MCF7 cells were found to be much less sensitive to PI3K inhibition than the high-AR cell lines. AR could be used to identify endocrine-resistant patients who would benefit from second-line PI3K inhibitor therapy.

Introduction

An estimated 246,660 new cases of invasive breast cancer are expected to be diagnosed in 2016 in the United States alone.1 While the exact aetiology is unclear, certain risk factors have been identified, with the majority related to prolonged oestrogen exposure. Risk factors include genetics, family history, increasing age, early menarche, late menopause, and high levels of sex steroid hormones (e.g., for women on the oral contraceptive pill or on hormone replacement therapy).2 Pertaining to genetics, those with BRCA 1 and 2 mutations are at a greatly increased risk, with some opting for prophylactic mastectomies and/or bilateral salpingo-oophorectomies in order to reduce their risk.3,4 Other rare genetic mutations – such as phosphatase and tensin homologue (PTEN) mutations in Cowden syndrome and p53 mutations in Li Fraumeni syndrome – have also been implicated.5,6 More recent studies have led to the discovery of various subtypes of breast cancer, and have elucidated the roles of different hormones and oncogenic mutations.

Subtypes

Four well-defined subtypes, based on cell receptor expression, have been identified: basal-like; human epidermal growth factor receptor 2 (HER2) enriched; luminal A; and, luminal B. Luminal A breast cancers are ER and progesterone receptor (PR) positive and HER2 negative. Luminal B tumour cells are hormone
receptor (ER and PR) and HER2 positive. The HER2-enriched subtype is hormone receptor (ER and PR) negative with HER2 amplification. Basal-like tumour cells are hormone receptor (ER and PR) and HER2 negative, and are so-called ‘triple negative’ tumours. Subtype is a prognostic factor; luminal A tumours account for about 72.7% of breast tumours in the United States and have a better prognosis than luminal B (4.6%), triple negative (12.2%) and HER2-enriched tumours (12%), with the latter three being more clinically aggressive. These subtypes are also useful in patient management and treatment choice.

Breast cancer management
Treatment is determined by stage of disease, size of tumour, tumour subtype, and patient age. Surgery remains the mainstay of breast cancer treatment, with radiotherapy, chemotherapy and endocrine therapy used as adjuvants. Endocrine therapy is highly dependent on the molecular profile of the tumour. ER-positive tumours can be successfully treated with complete oestrogen antagonists such as fulvestrant, selective oestrogen receptor modifiers (SERMs) such as tamoxifen, or therapies that prevent the synthesis of oestrogen, e.g., aromatase inhibitors (AIs) such as anastrozole. The stage of breast cancer is essential in determining optimal treatment. Non-invasive breast cancers are usually treated with breast-conserving surgery (BCS) and prophylactic radiation; invasive carcinoma, on the other hand, may require mastectomy, almost always requires a sentinel lymph node biopsy, and requires axillary clearance if there is nodal involvement. Adjuvant endocrine treatment methods for both invasive and non-invasive carcinomas vary depending on menopausal status. Studies suggest that premenopausal patients receive tamoxifen as first-line therapy, ovarian ablation as a suitable second-line therapy, and an AI as a third-line therapy. However, for postmenopausal women there is more variability in treatment methods. Five years of treatment with tamoxifen has until recently been seen as first-line therapy, followed by AIs as second-line therapy, and a switch to another AI as third-line therapy. The use of AIs for five years instead of tamoxifen is also commonly accepted, especially in patients with high recurrence risks. There has been prolonged debate over whether tamoxifen or an AI should be used as first-line therapy in postmenopausal women, with tamoxifen usually favoured in practice. However, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial showed that AIs compare favourably to tamoxifen in disease-free survival, withdrawals and side effects associated with tamoxifen’s partial agonist activity on the ER (including vaginal discharge, thromboembolic disorders, and endometrial cancer), suggesting that AIs should be seen as a first-line treatment.

Role of androgen receptors
There is now an increased recognition of the role of androgen receptors (ARs) in breast cancer, with about 60-70% AR positivity. The effects of ARs seem to vary based on the subtype in question. ARs suggest good prognoses in ER-positive breast cancers, where they help to balance oestradiol-induced cell proliferation. However, in certain classes of ER-negative cancers, AR expression has
been linked to poor prognosis along with increased proliferation, particularly in the molecular apocrine subtype, which is ER negative but AR positive. Therefore, AR has become a possible target in the treatment of breast cancer.

**PI3 kinase link with androgen receptors**

Because increased AR levels in certain cancers are a sign of poor prognosis, current studies focus on factors that could cause abnormalities in normal AR functioning. Of interest, a recent study reported a link between kinase domain PI3K mutations and increased AR levels. The PI3K pathway has also been linked with survival of letrozole-resistant (LetR) cell lines, in addition, an association has been established between the PI3K and other growth factor pathways with ligand-independent activation of the AR. Relapses after successful inhibition of the AR have been attributed to this. By this logic, an inhibition of the PI3 kinase pathway could be used as treatment for AR-positive tumours that do not respond well to conventional endocrine treatment.

**BEZ235 mechanism of action**

BEZ235 is a pan-class PI3K inhibitor, which has been shown to inhibit the PI3K/Akt/Mammalian target of rapamycin kinase pathway. It works by binding to the adenosine triphosphate (ATP) cleft of these enzymes, competitively preventing binding of ATP. The PI3K pathway has been implicated in various cancers, and therefore its inhibition by BEZ235 is a possible treatment option for various cancers. The mechanism of action can be seen in Figure 1.

**Hypothesis**

Breast cancer cells that express high levels of AR will exhibit greater sensitivity to the pan-class I PI3K BEZ235 (provided by Novartis).

**Aims**

1. Define the IC50 of BEZ235 for each of the following breast cancer cell lines:
   - MCF7 – endocrine sensitive;
   - ZR75.1 – endocrine sensitive; and,
   - LetR – endocrine resistant.

   The endocrine-sensitive cells are highly responsive to treatment by AI and tamoxifen, while the endocrine-resistant cell line is unresponsive despite being ER positive.

2. Evaluate if AR is wild-type or mutated in cells with varying sensitivity to BEZ235.

**Materials and methods**

**Cell models**

Previous work has shown that LetR cells express higher levels of AR than the sensitive MCF7 and MCF7aro cells (MCF7 cells overexpressing the enzyme aromatase) (Figure 2). The control line used was ZR75.1 cells, which have a luminal A profile like MCF7, but exhibit much higher levels of AR.

**Cell culture**

All cell culture work was carried out in a sterile fume hood with laminar airflow. All methods were performed using aseptic technique. Cells were maintained in an incubator at 37°C with a humid 5% (v/v) CO2 atmosphere.

**Routine passaging of cells in vitro**

Cells were grown in T-75cm² filtered tissue culture flasks (Sarstedt; Germany) and passaged when approximately 80% confluent. Maintenance work was carried out by removing the old media and washing cells with 5ml phosphate buffered saline (PBS; Oxoid Limited; Basingstoke, Hampshire, England). 2ml of 0.05% trypsin (v/v) 0.02% EDTA (v/v) solution (Sigma Aldrich) was used to detach cells from growing surface, for incubation for five minutes at 37°C. Trypsin was neutralised with 5ml of phenol red-free Minimum Essential Medium (PRFMEM; Gibco LifeSciences) and the cell suspension was transferred from the flask to a 15ml tube for centrifugation at 1,000rpm for three minutes at room temperature. The pellet was then re-suspended in the appropriate volume of suitable media and sub-cultured at a lower confluency into a T-75 flask.

**Endocrine treatment of cells**

MCF7 cells express ER and PR, are negative for HER2 amplification, and were obtained from the American Type Culture Collection (ATCC). These were maintained in minimum essential media (Sigma Aldrich; Germany), supplemented with 10% (v/v) foetal calf serum.
(FCS) (Sigma Aldrich) and 2mmol/l L-glutamine (Sigma Aldrich), along with 1% (w/v) Penicillin Streptomycin (Pen/Strep).

LetR cells were created by long-term treatment (>3 months) of MCF7aro cells with letrozole (Novartis; Basel, Switzerland). Cells were cultured in PRFMEM containing 10% (w/v) charcoal dextran stripped-FCS, androstenedione (10^{-9} M; Sigma Aldrich), letrozole (10^{-6} M) and G418 (200g/ml).

ZR75.1 cells were maintained in RPMI 1640 media (Sigma Aldrich) and supplemented with 10% (w/v) FCS, 1mmol/l L-glutamine (Sigma Aldrich) and 1% (w/v) Pen/Strep.

**Cell counting**

The cell pellet was re-suspended after centrifuging in 10ml of media. 15µl of this suspension was transferred to a 1.5ml Eppendorf tube along with 15µl of trypan blue (Sigma Aldrich). 10µl of this mixture was then pipetted onto a haemocytometer (Marienfeld Superior; Germany). Cells were counted manually under the microscope in each of the four 4x4 grids on the haemocytometer and averaged. The appropriate volume of cell suspension was calculated and seeded into a suitable culture plate for its purpose.

**Cell proliferation assay**

Cells were cultured, trypsinised, counted and seeded at a defined concentration. 50µl of the cell suspension was placed in each well at 3x10^3 cells per well. Cells were plated into a 96-well plate (Greiner Bio-One; Germany). Dimethyl sulfoxide (DMSO) was used as the vehicle control.

**Method development for IC50**

The IC50 is a measure of the effectiveness of a compound in inhibiting biological or biochemical function. This quantitative measure indicates how much of a particular drug/inhibitor compound is needed to inhibit a given biological process by half, in this case cell viability.

**Optimisation**

Cell concentration per well, drug concentration and treatment duration were optimised over a series of preliminary phases.

**Stage 1:** During the exploratory stage of the research the optimal cell concentration for treatment was determined. Cells were initially seeded at 1x10^3 and treated with BEZ235 and DMSO (control treatment) at varying concentrations for 24 hours.

**Stage 2:** This was the drug concentration optimisation stage. Following an evaluation of the results, the cells were seeded at 3x10^3 cells per well and treated for 24 hours using the same
concentrations as in Stage 1. Insolubility of BEZ235 at high concentrations led to an adjustment of drug concentrations.

Stage 3: Final changes were made and cells were seeded at 3×10^3 cells. The duration of the treatment was also adjusted to 48 hours to allow enough cell growth that would display adequate differences between the drug and control treatments.

**DNA isolation**
DNA extraction was carried out with a DNaseasy Kit (Qiagen). Pellets were harvested from six-well plates on which cells had been cultured. Pellets were stored in Eppendorf containers in a freezer at -81°C until DNA isolation was ready to be carried out. Cells were resuspended in 200µl of PBS and 20µl of proteinase K was added. 200µl of Buffer AL was added, the mixture was homogenised by vortexing and incubated for 10 minutes at 56°C. 200µl of ethanol was added to the mixture, followed by further vortexing. The mixture was transferred to a spin column and placed in a 2ml collection tube. It was centrifuged at 8,000rpm for one minute, with the flow-through subsequently discarded. This step was repeated after the addition of Buffer AW1. Buffer AW2 was added to the spin column and centrifuged for three minutes at 14,000rpm. The flow-through was discarded once again and the spin column was transferred to a 1.5ml microcentrifuge tube. DNA was eluted by adding 200µl Buffer AE to the centre of the spin column. The DNA was incubated at room temperature for one minute and centrifuged again at 8,000rpm. This step was repeated once again to optimise the yield.

**Results**
IC50 curves were graphed using the software GraphPad Prism 5. LetR and ZR75.1 cells (IC50: 0.001826 and 0.001064, respectively), which have high levels of AR, were more responsive to BEZ235 than the MCF7 cell line (IC50: 0.01030) (Table 1; Figure 3; Figure 4; Figure 5; Table 2).

**Discussion**
We compared the responsiveness to treatment with BEZ235 in ZR75.1 and LetR vs MCF7 cell lines. High levels of AR expression equated to greater sensitivity to PI3K/mTOR pathway disruption by BEZ235. This effect was seen when comparing IC50s for the cell lines with higher AR levels (ZR75.1 and LetR) with the IC50 for MCF7 cells, which express low levels of AR. The fact that ZR75.1 cells and MCF7 cells primarily differ in their expression of the AR further reinforces this point.

Most work on adjuvant treatment of breast cancer currently focuses on the role of ER, PR, and HER2, as these are the most commonly expressed hormone receptors in breast tumours. However, the role of the AR should not be understated, as it is becoming increasingly evident that the AR plays a role in the development, progression and prognosis of breast cancer. The results from this experiment indicate that there are interplays downstream in the signalling cascade, which could affect treatment response. This study shows the role of the AR in the PI3K pathway, which could be just one of many; however, we can ascertain that exploration of the AR in breast cancer could lead to a whole new realm of therapeutic options for patients. Assessment of AR expression could indicate which patients would benefit from PI3K inhibitors; this accentuates the need to develop a wider range of endocrine therapies and explore factors that can be used to optimise treatment for individual patients.

**Conclusion**
Clinical studies are currently being carried out in order to determine the tolerability of BEZ235 and its efficacy as an anti-tumour drug. However, there has not been much research done investigating the relationship and interplay between AR levels and the PI3K/mTOR pathway. More research must be carried out in order to discover factors that could help to select the best therapies for individuals based on their tumour’s receptor profile, particularly with regard to AR expression.

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References


Epidemiological evaluation of rotavirus burden and potential impact of vaccination in Uganda

Abstract
Rotavirus is an RNA virus that causes diarrhoeal disease and represents a significant cause of hospitalisation and death in children under five worldwide. The disease burden is particularly high in developing countries, including those in sub-Saharan Africa, where the population is young, sanitation is often poor and access to healthcare limited. Vaccination against the virus has been available since 2006, but population vaccination schedules have not yet been introduced worldwide. Vaccination programmes, including those in several sub-Saharan countries, have been successful in significantly relieving the burden of disease. Uganda, which has one of the highest rotavirus-associated death rates in the world, is scheduled to introduce the vaccine into its national schedule during 2016. As such, it seems an appropriate time to assess the current epidemiological status of rotavirus infection in Uganda, and to discuss important factors that must be considered in the implementation of the vaccine. These factors include cost-effectiveness and a dosing schedule for maximal efficacy, while minimising potential dangerous side effects like intussusception. If implemented properly and effectively, the rotavirus vaccine stands to save millions of lives in Uganda and around the world.

Introduction
Rotavirus is the leading cause of diarrhoeal illness in children under five, killing over 450,000 children annually. Infection with the virus occurs in all parts of the world; however, the burden of disease and death is greatest in Asia and Africa. In these regions, the threat of rotavirus is most substantial because of the lack of supportive care, such as rehydration and electrolyte therapy, often due to poor healthcare infrastructure and lack of funding. It is thought that the virus is transmitted via the hands of contaminated individuals, as countries with improved sanitation systems exhibit significantly decreased rates of infection. In Uganda, where 49% of the population is under 15 years of age, rotavirus is a significant cause of childhood mortality and poses a substantial healthcare burden. Newly developed and licensed rotavirus vaccines have proven successful in developing countries, and have the potential to help abate Ugandan childhood mortality. This paper will review the epidemiology of rotavirus infection in Uganda and explore the potential benefits of the introduction of a national vaccination programme.
Rotavirus

Rotavirus is a double-stranded RNA virus whose serotypes are determined by the proteins VP7 (G protein) and VP4 (P protein). These antigens are located on the outer capsid of the virus and elicit an antibody-mediated response, which facilitates partial humoral immune protection.\textsuperscript{3,9} A Cochrane review by Soares-Weiser et al. reported the presence of approximately 15 G and 26 P antigen types in human rotavirus strains, theoretically producing 390 (15Gx26P) combinations of various viral subtypes.\textsuperscript{2} This large genetic diversity results from point mutations creating new G or P antigens, reassortment of related strains causing antigenic shift, and crossing of animal strains with the capability to infect humans. Only five strains have been associated with the majority of human infections: G1P[8]; G2P[4]; G3P[8]; G4P[8]; and G9P[8].\textsuperscript{1,2,9,10}

Course of infection

Rotavirus is transmitted through the faecal-oral route, frequently due to inadequate hygiene, especially when preparing food. Following ingestion, the virus enters the villi of the epithelial cells lining the small intestine and replicates. The virus inhibits absorption of vital nutrients, including glucose and sodium, which subsequently causes luminal water retention and diarrhoea. Although humoral immunity increases with repeated infection, it fails to achieve complete protection, thus allowing re-infection at any age.\textsuperscript{1} The average incubation period for rotavirus is 48 hours, with fever and vomiting developing thereafter. Watery diarrhoea typically begins 24-48 hours after initial symptoms present, with up to 20 bowel movements per day. The illness typically lasts for three to eight days, with primary complications of dehydration, electrolyte imbalances and metabolic acidosis,\textsuperscript{1} which can be exacerbated in areas lacking access to basic medical care.\textsuperscript{3} Enzyme-linked immunosassay (EIA) and latex agglutination remain the laboratory diagnostic tools of choice for identification of rotavirus viral antigens in stool samples.\textsuperscript{1,5} Most deaths caused by rotavirus are seen in young children in developing countries in Asia and Africa; Angola and Uganda have the highest mortality rates in the world at 1.9% and 2.3%, respectively.\textsuperscript{3}

Uganda and rotavirus

Uganda has an estimated annual incidence of 10,944 non-severe and 576 severe cases of rotavirus per 100,000 people aged one to 59.\textsuperscript{13} A study conducted at the Mulago National Referral Hospital in Kampala showed that rotavirus accounted for 32.8% of cases of acute diarrhoea in children, most of whom were between three and 23 months old.\textsuperscript{14} Another 2010 study by Nakawesi et al. at the same hospital found that rotavirus accounted for almost half of the cases of acute diarrhoeal hospitalisations in children.\textsuperscript{15} This figure is consistent with WHO global networks for surveillance of rotavirus data, and the actual figure is likely somewhere between 30 and 50%.\textsuperscript{15}

Increased prevalence of rotavirus in Uganda

Nakawesi et al. also observed that breastfeeding children were 2.5 times more likely to contract rotavirus than those who did not. This is in contrast to previously published data, which suggested that breastfeeding confers some protection against contracting the virus.\textsuperscript{16,17} Nakawesi et al. explained the contrasting result of their study by hypothesising that the majority of infants included in their study were not exclusively breastfed, and therefore did not consume enough breastmilk to confer immunity.\textsuperscript{15} However, in a 2011 matched case-control study performed at the same hospital, breastfeeding failed to show protection against rotavirus infection.\textsuperscript{18}

The authors also found that dehydration in children resulted in a two-fold risk of contracting rotavirus. This finding corroborates previous literature and speaks to the higher disease burden in low-income countries, where there is more limited access to clean water for rehydration therapy.\textsuperscript{15} Studies conducted in sub-Saharan Africa (excluding Uganda) have also found that nutritional status, disease during the dry season, and age under two years are linked to the prevalence of rotavirus. Interestingly, no association between rotavirus and HIV has been found, and children infected with HIV have been shown to mount a similar seroresponse to rotavirus infection as those not infected with HIV, and to clear the virus effectively.\textsuperscript{15,19,21}

Sanitation is also an important factor contributing to disease burden. A study of the microbial risks to human health in the water in the Bwaise III slum in Kampala estimated that 20% of infections were due to rotavirus contamination, mainly from exposure to open surface water drainage channels.\textsuperscript{22} This study also found that the total disease burden from water-borne pathogens was 680 disability-adjusted life years (DALYs) per 1,000 persons per year. This is several orders of magnitude higher than the WHO reference level of tolerable risk.\textsuperscript{22}
Rotavirus vaccine

Medically, rotavirus gastroenteritis has no cure, although supportive therapy is frequently employed and typically includes fluid replacement and electrolyte replenishment.\(^1\) Two rotavirus vaccines have been approved and are used worldwide: RV1 (Rotarix®) by GlaxoSmithKline and RV5 (RotaTeq®) by Merck.\(^1,4,23\) RV1 is a monovalent, attenuated rotavirus vaccine of the common G1P strain. RV5 is a pentavalent vaccine derived from five naturally occurring bovine strains, which have undergone genomic reassortment to introduce features of the human rotavirus strains. Four of the strains express G1, G2, G3 and G4 human rotavirus surface proteins. The fifth strain expresses the P(8) surface proteins from human rotavirus strains.\(^2,4\) The vaccines were initially tested in developed countries, but recent concerns have arisen about the effectiveness of the vaccines within countries in Africa and Asia, which have the highest incidence of disease.\(^24,25\) Strain diversity in Africa is much more heterogeneous than Asia; predominant strains include G1, G9, G2, P[8], P[6], and P[4] P proteins.\(^26\) Although some variation exists between vaccine strains and circulating strains, evidence suggests that rotavirus vaccines provide both heterotypic and homotypic protection. However, the vaccine is less effective in developing countries.\(^2,10,22\) Currently, 79 countries have implemented rotavirus vaccination programmes. Financial aid from the Global Alliance for Vaccines and Immunization (GAVI) has enabled the implementation of rotavirus vaccine programmes in many low-income African countries. However, countries such as Uganda, which has one of the highest burdens of disease, have only recently planned a national rotavirus vaccination programme.\(^3,4,27\)

Vaccination strategies

Several evidence- and population-based strategies can be employed to attenuate the disease burden of rotavirus in Uganda. Introduction of a national rotavirus vaccination schedule offers the opportunity to reduce rotavirus-related disease. Of the ten countries comprising East Africa, eight have already incorporated the rotavirus vaccine into their national immunisation programmes. Uganda has yet to implement the vaccine, although according to the WHO Ugandan National Planning Cycles, introduction of the vaccine is planned for April 2016.\(^28\) Uganda has shown a preference towards the monovalent RV1 Rotarix vaccine, as have a majority of developing countries, due to longer shelf life and a shorter dosing schedule.\(^29\) The WHO recommends that rotavirus vaccines should be included in all national immunisation programmes, particularly in South Asian, Southeast Asian, and sub-Saharan African countries.\(^29\) The cost-effectiveness of a new health intervention is an important factor requiring consideration by decision-makers prior to its introduction.\(^3,15\) Reports on the cost-effectiveness of introducing the rotavirus vaccine in Uganda estimate that approximately four million cases of rotavirus and 70,236 rotavirus-related deaths from 2016 through to 2035 would be avoided,\(^20\) with an estimated cost per DALY averted of $34 USD in Uganda.\(^11\) Vaccines could potentially prevent 4.4 million DALYs.\(^30\) Administered orally, these vaccines are 85-98% effective in preventing severe rotavirus disease in infants and young children.\(^31\) RotaTeq (RV5) is given in three doses at ages two months, four months, and six months, while Rotarix (RV1) is given in two doses at ages two months and four months. The timing of the vaccines tends to differ between middle to upper-income countries and lower-income countries, since access to healthcare has greater barriers in low-income countries, making the Rotarix two-dose vaccine more appealing, with a higher chance of complete dosing. This is primarily due to existing vaccination schedules, and the logistics of delivering and storing multiple vaccines. In many low-income countries, poor health service access precludes some children from timely vaccination. The WHO rotavirus position urges countries to consider providing rotavirus vaccination to these children, even if it would be later than recommended.\(^32\) In low-income countries with a high burden of rotavirus disease, the protection provided by the licensed vaccines is lower (39% for RotaTeq and 49% for Rotarix) than that reported in high-income countries (about 85% for RotaTeq and 82% for Rotarix).\(^8\)

A birth dose strategy for rotavirus vaccination may have the potential to address these challenges.\(^13\) Rotavirus infection occurs at a younger age in low-income countries and early infection is often associated with more severe disease.\(^3,31\) Administration of the first dose of the vaccine at six weeks of age leaves a gap in protection. A birth dose would bridge this gap, and potentially enhance coverage and timeliness of vaccine completion, particularly in countries with immunisation-related challenges.\(^36\) Additionally, intestinal barriers to vaccine efficacy, such as interference from breastmilk antibodies or environmental enteropathy, may be limited if the vaccine is administered at birth when breast milk intake is still low and intestinal microbiota has not yet been established.\(^3,37,38,39\) Intussusception is considered rare in the first two months of life, so it is thought that administration of a birth dose could also improve the safety profile of rotavirus vaccines.\(^31\) Neonatal and infant vaccination with the RV3-BB rotavirus vaccine was found to be well tolerated and immunogenic.\(^35\)
Conclusion

The burden of disease of rotavirus in Uganda presents a significant strain on the healthcare system and continues to pose a threat to its young population. In sub-Saharan African countries, such as Malawi, Ghana, and Kenya, a vaccine schedule has been successfully implemented, and has prevented over 60% of severe disease in children in their first year of life. The introduction of the rotavirus vaccine in Uganda is a cost-effective solution to significantly reduce the burden of the virus. With the aid of the GAVI initiative, which provides rotavirus vaccines at reduced cost, the Ugandan Ministry of Health will be adding Rotarix to its national vaccination calendar in 2016. With the implementation of this prevention strategy, Uganda’s children stand to benefit for years to come.

References


The history, mystery, and management of fibromyalgia

Abstract
Fibromyalgia is a chronic condition characterised by widespread musculoskeletal pain and somatic symptoms of fatigue, depression and sleep disturbance. For years, patients presenting with longstanding regional pain were given a label of ‘chronic pain’. To date, the exact pathophysiological mechanism underlying the development of fibromyalgia has not been fully elucidated, although many theories have been put forth in the literature. The most prominent theory describes an underlying central neuropathophysiology characterised by altered pain processing. The use of novel functional imaging studies has provided us with potentially the most objective evidence to date of the mechanism of central sensitisation, which remains the most widely accepted theory to date. However, the most recent literature describes widespread small nerve fibre pathology, consistent with significant reports of peripheral neuropathic symptoms in patients with fibromyalgia. Other theories under investigation include roles for immune system abnormalities such as elevated levels of cytokines and hypoactivity of the hypothalamus-pituitary-adrenal (HPA) axis. There is also much debate regarding the role of vitamin D deficiency, with some studies suggesting a correlation between low levels of vitamin D and patient-reported pain scores. This review will discuss some of the prominent theories about fibromyalgia and the current recommendations for management of the disease.
Background

Fibromyalgia is a chronic condition characterised by widespread musculoskeletal pain with multiple soft tissue tender points symmetrically distributed across the body. Alloodynia, hyperalgesia, fatigue, sleep disturbances, and neurocognitive impairment are also features of the condition, which affects 2-3% of the population, predominantly middle-aged females.1,2 For years, patients presenting with longstanding regional pain for which a definite cause could not be identified, and for which inflammatory and biochemical markers were negative, were simply given a label of ‘chronic pain’, or diagnoses ranging from temporomandibular joint syndrome, to irritable bowel syndrome, to simply chronic back pain.3 A more coherent picture is now being drawn, with recent studies suggesting that syndromes characterised by chronic regional pain are not separate entities, but different manifestations of a sole central neuropathophysiology. This shifts the historical blame from a local pathologic process, corresponding to the region of pain, to the central nervous system.3 Other prominent theories describe a potential link between hypoactivity of the hypothalamus-pituitary-adrenal (HPA) axis and fibromyalgia.4,5 The roles of the immune system and vitamin D levels have also been extensively explored.6-11 In 1990, The American College of Rheumatology (ACR) released a set of diagnostic criteria for fibromyalgia. These included both a history of widespread pain – which is defined as pain above and below the waist, on both sides and in the axial skeleton – as well as at least 11 out of 18 identified tender points.12 However, this ignored major manifestations of fibromyalgia such as psychiatric and sleep disturbances. In 2010, these criteria were revised to include such manifestations, causing the ratio of women to men affected to fall from 10:1 to 2:1, which is in line with many other chronic pain disorders.13 In 2011 the criteria were further revised, eliminating physician assessment scores entirely. This most recent set of diagnostic guidelines includes the widespread pain index (WPI) scored from 0-19, indicating the number of areas of self-reported pain over the previous week, along with a symptom severity score involving self-reported fatigue, waking unrefreshed, cognitive disturbance, headaches, abdominal cramps and depression.14

Pathophysiology theories

The exact aetiology of fibromyalgia is currently unknown, but underlying pathophysiological mechanisms of central sensitisation, imbalances in systemic levels of pro-inflammatory and anti-inflammatory cytokines, and disturbances in the HPA axis are becoming more evident.6,8,10,11 Together with the two characteristic symptoms of alldynia and diffuse hyperalgesia, these theories are in line with the notion of an underlying central nervous system pathology in pain processing.13

Data from these studies are adding to an already impressive volume of evidence that points towards an underlying enhancement of pain processing in fibromyalgia.

Central nervous system

Studies have shown that patients with fibromyalgia have a lower pain threshold, with greater pain scores in response to heat, cold, electrical and pressure stimuli. Furthermore, these patients do not exhibit the typical exercise-induced analgesic response.13,16 However, these studies are often scrutinised for the lack of an objective pain scale, often resorting to patient-reported pain as a data reference.17,18 With the use of functional magnetic resonance imaging (fMRI) and positron emission tomography, regions of the brain central to pain processing, such as the insula and the anterior cingulate cortex, have been identified.19,20 In one study, fMRI demonstrated a decreased activation of the rostral anterior cingulate cortex (rACC) in patients with fibromyalgia as compared to controls. The rACC region is made up of a high density of opioid receptors, and is a vital descending inhibitory system.19 This dysfunction is in line with other reports regarding the inefficacy of opioids as a treatment in fibromyalgia.21,22 In another study using fMRI, patients with fibromyalgia produced a cerebral response to the application of a mild stimulus equivalent to that of the control group’s response to a stimulus of twice the magnitude.23 In one study of 10 patients with chronic regional pain syndrome, also characterised by altered pain processing, Freund et al. demonstrated enhanced cerebral response with the use of functional imaging.24 Data from these studies are adding to an already impressive volume of evidence that points towards an underlying enhancement of pain processing in fibromyalgia.

The use of structural imaging has also allowed for the demonstration of morphological changes in the brain: one study...
reported significant grey matter volume loss in patients with fibromyalgia.23 However, depression is a common psychiatric comorbidity in fibromyalgia, and is also associated with a higher rate of grey matter volume loss. When depression was controlled for in other fibromyalgia studies, this association lost its significance.26,27

Neurotransmitter levels have also been shown to be significantly altered in fibromyalgia, with an increase in those associated with pain transmission (such as glutamate, nerve growth factor, substance P, and the action of serotonin on the 5HT-2a/3a receptors). This is accompanied by a decrease in pain-attenuating neurotransmitters such as norepinephrine, gamma-aminobutyric acid (GABA), and serotonin acting on the 5HT-1a/1b receptors.13,28-30

One system that appears to be working paradoxically in fibromyalgia is the endogenous opioid system, which is normally responsible for inhibiting pain. There appears to be an increase in endogenous opioid activity, with concomitant decrease in μ-opioid receptor availability.13,31 This is in line with promising results produced by clinical trials on the use of naltrexone, an opioid antagonist, as a treatment modality in fibromyalgia.12,32

The pathophysiology of fibromyalgia is complex, however, and there is minimal but consistently growing evidence that peripheral nervous system abnormalities may also play a role.

Peripheral nervous system

Peripheral neuropathic symptoms described as ‘pins and needles’, and ‘hot’ and ‘tingling’ sensations are prevalent in fibromyalgia, with studies reporting 76-95% of patients using those terms as symptom descriptors.10,34,35 This is in keeping with other diseases with proven peripheral neuropathic pathology, such as diabetes mellitus, in which 66% of patients have a sensory neuropathy.36

Epidermal nerve fibre density has been shown to be a reliable indicator for the presence of small nerve fibre pathology, with one study reporting a diagnostic efficiency of 88%.37 Several studies have demonstrated the presence of this pathology by obtaining skin biopsies from patients with fibromyalgia. However, these studies have not controlled for the potential deconditioning and lack of physical activity in this cohort, which may confound these findings.38,39

Immune system dysregulation

Despite cementing its status as a disease of non-inflammatory aetiology, multiple studies have reported imbalances of cytokine levels in fibromyalgia.11,40-41 Cytokines, some of the immune system’s chemical messengers, can be divided into pro- and anti-inflammatory, with IL-1, IL-6 and IL-8 being some of the more prominent pro-inflammatory biomessengers.11

Several studies have reported increased levels of pro-inflammatory cytokines in fibromyalgia.13,42,44 In studies of patients receiving IL-2/LAK (lymophine activated killer) cell therapy and IFN-alpha for renal cell carcinoma45 and chronic hepatitis,46 respectively, classical symptoms of fibromyalgia such as diffuse pain and sleep disturbance developed. However, up to one-quarter of patients on interferon therapy will develop depressive symptoms, which include diffuse pain and sleep disturbance. No correction for depression was made, and thus further research into this relationship is needed.47 Furthermore, the literature has reported elevated levels of IL-8 in patients with fibromyalgia.48 While IL-8 has been shown to be implicated in the enhancement of anterior cingulate cortex processing in animals with chronic inflammatory pain, it did not display a significant association with clinical pain in fibromyalgia.49 Acute stress has been shown to be associated with higher IL-8 levels, which may account for the observed relationship.50 The number of studies on anti-inflammatory cytokines pales in comparison, with conflicting results reported. One study reports a positive association between IL-4 gene polymorphism and fibromyalgia, while others found none.51,52 Another study reported low levels of Th2 cytokines such as IL-4, IL-5 and IL-13.40,41 A search of the literature produced no evidence to support a role of IL-10, the body’s major inflammatory cytokine, in fibromyalgia. Until a decade ago, the dichotomy of Th1/Th2 cell balance dominated the immunology realm. However, Th17, a recently discovered subtype of T helper cells, has demonstrated a role in the development of autoimmune pathologies such as multiple sclerosis and psoriasis.53 The major cytokine secreted by the Th17 cell, IL-17, has also been shown to be elevated in fibromyalgia.44 Furthermore, one study by Kim et al. demonstrated a role for IL-17 in mediating pain hypersensitivity. However, further research is needed into the exact role of this cytokine in fibromyalgia.54

It is known that cytokines can sensitisre nociceptors and potentially modulate the HPA axis, but it is unclear how this would lead to central sensitisation.40,55 Rodriguez-Pinto et al. have proposed the use of cytokine and chemokine levels as possible biomarkers of fibromyalgia, with implications for fostering future treatments.40
The role of vitamin D

Vitamin D deficiency has been implicated as a potential component in the pathogenesis of a host of conditions, ranging from multiple sclerosis and inflammatory bowel disease to Parkinson’s disease and depression. Vitamin D deficiency and fibromyalgia, the literature suffers from conflicting reports regarding both the strength of association and the implications of vitamin D supplementation as a potential treatment modality.

Vitamin D has well known anti-inflammatory properties, and low level states have been postulated to increase levels of inflammatory cytokines, resulting in increased central sensitisation to mechanical pain. The central nervous system mechanisms of attenuating or suppressing pain are theorised to become dysfunctional if vitamin D levels are low.

In one study, 69.3% of patients who met the 1990 ACR criteria for fibromyalgia were found to have low levels of vitamin D. These results were similar to those obtained by von Kanel et al., which found that 71% of chronic pain patients were vitamin D deficient. While one randomised controlled trial found no significant difference in vitamin D levels between patients with fibromyalgia and controls, the expected rise of vitamin D levels in the summer was absent in those with fibromyalgia. Armstrong et al. reported a significant association in fibromyalgia patients between low vitamin D levels and anxiety or depression. Both these findings can potentially be explained by a lack of sun exposure, prevalent in patients with fibromyalgia due to the impact of disease on patient activity.

Evidence has also shown that by supplementing vitamin D, symptoms of pain in fibromyalgia were reduced. Another study suggested a role for low levels of vitamin D in augmenting central sensitivity to physically evoked pain, which actively involves centres of the brain that are distinct from those involved in spontaneous pain.

Managing fibromyalgia

The literature on fibromyalgia management is currently dominated by trials of complementary and alternative therapies, underlining the limitations of modern medicine in treating fibromyalgia.

Management of fibromyalgia must be carried out in a primary care setting, unless clinically indicated otherwise. Patients whose diagnoses are in question or who are refractory to initial therapy warrant a referral to the relevant departments, such as rheumatology, for further investigation. The general consensus among clinicians on the initial approach to fibromyalgia includes pharmacological monotherapy in addition to non-pharmacological treatments such as patient education, cognitive behavioural therapy and exercise.

Non-pharmacological therapy has been reported to have effects of larger magnitude than its pharmacological counterpart. A diagnosis is often followed by a sharp decline in access to healthcare, fewer referrals, fewer drug prescriptions, and less diagnostic testing. A diagnosis often provides a source of relief to patients who have been suffering from an ‘invisible disorder’ that is widely misunderstood by both the public and clinicians. Highlighting this knowledge gap, Jay et al. reported receiving a patient referred by a primary physician for “fibromyalgia of the right shoulder”.

Secondary fibromyalgia

Patients with fibromyalgia can be categorised clinically into two groups – one in which no biological evidence of inflammation can be found, and another in which a comitant inflammatory condition such as rheumatoid or osteoarthritis exists. The latter is also known as ‘secondary fibromyalgia’.

In the latter subset of patients, it has been proven that pain eventually centralises and becomes unresponsive to peripherally directed treatment modalities, such as NSAIDs and opioids, and more responsive to centrally acting treatments. It has been proposed that this centralisation of the pain appears to be driven by continuing peripheral nociceptive input. As such, identifying individuals at risk of developing this centralised pain state and intensively treating them at the time of these acute pain episodes could be essential to ‘preventing’ the development of fibromyalgia. By shifting the research landscape from the management of symptoms of fibromyalgia to prevention, our ability to combat fibromyalgia may potentially improve.

Conclusion

Numerous studies to date have attempted to outline the mechanisms underlying fibromyalgia. The use of novel diagnostic imaging such as fMRI and positron emission tomography has provided potentially the best objective evidence to date of the mechanisms of central sensitisation in fibromyalgia. However,
the role of numerous other factors, such as vitamin D deficiency and inflammatory biomarker elevation, have yet to be fully appreciated, with conflicting results in the literature.6,9-14

The most recent evidence suggests that small fibre neuropathy potentially plays a role in the pathogenesis of fibromyalgia. It has been postulated that pain-inhibiting nerve fibres are selectively destroyed, rendering the remaining fibres more sensitive to inflammatory mediators. However, much research is needed into the extent of its role in the pathogenesis of fibromyalgia and, to date, central sensitisation remains the most widely accepted theory.39,73-75

Further studies would allow for a more holistic understanding of fibromyalgia, which is essential to adequately manage this chronic, and oftentimes debilitating, condition.

References


The road to the gold standard: whole genome sequencing in the clinic

Abstract
Costs and time involved in generating whole genome sequences with next-generation technology are continually dropping, and in this regard are nearing feasibility in clinical settings. The most significant obstacles to clinical application now derive from the massive amounts of data generated by each genome sequenced. Storage, analysis and interpretation pose technical and knowledge-based challenges to researchers, who must also confront ethical, legal and social issues raised by mass (electronic) storage and sharing of inherently identifiable data. Medical genomics as a field is still new. There is a dearth of established standards for the return of results to clinicians and patients, and few evidence-based guidelines pertaining to most of the variants identified by whole genome sequencing (WGS). However, the ability to comprehensively identify all genomic variants holds thrilling opportunities for personalised medicine. Platforms to integrate patients’ clinical information with their genomic data are being developed and tested with promising results. The statistical power to associate genotypes with phenotypes and clinical outcomes continues to rise; initiatives like the UK’s 100,000 Genomes Project are paving the way for clinical adaptation. Currently, narrower targets than the whole genome are more feasible in the clinic, but there is a reasonable expectation that it will eventually become the ‘gold standard’ in personalised medicine.
Background

Next-generation sequencing (NGS) technologies can now sequence the entire human genome in less than three days and, according to industry claims, at a total cost of $1,000 USD or less. This “massively parallel sequencing” generates short “reads” or nucleotide sequences from a DNA sample and aligns the reads against a standard reference genome in a high-throughput process. Sequence variants are identified by comparing the sample and reference genomes, and stored in a variant call file (.vcf) containing the several million variants each genome typically contains. Medical geneticists and clinicians then compare the data with a genotype-phenotype database, interpreting which are pathogenic and which are “actionable” (have an established intervention and an agreed-upon policy on whom to treat), and provide results to the patient. With the ability to rapidly generate massive amounts of genomic data, analysis of this data has now overtaken sequencing as the major challenge and time-consuming process. Genome analysis encounters technical, legal, ethical, and interpretive obstacles. Since a complete, standardised, fully annotated and linked genotype-phenotype database does not exist, the reality is that the protocol above represents the ideal model rather than the practical reality. It is statistically challenging to assimilate enough evidence to determine pathogenic significance for variants, particularly rare or unique ones. This makes practical interpretation of variants challenging. Several methods are being utilised to raise statistical power but the problem persists, especially as there often exists little to no information on phenotypic clinical presentations associated with specific variants.

Training and education

To work with genomic technology, clinical laboratory staff must be computationally skilled and adequately trained in sample and data collection, preparation, analysis, and interpretation. Pathologists play a crucial role in assessment of specimens; recognising this, several major institutions have incorporated genomics training into pathology residencies, along with online resources and educational programmes to address the increasing need for medical professionals competent in the growing field of genomic medicine. There are also academic reviews written specifically for clinicians on implanting current technology in practice, and organisations such as the College of Genomic Medicine aim to train and update practising clinicians in these areas. Laboratories are certified – for example, by the Clinical Laboratory Improvement Amendments programme – to ensure the quality and reliability of sequencing and analysis. The ultimate goal is to ensure downstream accuracy, identify medically important variants, and maximise utility for clinicians and patients.

Challenges to evidence-based progress:

ethical, legal, social

Data sharing and integration

Challenges to the uptake and widespread implementation of WGS in clinical practice include formulating ethical policy for conducting research, creating decision frameworks for clinical practice, and overcoming institutional and practical inertia to implement new technology. Issues of data sharing, the electronic health record, and informed consent in a technologically advanced era of healthcare information assimilation and storage are particularly relevant to the formulation of ethical policy. Decision frameworks require the establishment of criteria for ‘actionability’ of variants for return to clinicians, return to patients, and support in choosing interventions, which in turn requires efficient and ethically acceptable data sharing. Concerns about consent to long-term (and possibly indefinite/irreversible) storage of genomic information have resulted in the limitation of accessibility of genomic data collected in these projects to very specific uses and groups of people. Widespread accessibility of genomic databases is difficult to arrange while respecting privacy and confidentiality. Research on these ethical, legal, and social issues has long been acknowledged as necessary and is funded alongside empirical research.

Statistical analysis identifying relationships between genotype and disease alone is not adequate to create clinical guidance. Systems biology and systems medicine aim to integrate data including genomics, proteomics, and bioinformatics with clinical observations. This is crucial in order to understand disease aetiology, progression, and characteristics in the real world. Bioinformatics tools to integrate clinical, biological, and genomic data are in development, and some of the early products show great promise for personalising treatment, particularly in oncology, but their use will grow slowly as the evidence base from research and drug development gradually expands. Current efforts like the electronic Medical Records and Genomics (eMERGE) network aim to integrate the electronic health record with compilations of biogenetic information in an ethically competent manner, and to test frameworks for validating variants.
WGS invariably identifies variants in patients’ genomes not related to the stated purpose of the test. These ‘incidental findings’ can have a significant impact on patients’ well-being in terms of future planning, healthcare decisions, and mental and emotional health. The American College of Medical Genetics and Genomics has released recommendations for return of incidental findings from clinical WGS and whole exome sequencing (WES) testing, but these guidelines have been accused of ignoring the patient’s right to refuse the return of results. This ‘right not to know’ presents a complex challenge to the establishment of criteria and procedures for returning findings while providing the full disclosure essential to patient autonomy. Several eMERGE projects are examining this topic, and large-scale initiatives including the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) produce evidence-based reviews on the utilisation of genomic tests. These projects form part of a larger effort to prime NGS technologies for regular clinical implementation, as well as clinical decisions in utilising and returning results to patients. Physicians often rely on referral to or collaboration with medical geneticists in providing care based on genomic testing; however, demand for these specialists may soon overwhelm availability. In cases where evidence-based decision-making is not possible, clinicians must use their best judgment (or institutional policy, where it exists) to decide what course of action to take based on a patient’s genomic findings. ‘Early-adopter’ institutions will continue to be essential in establishing, troubleshooting and modelling use of genomic testing and utilisation in clinical settings. They act as examples to convince institutional stakeholders to fund genomic testing regimens – currently a major obstacle to establishment of genomic testing in the clinic.

Return of findings and evidence-based decisions

WGS invariably identifies variants in patients’ genomes not related to the stated purpose of the test. These ‘incidental findings’ can have a significant impact on patients’ well-being in terms of future planning, healthcare decisions, and mental and emotional health. The American College of Medical Genetics and Genomics has released recommendations for return of incidental findings from clinical WGS and whole exome sequencing (WES) testing, but these guidelines have been accused of ignoring the patient’s right to refuse the return of results. This ‘right not to know’ presents a complex challenge to the establishment of criteria and procedures for returning findings while providing the full disclosure essential to patient autonomy. Several eMERGE projects are examining this topic, and large-scale initiatives including the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) produce evidence-based reviews on the utilisation of genomic tests. These projects form part of a larger effort to prime NGS technologies for regular clinical implementation, as well as clinical decisions in utilising and returning results to patients.

Oncology

The affirmation that genome instability is a major contributor to cancer development was a crucial result of early WGS implementation in the field of oncology. In research and clinical practice, genomes of tumour cells are sequenced and compared to non-cancerous cells from the same individual. This allows tracking of the genomic changes that occur between normal and cancerous cells in an individual – ‘somatic variants’ – stored in databases such as the Catalogue of Somatic Mutations in Cancer (COSMIC) or The Cancer Genome Atlas (TCGA). Somatic variants across individuals with tumours of varying types are compared to reveal pathways leading to cancerous growth in specific types of cancer, as well as commonalities between them. Variants found can be looked up in cancer databases to determine whether they are ‘druggable’ targets, which have responded well to a certain pharmacological treatment. This is the idea behind personalised cancer care – find the best treatment option based on an individual’s profile of genomic, histological and other clinical information to achieve the best outcomes (Figure 1).

As tumours grow, subpopulations of cells diverge genetically, as they acquire different mutations and continue to proliferate. This ‘intratumoural heterogeneity’ is at least partially responsible for the phenomenon of treatment resistance. Metastatic tumours can also develop differentially – ‘inter tumoural heterogeneity’ – with similar implications for treatment. The use of WGS and other NGS technologies to comprehensively identify tumour heterogeneity, and to identify treatment options based upon...
heterogeneity and temporal development of somatic mutations, is currently being assessed in several different trials for clinical feasibility. Histological assessment can provide a great deal of practical information about a biopsy, and indeed is the standard by which neoplasmic growth is determined, but it is subjective, and on its own cannot capture the vast heterogeneity of the cancer genome. The genetic characterisation of an individual’s cancer is therefore crucial for personalised diagnostic, prognostic and treatment purposes. A recent study found that in 43% of tumours examined, mutation similarities between tumours of different anatomical sites and tissues of origin were more pronounced than between different tumours of the same anatomical site of origin. Trials testing the efficacy and feasibility of this concept – recruiting cancer patients for treatment trials based on shared genetic aberrations rather than site of origin – are underway. In addition to identification of appropriate treatment, early detection of, and response to, cancer in an individual is crucial for a good prognosis. Recent investigation of circulating cell-free tumour DNA (ctDNA) as a cancer biomarker, and sequencing of it to characterise tumours genetically, has yielded cautiously optimistic results as a relatively non-invasive diagnostic and monitoring tool for cancer progression and treatment response. It can also be used to monitor cancers to assess treatment resistance. Entire genomes can be sequenced with a high enough sample titre of ctDNA. Albeit in the early stages of research, this has exquisite potential to improve cancer treatment and research in terms of quality and patient tolerability if it proves effective and feasible.
Summary

In theory, the ultra-systematic and comprehensive variant identification of WGS eliminates much of the time and money cost of running sequential single-gene tests. It is ideal for detecting the maximum amount of genetic variants upon which to base treatment consideration, and has the advantage of rarely needing PCR or other techniques for amplification before sequencing – making it intrinsically more accurate than WES or targeted sequencing, which use enrichment techniques that could potentially introduce amplification-related sequence errors. However, at present WGS is used (nearly) solely in research settings. Too much data, with too little known about non-exomic variants, is generated for clinical use. Outside of clinical trials, WES or other targeted sequencing strategies are used in order to generate data relevant to clinical interpretation and use. Realistically, targeted gene sequencing and/or WES will be implemented before WGS in clinical contexts, as most anti-cancer drugs (and drugs in general) target proteins altered by aberrations in the exome. Costs and time involved in WGS will continue to decrease as demand for the technology grows, although the initial investment in equipment and staff training is substantial. Individual institutions will only bear the costs to start the programme once evidence-based reviews, public pressure, and large-scale initiatives – like the 100,000 Genomes Project – provide a great enough stimulus.

In the short term, WGS will be almost exclusively used in clinical trials and research, but the knowledge it produces will filter down to inform and help interpret WES and other targeted clinical genetic tests. WGS identification of pathogenic variants will also continue to inform pharmaceutical development. Despite its currently limited utility in the clinic, WGS is already informing research and will firmly establish a supportive role in medicine in the near future, with real potential to become the gold standard in personalised and genetic medicine in the long term.

References


Continuous glucose monitoring: a sweet deal for paediatric type 1 diabetics

Abstract
Children diagnosed with type 1 diabetes mellitus (T1DM) are at particular risk for long-term complications, including diabetic retinopathy, neuropathy, and nephropathy. Over the last few decades, clinical advancements in glucose monitoring and methods of insulin delivery have improved quality of life in T1DM, making strict glycaemic control, which can reduce long-term complication risk, more achievable. The continuous glucose monitor (CGM) is a minimally invasive subcutaneous device, which assesses subcutaneous interstitial glucose levels at five-minute intervals. Used in conjunction with multiple daily insulin injections, or continuous subcutaneous insulin infusion via insulin pump, the CGM has been proven to enhance metabolic control, reducing HbA1c levels as well as time spent in hypoglycaemia. Furthermore, CGM allows for retrospective analysis of blood glucose trends by clinicians, leading to individualised and precise management strategies. However, limitations to its use include cost efficacy, sensor accuracy, and insertion site irritation. This review will discuss the potential benefits and limitations of CGM use in a paediatric population, and the recommendation that CGM be made available to any paediatric diabetic who requests its use.

Introduction

Type one diabetes mellitus (T1DM) is a chronic autoimmune condition characterised by a total lack of insulin production by pancreatic beta cells. In genetically susceptible individuals, an interplay between genetic and environmental factors leads to the early development of islet cell autoantibodies, which target insulin-producing cells, thereby rendering individuals severely glucose intolerant.

Prior to the discovery of insulin, doctors could do little for children diagnosed with T1DM. Changes in diet, including carbohydrate restriction, had little impact on disease progression, and death shortly followed diagnosis. When insulin was first derived from the pancreases of cattle and pigs in 1921, the prognosis of T1DM improved drastically. In 1978, biosynthetic human insulin was first developed, with the advent of various slow- versus fast-acting insulin types shortly thereafter.

Nowadays, children diagnosed with T1DM are immediately commenced on lifelong insulin therapy to prevent severe long-term complications, such as neuropathies, retinopathies, nephropathies, early cardiovascular disease, and death. Strict glycaemic control – defined as glycosylated haemoglobin (HbA1c) levels <7% – has been shown to significantly reduce the risk of these sequela for the estimated 500,000 children worldwide who currently live with T1DM.

Over the last few decades, clinical advancements in glucose monitoring and methods of insulin delivery have improved the quality of life of people with type one diabetes, making strict glycaemic control more achievable. This article reviews the literature available on one relatively new advancement, the continuous glucose monitor (CGM), which, when combined with insulin therapy, has the potential to aid the paediatric population with T1DM to achieve target management goals.

Management of paediatric diabetes mellitus

Management of T1DM can be broken down into two main components: insulin analogue therapy; and, self-monitoring of blood glucose (SMBG) levels.

Insulin analogue therapy consists of a basal dose of insulin to control glycaemic levels throughout the day (‘background’ insulin), as well as bolus doses of insulin taken for meals. Insulin is usually delivered via one of two methods: multiple daily injections (MDI); or, continuous subcutaneous insulin infusion (CSII) via an insulin pump. While both methods have proven effective, multiple studies have shown CSII to be superior to MDI in the paediatric population – perhaps because it involves one needlestick every three days rather than the four to eight daily injections required for MDI therapy.

SMBG uses finger-prick testing with a glucometer to analyse capillary blood glucose levels. This has long been the gold standard for diabetic self-testing because of its high accuracy rate. However, glucometers only allow patients to assess glycaemic levels periodically; therefore, their overall efficacy in contributing to enhanced glycaemic control is highly user dependent. A more recent technological advancement, the CGM, mitigates the glucometer’s limitation of intermittent testing. This minimally invasive device sits just beneath the skin and assesses subcutaneous interstitial glucose levels at five-minute intervals, providing a systematic flow of data, which can be used for both real-time and retrospective analyses.

The majority of people with T1DM are diagnosed in childhood and early adolescence, when strict glycaemic control is more difficult to attain than in the adult population. Children and adolescents may not understand the implications of the disease, and variations in exercise and diet can make management difficult. In adolescents, this is at least partly attributable to physiological changes and hormonal fluctuations associated with puberty, which can affect insulin absorption; additionally, psychological issues such as denial of the illness in an attempt to fit in with peers can lead to poor adherence to insulin therapy.

While maintenance of normal blood glucose levels is crucial in diabetes management, intensive insulin therapy increases the risk of hypoglycaemia. Hyperglycaemia (capillary glucose levels >8mmol/l) may lead to the abovementioned complications, but hypoglycaemia (<4.0mmol/l) also poses a real threat, especially to the paediatric population. Many of these episodes of hypoglycaemia occur at night, during sleep. Although it is possible that a hypoglycaemic event will awaken the patient, severe hypoglycaemia can rapidly lead to convulsions, coma, and even death, if not treated promptly.

Multiple episodes of hypoglycaemia may eventually result in a state of ‘hypo-unawareness’, in which a diabetic patient does not realise that their glucose levels are dangerously low. This is especially common in the very young subset of patients, who may be unable to adequately express their symptoms, even if aware of them. In fact, the fear of hypoglycaemia has been shown to be a major contributing deterrent to adequate control for people with type one diabetes. The overall goal of intensive diabetes management is therefore to reduce HbA1c levels without increasing the number of hypoglycaemic events.

The advantages of continuous glucose monitoring

One undisputed advantage of CGM is improved metabolic control and thus decreased risk of long-term complications. A meta-analysis...
of randomised controlled trials comparing CGM to SMBG in paediatric T1DM patients indicates the potential of CGM use, with either MDI or CSII, to effectively reduce HbA1c levels when compared to SMBG.18 Other independent studies show consistent results.6,16,17 Studies also indicate significant decreases in post-prandial and nocturnal glycaemic deviations when using the CGM in combination with an insulin pump (known as a sensor-augmented pump or SAP).18 When compared to MDI, SAP use has also been shown to decrease HbA1c levels, with more paediatric participants achieving their age-specific HbA1c targets.19 This can be explained in part by the use of alarms triggered by hyperglycaemic excursions, which allow for improved daytime dosing of insulin in response to hyperglycaemia. In addition to this reduction in HbA1c levels, multiple studies have shown that CGM use leads to a decreased number of hypoglycaemic episodes and overall total amount of time spent in hypoglycaemia, both daily and nocturnally.20,21 The use of alarms indicating hypoglycaemic episodes may be partially responsible, although one study found that over 50% of nighttime alarms fail to awaken patients.22 Retrospective data analysis by clinicians leading to adjustments in insulin dosages likely has a more profound effect on these findings.14

Another important advantage of CGM use is enhancing the understanding of T1DM and disease management by both real-time and retrospective data analysis. Clinicians can make precise adjustments to patient management after analysing trends in glycaemic levels in response to exercise, food intake and even examination stress (in adolescents).23 Seeing the effects that these activities have on their glycaemic levels may inspire confidence and independence in managing the illness for patients, who are at increased risk of anxiety and depression,24 as well as for parents, who bear the brunt of the work of diabetes management and are also at increased risk.25,26 Psychological relief may also be conferred by improved metabolic control, decreases in hypoglycaemia, and real-time and retrospective data analysis allowing for better management of the disease.27 All of these factors may contribute to future maintenance of glycaemic control and quality of life.

Potential limitations to continuous glucose monitoring

Cost efficacy

The benefits of CGM are largely undisputed. Meta-analysis of studies conducted in the United States has shown that CGM use is likely to be the most cost-effective in a subset of patients with high baseline HbA1c levels (indicating poor control) and in patients who are able to use the CGM frequently (at least six days per week),28 although no data is available on the paediatric subpopulation in particular.23 Due to variations in the literature, as well as the relatively recent evidence indicating its effectiveness, health insurance reimbursement and government funding of the devices have been restricted to a large extent, although this is slowly beginning to change in much of Europe.28 Unpublished analyses of cost-effectiveness in both Sweden and the Netherlands found the cost-effectiveness to be €36,000-52,000/QALY and €21,000/QALY, respectively, and the CGM system is now reimbursed by these governments for patients meeting certain criteria.27 The HSE long-term illness scheme currently covers the cost of CGM sensors in the Republic of Ireland, and reimbursement protocols vary throughout other European countries.29 If not reimbursed, maintenance of CGM is costly and may be a deterrent to regular use, which as previously mentioned is vital to its efficacy. Furthermore, for a few months after transition to CGM, multiple appointments with a multidisciplinary diabetes team and experts in CGM use are necessary. Although proven to be highly beneficial, these appointments may also contribute to up-front (and overall) costs.23

Sensor accuracy

The first CGM system – Medtronic’s Minimed system – was approved in 1999.30 Initially used only for retrospective analysis, subsequent generations of CGM devices have improved in accuracy, as well as percent functioning, as measured by mean difference between glycaemic sensor and reference levels. While sensors are 80-91% accurate for levels in the hyperglycaemic range, and 73-76% for those in the target range, the sensors are only 57-66% accurate at indicating hypoglycaemia and potentially overestimate the frequency of nocturnal hypoglycaemia.23 SMBG using glucometers has been shown to have at least 97% accuracy for all three glycaemic states.23 For this reason, there is an ongoing need to calibrate the sensors using glucometer testing at least every 12 hours.23 Due to the potential for inaccurate readings, patients and guardians are routinely instructed on the importance of confirming hypo/hyperglycaemic episodes with finger stick testing before treating either, to avoid unnecessary risk.23,31

General irritation by sensor site and ‘alarm fatigue’

Despite low rates of sensor site infection and cellulitis,14 skin irritation from sensor adhesives, pain at insertion, retained subcutaneous sensor tips, and annoyance at alarms have caused some concern among patients and their parents/guardians.32 However, despite these issues, overall satisfaction with CGM use is high among patients and guardians.23
Latest advancements, ongoing clinical trials and the future of CGM

The journey to a closed loop system or ‘artificial pancreas’

The closed loop system or ‘artificial pancreas’, as regarded by some, has been undergoing clinical trials for multiple years. Essentially, the system is composed of CGM coupled with CSII via an insulin pump. The modified insulin pump uses specific algorithms to secrete appropriate amounts of insulin in response to glucose level signals from the CGM. In theory, this should obviate the need for manual boluses at meal times; however, available literature indicates multiple limitations, the most prominent being lag time between sensor signalling reaching the pump and actual changes in glycaemic levels. Due to these limitations, the system is not currently utilised clinically, and is unlikely to be for a number of years.

MINIMED 640G by Medtronic

In 2014, Medtronic launched its Minimed 640G system, a semi-closed loop system composed of an integrated insulin pump and CGM sensor, modified to especially target nocturnal hypoglycaemia. The CGM sensors detect when glucose levels are falling below the normal range and send wireless signals to the insulin pump to suspend the release of the maintenance dose of insulin until glucose levels rise out of the danger zone, at which point delivery is resumed.

One significant benefit of this device is effectively reducing nocturnal hypoglycaemic events (and the fear of them) without the need of alarms to disturb the patient’s sleep. This encourages intensive management of T1DM in the paediatric population, in which hypo-unawareness is especially common. While no data is yet available on the long-term benefits or risks of this particular system, this is likely the most beneficial advancement to date in the management of paediatric T1DM, and towards the development of a fully automated, closed-loop system.

Conclusions

Paediatric patients with T1DM face the challenge of maintaining glycaemic levels within target range throughout the day and night. Findings that the paediatric population has overall higher HbA1c levels and decreased control when compared to the adult population make it vital to identify methods of increasing control and reducing risk of long-term complications. CGM is effective in reducing paediatric HbA1c levels, number of hypoglycaemic events, and overall time spent in hypoglycaemia. Furthermore, CGM allows for analysis of trends, which can be used by clinicians to alter patient management for long-term benefit. Despite some limitations to its use, it has been recommended that CGM be supplied to any paediatric patient who desires it, and it is especially useful in those with high baseline HbA1c levels, nocturnal hypoglycaemia, and those capable of maintaining regular CGM use.

References


I eat, therefore I am: the gut–brain axis and appetite control

Abstract
Traditionally, obesity has been viewed as a simple disease of excess calorific intake in the context of a sedentary lifestyle. However, while an increase in energy consumption without corresponding expenditure is a key force in the initial development of obesity, a number of homeostatic mechanisms conspire to maintain high adiposity in individuals who are already overweight. Both central neuronal mechanisms and peripheral endocrine signals drive increased appetite and reduced metabolic rate in the obese. This prevents weight loss from occurring as quickly as one would expect, and makes sustained weight loss of more than 15% almost impossible. Currently, the most effective therapy for obesity is bariatric surgery. While previously believed to effect weight loss through malabsorption, restriction of stomach capacity or both, it is now shown that these operations fundamentally change the internal milieu of obese individuals, favouring weight loss and a reduction in appetite via cumulative changes in neuroendocrine signalling. This has led to some exploration of methods to directly affect the final common pathways in the brain and more efficiently produce weight loss.

Introduction
Obesity is fast becoming a global epidemic. For the first time in human history, more people are dying as a result of relative calorie excess than of calorie deficit. In developing nations, obesity and malnutrition coexist to create a ‘double burden’ of disease on already stretched health systems. The traditional medical approach of prescribing increased exercise and reduced calorie intake, although shown to produce modest, clinically significant weight loss (usually around 5-10%), is often difficult for patients to adhere to in the first instance and is prone to recidivism. The interest this creates in pharmacological and surgical means of treating obesity has resulted in greater understanding of how our appetite is regulated.

Acquisition of calories and nutrients necessary for survival creates a powerful selection pressure on an organism. Evolution has thereby resulted in a complex homeostatic network in individual organisms to regulate appetite and prevent acute changes in adiposity. In humans, powerful neuroendocrine interplay exists between the digestive system, which initially receives and absorbs nutrients ingested by the organism, the adipose organ, a large endocrine organ involved in both energy storage and anorexigenic signalling, and the brain, the centre of behaviour. Greater understanding of the crosstalk between these three systems is required in order to facilitate the treatment of the obese patient, and ultimately to reduce the level of obesity and its concomitant complications in the future.

The lipostat hypothesis
Despite our general tendency to get bigger when calories are no object, individually mammals tend to ‘guard’ their weight. A number of experiments illustrate this: animals were either overfed or underfed for a relatively short time frame, then allowed an ad libitum diet. The animals exhibited compensatory behavioural and metabolic changes to restore their original weight, suggesting that there is a sliding set point, which internally monitors weight gain and loss and prevents drastic changes. This ‘lipostat’ is situated – like many homeostatic regulatory centres – in the hypothalamus.

The lipostat purposefully integrates the peripheral signals of dietary intake and the central signals of satiety, and translates them into appropriate behavioural, metabolic and appetite changes, which maintain weight at its typical level. This is important from a homeostatic perspective: a 1% miscalculation of calorific intake or expenditure (around 20kcal a day, equivalent to a single serving of cabbage) would result in the accumulation of an extra 1kg a year or >50kg over the average adult lifespan.

It also means that once the set point has been driven upwards (as in obesity), the lipostat modifies energy expenditure and calorie intake to maintain our internally determined weight. Therefore, the traditional medical mantra of ‘eat less, move more’ may not be sufficient for long-term, meaningful weight loss in those who are clinically overweight/obese.

Peripheral signals: signs of dietary intake
Three separate organs act as peripheral nutrient sensors to the hypothalamic centres involved in appetite: the stomach/small intestine, the pancreas and the adipose organ. Each contributes either to acute appetite regulation (satiety following a meal) or the long-term control of eating. Signals may be endocrine, neural or neuroendocrine in nature, and can be produced by direct sensing of the relevant constituents of food (e.g., fatty acids) or by mechanotransduction (stretch of the viscera leading to relevant hormone release or neural afferent firing). This gives the central integrating regions of the brain a sense of the volume and type of meal that has been ingested.

Signals from the periphery are almost all stimulated by dietary intake. A variety of mechanisms highlight the complexity of appetite regulation; the major determinants of satiety from the periphery, however, are anorexigenic (stimulate feelings of fullness).

Anorexigenic (appetite-suppressing) signals
Simple neuronal mechanisms act via the vagus nerve. Stretch of the stomach increases the rate of vagal afferent firing, which is processed initially in the nucleus tractus solitarius before projecting to the hypothalamus. As the stomach stretches and mechanotransduction increases, the feeling of fullness increases proportionally.

Neuroendocrine mechanisms also increase the activity of the vagus nerve, either via receptors (e.g., CCK1 receptors responding to cholecystokinin and leading to increased vagal afferent firing) or by increasing gastric stretch, such as the reduction of intestinal motility by peptide tyrosine tyrosine (PYY). The central role of the vagus nerve in communicating satiety signals from the gut is underlined by evidence that vagotomies in animal models often result in a loss of anorexigenic hormone signalling, resulting in overfeeding and weight gain.

Hormones also act centrally to produce feelings of satiety. Glucagon-like peptide 1 (GLP-1), perhaps better known as an incretin since the addition of exenatide to the pharmacopoeia for
diabetes, has an important role in generating central satiety. Delivery of GLP-1 antagonists centrally promoted overeating in experimental rodent models,\textsuperscript{10} additionally, the SCALE study recently illustrated that the GLP-1 analogue ‘liraglutide’ produced meaningful weight loss as an adjunct to diet and exercise.\textsuperscript{11} Pancreatic peptide (PP) also acts centrally via Y4 receptors and increases proportionally with the calorie content of ingested food boluses.\textsuperscript{7} Two hormones increase proportionally with fat mass: insulin, a pancreatic hormone secreted in response to food ingestion, and leptin, an adipokine directly secreted from adipose tissue. These hormones act as acute and chronic negative feedback loops.\textsuperscript{7} Mice lacking leptin (ob/ob) are indistinguishable from their heterozygote littermates at birth, but quickly gain weight through massive overeating. Rarely, human obesity has been shown to be associated with a loss of leptin function; however, in the vast majority of patients leptin is massively oversecreted.\textsuperscript{12} This has important implications for how the hormone is sensed centrally and reduces the lipostat’s ability to appreciate total fat mass.

**Orexigenic signals**

There is a single orexigenic signal secreted in the periphery: ghrelin, a peptide secreted from the stomach, acts on its receptor (GHS-R) to stimulate appetite. Ghrelin levels are highest while fasting and are higher in individuals who are chronically fasted (such as those with anorexia nervosa and people on weight loss diets). Ghrelin acts throughout the gut–brain axis to increase gastric motility, gastric acid secretion and calorific intake.\textsuperscript{7}

**Central signals: our hedonistic brain**

The brain is the integrative centre of the whole organism, allowing appropriate responses to both external and internal stimuli. Two important groups of neurons have been identified: an orexigenic group, Agouti-related peptide/neuropeptide Y neurons (AgRP/NPY); and, an anorexigenic group, pro-opiomelanocortin neurons (POMC). AgRP neurons are stimulated by ghrelin and inhibited by PYY, leptin and insulin. In POMC neurons the inverse is true.\textsuperscript{13} This bimodal system of antagonistic neurons integrates peripheral signals, producing an appropriate feeling of hunger or fullness. The result is a sensitive homeostatic sensor, which monitors input and modulates output by multiple afferent pathways, such as the paraventricular hypothalamus, dorsomedial hypothalamic nucleus and the limbic system.\textsuperscript{14} This acts via a second order set of neurons to alter metabolism by regulating thyroid hormone signalling, and behaviour via efferents to higher cortical centres.\textsuperscript{13,16} The cortex also plays a role, with modifications in taste, smell and memory, all driven by activity in the arcuate nucleus and circulating appetite-regulating hormones.\textsuperscript{17}

**Alterations in signalling in the obese patient**

So why, in spite of such overwhelmingly complex homeostatic machinery, do people become obese? As individuals gain fat mass, levels of insulin and leptin secretion increase. As is seen in type II diabetes mellitus (T2DM), high circulating levels of insulin result in tissue becoming resistant to its effects, and failure of peripheral tissues to uptake glucose.\textsuperscript{18} A similar process occurs in the central nervous system in regards to leptin: as higher levels accumulate in the blood, the brain ceases to respond appropriately, negating leptin’s influence as a satiety signal.\textsuperscript{12} Subsequently, as patients increase their energy expenditure (exercise) or reduce calorie intake (diet) in order to lose weight, GLP-1, PYY and other anorexigenic hormones are suppressed in favour of ghrelin secretion.\textsuperscript{11} This acts via central mechanisms, resulting in changes in behaviour and metabolism that prevent effective weight loss, making it difficult for patients to attain sustained and clinically meaningful changes in fat mass.

**Bariatric surgery: anatomical or biochemical intervention?**

An emerging therapy for obesity is bariatric surgery, particularly the Roux-en-Y gastric bypass. This procedure was developed to produce weight loss through restriction of total stomach volume (producing earlier vagal stimulation by stretch) and malabsorption.\textsuperscript{1} However, it has since come to light that this mechanism alone is unlikely to result in the sustained weight loss seen in patients postoperatively. Some 85% of patients with T2DM became normoglycaemic following the procedure, independent of weight loss. This suggests that some change is elicited in hormonal signalling and, ultimately, the gut–brain axis.\textsuperscript{19}

Weight loss following a Roux-en-Y gastric bypass is dissimilar physiologically from weight loss due to starvation, exercise or dieting. With the traditional ‘eat less, move more’ paradigm, ghrelin increases and GLP-1 and PYY decrease to create an appetite-stimulating hormonal milieu. Following Roux-en-Y the inverse is true.\textsuperscript{20} The chance of a person having a significant response to Roux-en-Y bypass, or losing a clinically significant amount of weight following surgery, can be predicted with some
accuracy by measuring these hormones. Leptin is reduced to levels comparable to lean subjects, indicating a return to a non-obese hormone profile. Finally, non-specific inhibition of hormone signalling with somatostatin allows for an increase in appetite as tested by an ad libitum meal.

Unfortunately, this surgery also carries the risk of developing malabsorption and dumping syndromes; thus, it is only reserved for individuals with very high BMIs (40kg/m² without comorbidities or 35kg/m² with comorbidities). Evidence is beginning to accumulate for a less drastic operation, the sleeve gastrectomy, which carries a lower risk of mortality and morbidity but also has a reduced chance of producing sustained weight loss and a change in obesity-related disease.

Deep brain stimulation: neuromodulation of a final common pathway

While the hormonal control elicited by gastric bypass is impressive, researchers are now considering how best to manipulate the final common pathway of satiety. Deep brain stimulation (DBS) is currently indicated for a number of diseases (notably Parkinson’s disease) with impressive reductions in symptoms. This intervention requires stereotactic placement of electrodes in the brain (around the lateral hypothalamus), but eliminates the risk of malabsorption. It is arguably more precise than the Roux-en-Y by consistently affecting the final common pathway.

Although research is only beginning in this intriguing approach to a common illness, results are reasonably promising. A 2013 pilot study of bilateral implantation of DBS electrodes (developed for Parkinson’s disease) into the lateral hypothalamic nuclei of three patients with intractable obesity was performed safely and had some evidence of efficacy. A major limiting factor of this study was that the electrodes that are produced for Parkinson’s neuromodulation are too large to target the specific areas of the lateral hypothalamus associated with appetite; however, as the technology develops, more success may emerge from this approach to the treatment of obesity. Additionally, a wide range of alternative targets is being explored – such as elements of the brain’s reward circuitry (nucleus accumbens) – suggesting new directions for the future of bariatric surgery.

Conclusions

Obesity has historically been associated with poor health. Hippocrates reportedly stated: “Corpulence is not only a disease itself, but the harbinger of others”. In the modern era of energy-(and calorie-) sparing devices for work and easy availability of calorie-dense foods, a veritable epidemic of ‘corpulence’ has emerged. While the best solution to this problem is prevention, there will inevitably be individuals who gain enough weight to endanger their health.

Medical treatment of obesity has historically been simplistic and has neglected the complexity of human biology and the powerful homeostatic mechanisms to prevent sudden changes in physiology. Prescription of diet and exercise will continue to be the mainstay of treatment in the overweight, but an awareness of the limitations of this strategy is an important consideration for clinicians.

Understanding the gut–brain axis also allows for tailoring treatment of the obese patient in novel ways, by using GLP-1 agonists as an adjunct for weight loss or utilising surgery (bariatric or neurological) to fundamentally alter the communication pathways between these organs, as discussed above. Ultimately, this will produce a range of therapies that are: a) effective; and, b) enduring in the fight against obesity, reducing patient morbidity and mortality, and allowing individuals to lead healthier, happier and longer lives.
References


The artificial womb: bridging the gap between embryo culture and the incubator

Abstract
Advances in life support devices and ex vivo embryo culture in artificial endometria present a framework for the development of the artificial womb, a device capable of supporting long-term extrauterine gestation. We review the potential medical impact of such technology, proof-of-concept animal studies, related research, and emerging epigenetic, neurologic and heritability challenges in supporting extrauterine culture and gestation. Additional research is needed in a number of areas, particularly regarding poor outcomes in embryo culture. In addition, we examine ethico-legal, social and fiscal considerations, with a view towards preparing regulatory ethico-legal policies in anticipation of such technology. Finally, stakeholder engagement is called for to see the integration and implementation of existing technologies, and the development of the artificial womb as a clinical device of promising utility.


Opening
"[W]arm on their cushion of peritoneum and gorged with blood-surrogate and hormones, the fetuses grew and grew ... “

Brave New World, Aldous Huxley, 1931

Advances in in vitro fertilisation (IVF), foetal incubation and neonatology continue to reduce the essential time foetal gestation is required to spend in utero. The prospective endpoint is ‘ectogenesis’, using an artificial womb as an achievable life support device capable of supporting in vitro gestation until viability, thus bridging the gap between IVF and conventional incubation in prematurity.1-11 In this article, we examine the conceivable impacts, latest research, and challenges of ectogenesis, and explore relevant fiscal and ethico-legal considerations.
Relevance and potential benefits

Due to the limitations of neonatal medicine and technology, at present life is not viable outside the womb prior to approximately 23-24 weeks' gestation. Thus, neonatology reviews are increasingly calling for the development of an 'artificial womb' – a device capable of supporting long-term extra-uterine gestation – to minimise the morbidity and mortality of prematurity. Expert opinion holds that such a device is feasible to support gestation from as early as 14 weeks with modern knowledge and technology.

Current challenges to foetal diagnostics and therapy in the uterine environment include accessibility, therapeutic failure and procedure-associated adverse events, such as miscarriage, at rates of 0.81% in amniocentesis or 1.6% in foetal transfusion, in the developed world. In addition, owing to therapeutic limitations, multi-foetal pregnancies and maternal-foetal disease may currently be indications for termination. The total accessibility of the foetal environment offered by ectogenesis creates significant potential for novel solutions in minimally invasive foetal monitoring, surgical access and delivery of therapeutics, all of which (potentially) function to alleviate the morbidity and mortality associated with extreme prematurity, structural anomalies and multi-foetal pregnancy. In addition, strategic transfer to, or conception in, the artificial womb could also significantly reduce the morbidity and mortality of pregnancy; roughly 15% of all pregnancies involve potentially life-threatening complications, resulting in 10 and 28 maternal deaths annually per 100,000 pregnancies in the UK/Ireland and the US, respectively.

The artificial womb would obviate harmful environmental exposures, including in utero infection and teratogens (e.g., foetal alcohol syndrome). Eliminating just one common virus, cytomegalovirus, could lead to substantial reductions in mortality, morbidity and associated costs; 40,000 congenital cytomegalovirus infections in the US are responsible for approximately 400 deaths and 8,000 serious permanent neurodevelopmental and sensory disabilities annually. Total ectogenesis – denoting conception to delivery in the artificial womb – could circumvent infertility, particularly due to uterine absence or disease. Additionally, it could reduce international surrogacy arrangements, which disproportionately rely on socioeconomically vulnerable women. Readily available ectogenesis could mitigate the considerable post-pregnancy morbidity for women, including backache (45%), sexual dysfunction (20%), bowel problems (17%) and urinary incontinence (11%) six months after delivery.

Research and challenges in ectogenesis technologies

Proof-of-concept research

First attempted in 2003, total ectogenesis involves support from embryo culture to full term. Liu et al. reported growing a mouse embryo to term in a bioengineered uterus (albeit with deformities). However, in a follow-up experiment, the group transferred murine embryos grown on engineered uterine tissues (EUs) to the abdominal cavity – not the uterus – of adult mice at seven days, and left controls in vitro. Four days short of term, researchers removed all embryos for comparison; those in vitro had developed hearts, but died. However, the embryos transferred were anatomically normal and apparently healthy. In spite of such findings, Liu halted her experiments in response to pressure from interest groups and ethical concerns.

Such proof-of-concept research highlights challenges to the successful application of ectogenesis in bridging the gap between embryo culture and the incubation of mature foetuses. At present, devices performing all the necessary functions of life support at later gestations – incubation, gas exchange, waste removal and nutrition –
exist. Cardiorespiratory, gut, and kidney replicators are present in the form of extracorporeal membranous oxygenation (ECMO), total parenteral nutrition, and dialysis, respectively, and can be used in conjunction with the previously listed life support mechanisms. These devices have proven to be of immense clinical value; however, research to implement their long-term integrated use in earlier gestations has yet to progress beyond animal studies.2,25-27

Proof-of-concept research for extended foetal extraterine life support in the 1990s successfully incubated goat foetuses in artificial amniotic fluid, providing gas exchange using extracorporeal supplies of blood via umbilical access. Physiologic stability was maintained in foetuses of 120-128 days (of total gestation – approximately 150 days) for periods in excess of 500 hours, with subsequently stable blood gas exchange and survival upon removal. Results in similar animal studies clearly indicate the viability of such devices in the extended extraterine incubation of a premature foetus utilising umbilical arteriovenous ECMO.25-28

Device challenges and neuroplasticity

Assist devices currently undergoing development include the ECMO-type neonatal oxygenator NeonatoX, which has been successfully implemented with preterm lamb models. Its continued refinement includes miniaturisation to rectify inappropriate shunt fractions associated with congestive heart failure.1 Additional challenges to clinical application of such a device include the potential inflammatory and infectious sequelae of blood-priming to initiate the circuit with non-foetal blood.1 Applicability to earlier generations or total extrauterine gestation demands further research into the integration of other life support functions, in order to more fully recapitulate placental function of the maternal uterus.11

As incubator and life support technologies have progressed, key challenges in replicating the requisite stimuli for development have arisen. Mimicking the “tactile, kinaesthetic and vestibular concomitants of maternal speech, movement and physiology”29,29 is critical to support neuroplasticity and prenatal sensory competence.29,30 This is fundamental, as prenatal plastic changes and fine-tuning in neural assemblies that are required for speech perception and understanding, among other functions, are stimulus or learning induced.29-31 Conversely, the harms of inappropriate or absent stimuli are highlighted by a 2014 review finding that noisy, high-frequency environments disrupt functional organisation of auditory cortical circuits, possibly increasing the risk for disorders of hearing, language and attention.32

Embryo quality and epigenetics

In terms of maximising embryo quality, the immediate post-fertilisation culture environment is the most important determinant.33 However, existing gamete collection and embryo culture methods involve hormonal, physical, thermal and other stresses, which alter epigenetic profiles, DNA methylation patterns, and gene expression.34-35 This is reported to exceed the adaptive capacity of embryos, lowering developmental capacity in animal models36 and resulting in significantly increased anatomical birth defects in children conceived by IVF and/or intracytoplasmic sperm injection (ICSI) – with a meta-analysis pooled risk estimation of 1.37.37,38 One logical concern is epigenetic heritability of poor outcomes. Murine models have demonstrated transgenerational inheritance of altered epigenetic reprogramming, resulting in adulthood obesity, anxiety disorders and memory impairment.39 The potential risks of unfavourable transgenerational inheritance in human populations present potentially significant challenges to the continued culture of embryos. Ultimately, embryo culture methods are suboptimal, and additional studies of altered gene expression are necessary to further interrogate aberrant imprinting, and to elucidate how previously identified candidate genes and pathways are disrupted.35,36

Currently, research involving engineered EUTs aims to recapitulate the microenvironment of the maternal uterus with enhanced fidelity. EUTs already offer the ability not only to support murine embryo growth, but to also markedly improve development rate and quality compared to standard IVF control culture media.40 These more closely simulate utero-embryonic metabolic interactions, and provide the complex mélange of chemosensory, nutritional and immunologic signalling factors for optimum early gestation. In addition, they provide a high-fidelity model for study of maternal-embryonic interactions towards maximising outcomes in ectogenesis.29,25
Ethics and attitudes

Motherhood

A wealth of literature demonstrates complex debate on whether mother-child relationships and female identity will be damaged by ectogenesis, or whether it will liberate women to escape gender constraints and procreate, similarly to men, without compromising health or socio-economic position. Significant division of opinion surrounds ectogenesis and termination. Ultimately, all embryos are potential candidates for extra-uterine viability. This reframes the medicolegal understanding of abortion, dissociating termination of pregnancy from termination of offspring/motherhood, with opinion divided on how this might empower or disempower the parties involved.11

Genetic studies show that miscarriage often functions as a natural screening mechanism, involving termination of compromised or non-viable pregnancies, e.g., in aneuploidy.41 The ethico-legal considerations of replicating natural mechanisms in recognising and terminating severely compromised offspring would fall under abortion laws in many jurisdictions and may be complex in practice. How might this affect the legality of, or requirements for, termination? Should the decision-making capacity regarding bringing a conception to term be shared by both parents, having both contributed gametes equally, or revert to the state in certain jurisdictions? Might inalienable legal rights be afforded from conception, and a legal responsibility on parent or state be proposed to bring all conceptions to term? How might viability, disease burden, quality of life, cost or legal capacity issues be assessed? In quality of life cases, how might medical, parental or legal opinion be interpreted?

Societal demand

In addition, it may be argued that there is an ethical imperative for state-funded pursuit of ectogenesis. Regarding healthcare in terms of distributive justice, it is argued that natural inequalities may generate a *prima facie* right to restitution (e.g., state-funded infertility treatment). In the *Cambridge Quarterly of Healthcare Ethics*, Smador argues that reproduction is a societal demand, which unequally imposes risk on women.

The health-related risks and social detriment of pregnancy may constitute a recognisable health-oriented need and natural injustice. Smador thus contends an imperative on the state to redress this *prima facie* right to restitutive justice by pursuing ectogenesis research and availability.42

A pilot study in Israel, of mostly Jewish women, revealed majority support for: ectogenesis for wombless women (74.5%), foetus-saving ectogenesis (65%) and women’s right to freely choose ectogenesis to avoid the risks and burdens of pregnancy (39%). Men, single people, secularists, and academic degree holders were found to have a more positive attitude towards ectogenesis.43

Fiscal considerations

Private investment and commercial markets

Considerable return on developmental costs is conceivable in commercial reproductive and infertility markets. Conventional IVF is high cost, with suboptimal pregnancy rates per embryo transfer, while surrogacy carries ethico-legal concerns. The perfected artificial womb could provide better health outcomes, at higher success rates, while avoiding time lost through failed embryo transfers.44 The potential market for ectogenesis is estimable from the high-growth sectors of surrogacy – over $2 billion USD in India alone19 – or the international IVF market, valued at $9.3 billion in 2012, and an anticipated $21.6 billion by 2020.45 In addition, commercially available ectogenesis could be marketable as avoiding the morbidity, potential mortality, socioeconomic losses, career discrimination46,47 and direct medical costs associated with vaginal and caesarean birth in the US – $32,093 and $51,125, respectively.48

State interest – prematurity and environmental factor morbidity

The human and state-borne financial costs of prematurity and morbidity due to environmental exposures are conceivably significant enough to support state-level interest in an alternative that is either financially competitive, or carries such medical advantage as to compensate cost–benefit ratios. On a ‘per child’ basis, there is wide scope for strategic early transfer to the artificial womb to undercut the relative opportunity cost of US care at superior medical outcomes, with a 2013 review finding mean preterm-associated costs as high as $326,953.49

The annual societal economic burden of prematurity in the US alone was $26.2 billion in 2005, including direct medical costs of between $4.62 and $13.38 billion and special education costs of approximately $370 million.50

Conclusion

We have examined the impacts of, latest research in, and challenges to partial and total ectogenesis, in addition to fiscal and ethico-legal considerations. As discussed, additional research is needed in a number of areas, particularly regarding poor outcomes in embryo culture. There is time in anticipation of such technologies to prepare regulatory ethico-legal policies towards best practice. Finally, stakeholder engagement is called for to see the integration and implementation of existing partial ectogenesis technologies and development of total ectogenesis sooner rather than later.
References


Antibiotics in the 21st century: a fight against a familiar foe

Abstract
Antibiotics form the cornerstone of treatment against infectious disease and have helped to drastically reduce mortality rates since the turn of the twentieth century. Through the years, antibiotic development has progressed through different phases of discovery techniques, but has now reached a dipping point in its productivity for a multitude of reasons, both scientific and financial. Furthermore, antimicrobial resistance (AMR) threatens to undo all the progress achieved by these miraculous drugs that were discovered, no less, from the culture of other soil microorganisms. Recent strides in technology and legislation hope to drive resurgence in the field. This is exemplified by teixobactin, a promising new antimicrobial compound, which has been hailed as one of the most exciting scientific discoveries of 2015. This article explores the historical journey of antibiotic discovery, the issues surrounding AMR, the challenges faced by antibiotic research and development (R&D), and the new and innovative strategies being employed to overcome these hurdles.

RCSIsmj staff review

A brief history of antibiotic discovery
The discovery of antibiotics revolutionised medicine by drastically improving the efficacy of treatment of infectious disease, which was the greatest contributor to mortality statistics in the pre-1900s era. The Centers for Disease Control and Prevention (CDC) in the United States (US) reported a rapid decline in infectious disease mortality from 1900 to 1999, crediting the development of antibiotics as a major contributor to this phenomenon.\(^1\)

Antibiotics remain some of the most effective agents in a physician’s arsenal against infectious disease, and have helped to pave the way for groundbreaking advances in other fields of medicine, such as surgery, transplantation medicine, intensive care and oncology.

The development of the very first antibiotic began with Alexander Fleming’s discovery of penicillin in 1928,\(^2\) catalysing an age of antibiotic discovery – in particular the beta lactams, one of the main classes of antibiotics utilised in clinical practice to this day.\(^3\) The golden era of antibiotic discovery, from the 1940s to the 1960s, saw an explosion of new antibiotics discovered through systematic screening of soil microorganisms for antimicrobial activity.\(^4\) Roughly two-thirds of ‘natural product’ antibiotics (natural substances produced by microorganisms) were isolated from soil *Actinomycetes*.\(^5,6\) However, this method of antibiotic discovery was restricted to
cultivable soil microorganisms and dwindled during the 1970s as a result. As new discoveries became scarce, scientists began utilising semi-synthetic methods to modify pre-existing antibiotic scaffolds, altering their activity and improving their pharmacokinetic properties.6,7,8

Synthetic approaches came to the forefront of antibiotic discovery in 1995, when the first complete bacterial genome (Haemophilus influenzae) was sequenced.6 The advent of genomics facilitated the exploration of a multitude of new genes and, in turn, the foundation for a target-based approach to screen for new classes of antibiotics.6 Major pharmaceutical companies quickly adopted these high-throughput screening techniques; however, roughly two decades later, they have seen limited success.6 To date, the only clinically-approved antibiotic discovered via high-throughput screening is bedaquiline, an anti-tuberculosis agent.10 The collective failure of target-based screening to identify novel antibiotics has been implicated as one of the reasons why many pharmaceutical companies have withdrawn from antibiotics research and development (R&D). Currently, only four large multinational pharmaceutical companies retain their antibiotic R&D divisions (GlaxoSmithKline, AstraZeneca, Merck and Pfizer) and as a result, the last two decades have seen a significant void in the discovery of novel antibiotics.11

Table 1: The ESKAPE pathogens.

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<th>Letter</th>
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<tr>
<td>E</td>
<td>Enterococcus faecium</td>
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<td>K</td>
<td>Klebsiella pneumoniae</td>
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<tr>
<td>A</td>
<td>Acinetobacter baumannii</td>
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<td>P</td>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>E</td>
<td>Enterobacter spp</td>
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FIGURE 1: Representation of the 20-year discovery void in the antibiotic research and development timeline. The 1940s to the 1960s represents the period of greatest productivity in terms of antibiotic discovery, which was catalysed by the discovery of penicillin.29
Antibiotic resistance

Since the dawn of antibiotic discovery, experts have voiced concerns regarding the threat of antimicrobial (antibiotic) resistance (AMR), most notably Fleming, who foretold the development of penicillin resistance in his Nobel Prize acceptance speech.\textsuperscript{12,13} Today, AMR is a serious global health issue; the World Health Organisation (WHO) recently described it as the “single greatest challenge in infectious diseases today”.\textsuperscript{14} The CDC estimates that every year over two million people become infected with antibiotic-resistant bacteria and at least 23,000 die as a result.\textsuperscript{13} In addition to the mortality and morbidity associated with AMR in the US, it also generates an economic burden of $20 billion USD in excess healthcare costs.\textsuperscript{16} In the past, AMR was confined to hospital-acquired infections and immunocompromised patients; however, it has now begun to spread into community-acquired infections.\textsuperscript{4}

AMR can be classified into two different types: intrinsic and acquired. Intrinsic AMR refers to inherent characteristics of a microorganism that render it resistant to antibiotics, which do not change in response to antibiotic selective pressure. In contrast, acquired AMR is the product of microbial evolutionary change, conferring a survival advantage on resistant organisms\textsuperscript{17} that has been accelerated by the selective pressure of antibiotic drugs used by humans. The main contributors to this selective pressure are the medical and agricultural sectors, which widely misuse and overuse antibiotics.\textsuperscript{6,18} Acquired AMR is exemplified by the cautionary tale of the development of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) around the 1960s, which was fuelled by the uncontrolled use of methicillin in hospitals. The modifiable nature of acquired AMR suggests that the rate at which resistance develops can be controlled via infection prevention efforts, efficient infection diagnostics, and antibiotic stewardship during treatment.

The rapid evolution of AMR is a result of bacterial genetic plasticity, allowing for spontaneous and consistent acquisition of mutations through horizontal gene transfer (HGT) and chromosomal mutations. These genetic changes manifest through modification of target proteins, enzymatic inactivation of drugs and prevention of target access. The frequency of mutations can be increased in response to loss of DNA repair or proofreading and the induction of pro-mutagenic pathways.\textsuperscript{19} HGT facilitates the rapid spread of resistance genes between species via mobile genetic elements such as plasmids, leading to the emergence of multi-drug resistant (MDR) strains of bacteria dubbed ‘superbugs’. The ‘ESKAPE’ pathogens are responsible for most MDR infections.\textsuperscript{20} The most worrisome pathogens exhibit pan-drug resistance, resulting in minimal therapeutic options; these include \textit{Acinetobacter baumannii}, \textit{Pseudomonas aeruginosa}, carbapenem-resistant \textit{Enterobacteriaceae} and the recently identified New Delhi metallo-β-lactamase-1-expressing \textit{Enterobacteriaceae}.\textsuperscript{4,15}

Challenges in antibiotic development

In an effort to address the concerning lack of progress in developing novel antibiotics against MDR infections, the Infectious Diseases Society of America launched the 10x'20
Initiative for the development and approval of 10 new antibiotics by 2020. A recent update reported that only two new antibiotics (telavancin and ceftaroline fosamil) had been approved for marketing in the US, and these numbers were part of a downward trend. Antibiotic R&D is a formidable task that requires substantial monetary investment to develop a new compound without any guarantee of success. Ironically, despite their life-saving capabilities, antibiotics are inherently less costly, are administered for a shorter duration than many drugs used to treat chronic medical conditions, are curative by nature, and tend to be held in reserve in an effort to delay AMR development. These factors mean that antibiotics generate less net return on investment and are logically less appealing investments for pharmaceutical companies. The field of antibiotic development currently relies on the efforts of small pharmaceutical and biotechnology companies, which often lack the resources to develop potential drugs in large-scale clinical trials, therefore impeding much-needed progress. Researchers face equally formidable obstacles in the search for new antibiotics. Breakthroughs have become elusive due to over-mining of natural products and unsuccessful synthetic approaches. In the last decade, the focus of the field has been limited to targeting resistant strains of gram-positive organisms such as MRSA and vancomycin-resistant Enterococci (VRE). Recent data suggest that resistance rates in these gram-positive pathogens have stabilised or decreased, but the incidence of drug-resistant tuberculosis and gram-negative strains has been increasing. The emergence of new resistant gram-negative pathogens is particularly worrisome due to their intrinsic resistance to many antibiotics, making drug design problematic. Gram-negative organisms have an outer membrane that is impermeable to amphipathic drugs. Additionally, their inner membranes and efflux pump systems also deter hydrophilic molecules from entering the bacteria. One notable example is the enterococcus species, which is inherently resistant to beta-lactams such as penicillins, cephalosporins and carbapenems. The ESKAPE pathogens, most notable for causing life-threatening MDR infections, are predominantly gram-negative pathogens, and physicians are sorely in need of therapeutic agents to counteract these life-threatening infections.

**Strides in the right direction**

Economic incentives and new collaborative efforts are needed to address the commercial failure of antibiotics. Government initiatives encouraging pharmaceutical companies to undertake antibiotic R&D have been launched on both sides of the Atlantic. In 2011, the US Congress introduced the Generating Antibiotic Incentives Now (GAIN) Act, which detailed new incentives to advance antibiotic development. The European Commission founded a public–private collaboration, the Innovative Medicines Initiative (IMI), with initial funding of €223.7 million, to be used to tackle AMR and to speed the delivery of new antibiotics to patients. The IMI has also funded a multinational public–private consortium, Driving Re-Investment in R&D and Responsible Antibiotic use (DRIVE-AB) to develop alternative economic strategies allowing for sustainable development of novel
antibiotics, while balancing appropriate usage of said resources. A recent review on AMR commissioned by the UK Government has proposed the formulation of a global innovation fund to reward groups developing new antibiotics with lump sums. Innovative solutions are needed to address the scientific bottleneck facing antibiotic development. Scientists have taken to expanding their field of research on a macroscopic level by exploring other ecological niches in search of antibiotic agents. Promising new compounds have been sourced from deep sea sediment bacteria, marine flora and fauna, and bacterial symbionts of insects, fungi and myxobacteria. Other novel research avenues to overcome AMR include targeting molecular mechanisms of AMR, virulence factors, antimicrobial peptides, and bacteriophages, as well as repurposing genomic-based antibacterial screening with new tools such as combinatorial chemistry.

One untapped resource postulated to be a new avenue for antibiotic discovery is that of uncultivable soil microorganisms. Data suggests that the number of discovered antibiotics represents only 10% of the screened bacterial strains and only 1% of all microorganisms. A recent success story is teixobactin, the first new class of antibiotics with a novel mechanism, which was discovered using new technology for culturing soil microorganisms – iChip – a multichannel device that allows the diffusion of nutrients and growth factors from the soil into separated chambers to allow for growth of previously uncultivable bacteria. A soil sample is diluted down to approximately one bacterial cell per given chamber and placed back into its original environment. The growth recovery using the iChip technology is approximately 50% and significantly greater than the 1% yield from soil that will grow on a nutrient Petri dish using traditional culture methods.

Teixobactin was isolated from a new species of β-proteobacteria named Eleftheria terrae, which is related to Aquabacteria. It is a depsipeptide molecule that acts as a cell wall inhibitor by binding two precursors of bacterial cell wall polymers: lipid II (peptidoglycan) and lipid III (teichoic acid). Structural analysis of teixobactin demonstrated a unique chemical scaffold unlike existing antibiotics, a highly desirable trait for new antibiotics. Teixobactin exhibits excellent activity against gram-positive pathogens extending to drug-resistant strains, but has no activity against gram-negatives.

There is an intriguing lack of development of resistance to teixobactin during in vitro and in vivo testing; however, despite these promising results, teixobactin has yet to undergo clinical trials in humans, so its success remains to be proven despite the initial enthusiasm about its potential. The authors have postulated that the reason behind the lack of resistance development is due to teixobactin’s unique targets; lipids are essential to cell wall synthesis and are synthesised from organic precursors, whereas proteins are encoded by genes that can easily mutate in response to selective pressure.

Post-antibiotic era?

The threat of AMR and the diminishing antibiotic pipeline has led many experts to ponder whether a post-antibiotic era is imminent, in which common infections and minor injuries...
become lethal. In the past, antibiotic development just barely kept pace with the rate of bacterial evolution, and the lengthy lack of productivity in the pipeline certainly has left a sizeable gap between the two. In order to close this gap, collaborative efforts are necessary, as the problem has now become too large for one sector to handle on its own.

Government and health organisations have begun taking action towards combating AMR development via public health prevention and antibiotic stewardship. Concerted efforts have been made in legislation and funding towards revitalising the antibiotic discovery industry. The research community has also stepped forward with a variety of new approaches to tackling the elusive issue of novel antibiotic discovery. Only time will tell whether AMR can be held at bay long enough to allow for these efforts to come to fruition, and the hope is that human innovation can indeed make up for lost time and allow us to continue in this age-old battle against the microbes.

References


Watch this space: bringing medicine beyond Earth’s boundaries

Abstract
Since the first manned flight by Yuri Gagarin in 1961, the human race has strived to push the boundaries of manned space travel. Originally driven by curiosity, in more recent years the new goal is to extend the range of human habitat beyond Earth’s limits. This will require extended duration space flights. However, humans evolved in the presence of gravity and Earth’s particular atmosphere. Leaving this protective environment poses a myriad of challenges to the human body, including microgravity, solar proton radiation, prolonged confinement and isolation, absence of natural light and circadian rhythm changes. Key effects identified include loss of bone density and muscle strength, adverse psychological changes and increased cancer risk. Future missions will routinely demand complex and physically demanding tasks, and astronauts will be unable to receive additional resources or communications from Earth in a timely manner. It is essential that effective countermeasures be developed to maintain or enhance human performance in microgravity. Increasing private sector investment in commercial space travel also means that future passengers will be a more diverse population that may be less tolerant to space travel than current astronauts. This increases the likelihood of life-threatening in-flight surgical or psychological emergencies. With current flights including only one crew member with limited medical training, changes will need to be made to medical protocols to ensure mission success, such as prophylactic appendectomies and the inclusion of emergency physicians in future crews.
Introduction

Driven by innate curiosity, fear of the unknown and potential commercial gain, humans have long strived to push the boundaries of manned space travel since that first flight by Yuri Gagarin in 1961. Recently, we have identified a new goal: to extend the range of human habitat beyond Earth through colonisation of other planets and prolonged space travel. However, leaving the protective cocoon that we evolved in, no longer cushioned by the presence of gravity and a precise balance of gases, poses a myriad of challenges to the human body – as demonstrated in the book (turned major motion picture) The Martian by Andy Weir. These include microgravity, radiation, prolonged confinement and isolation, and changes in circadian rhythm. Key effects identified include loss of bone density, decreased muscle strength and endurance, adverse psychological changes, and increased cancer risk due to high-energy radiation. Unshaken by these dangers, we are rapidly making the advances in research and technology necessary to make extraterrestrial colonisation a reality. Missions will routinely require astronauts to perform complex and physically demanding tasks, so it is essential to minimise adverse effects, particularly in light of the fact that astronauts will be unable to receive additional resources or communications from earth in a timely manner. With increasing private sector investment in commercial space travel, the passengers of future flights will also be a more diverse population, potentially less tolerant of space travel than the robust and rigorously trained athletes of today.

Cardiovascular adaptations

The cardiovascular system appears to adapt the most appropriately to microgravity. The most frequently documented changes are related to shifts in body fluids and mild arrhythmias. During space flight, lack of gravity-induced hydrostatic forces lead to a cephalad shift and equilibration of fluid from lower extremities to the trunk and upper extremities. This manifests as nasal congestion and the classic “puffy face/bird leg” appearance of astronauts. Fluids shifting towards the head distend the baroreceptors of the central vasculature, resulting in suppression of the renin-angiotensin-aldoctosterone system (RAAS) and a 10% reduction in total blood volume. These effects decrease over time, but remain present for the duration of the flight. Increases in heart rate and premature atrial and ventricular contractions have also been reported in 30% of astronauts during extravehicular activity, launch and orbit, thought to be due to catecholamine hyperactivity. So far, crew members have tolerated these episodes well, but passengers on future flights will likely be much less conditioned. This should be noted when developing future preflight medical evaluations.

Musculoskeletal adaptations

One of the best-understood consequences of space flight is the impact of microgravity on the musculoskeletal system. Bone and muscle are active, dynamic organs that quickly respond to the physical forces exerted upon them. Space flight neutralises the gravitational loading required for skeletal remodelling and muscle growth, leading to significant loss in bone density and widespread muscle atrophy. Suboptimal nutrition, reduced vitamin D due to low levels of natural light, and higher ambient levels of CO₂ lead to respiratory acidosis and increased bone resorption. Postural muscles atrophy most due to their relatively unloaded state. After two weeks of space flight, muscle mass decreases by 20%, extending to 30% by three to six months. The loss of bone density is much more concerning, beginning immediately upon arrival in space, with a 60-70% increase in urine and faecal calcium loss within the first few days. This continues with a 1-2% loss per month in weight-bearing bones; hence, osteopaenia could become a limiting factor in mission duration. Future missions will inevitably involve strenuous physical work and extravehicular excursions, so increased risk of fracture is a real concern.

Countermeasures focus on the prevention of bone loss with exercise and dietary measures, including low-salt and high-calcium diets, and vitamin D and protein intake. Pharmacological agents are avoided due to the potential for serious side effects that the crew may not be equipped to deal with. In-flight exercise programmes lack the impact forces associated with Earth’s gravity and are insufficient. Additionally, the current two-hour daily exercise regimen consumes valuable oxygen, food, water and crew time, and will only increase with longer flights. One alternative proposal is to use intermittent artificial gravity; recent studies indicate that human subjects may undergo daily exposure to artificial gravity without suffering debilitating motion sickness, and periodic exposure is effective in maintaining muscle mass. However, this is a costly and difficult engineering task.

Radiation exposure

Perhaps the most sinister health concern is exposure to radiation beyond Earth’s orbit, which is vastly different to the ionising type to which humans are usually exposed, and is thought to produce distinct biological damage. Astronauts incur substantial but poorly understood risks of carcinogenesis and degenerative disease. Solar flares are particularly concerning due to their unpredictable nature, while high energy (HZE) ions are the main contributor to the risk due to their high ionisation power. During a three-year mission to Mars, every cell nucleus in the body would be hit by a proton or secondary electron every few days, and a HZE ion once a month. This
would culminate in a whole-body dose of radiation equal to approximately 1 Sievert or more. The risk of cancer is significantly increased by this exposure, and has prompted studies on how the risks – particularly of tumorigenesis – might be minimised.19 Radiation exposure also has significant impacts on the human reproductive system, particularly in females. Flights to date have been considerably shorter than the average menstrual cycle length, so no on-shuttle studies have been conducted to determine the impact on the hypothalamic-pituitary-ovarian axis. The main concern is that anovulation or hypothalamic amenorrhea and reduced oestrogen levels (which contribute to risk of osteoporosis) could occur.19–21 Radiation exposure, combined with the increased retrograde menstruation during space flight, may predispose to the development of endometriosis.22 The risks of these effects can be largely controlled by oral contraceptive or hormone replacement therapy. Due to radiation levels associated with any space flight, and consensus that no embryo could appropriately adapt to microgravity, pregnancy in space is currently not feasible.23 More research needs to be carried out on shielding options, including potential radioprotective drugs.

**Psychological adaptations**

NASA has predicted that psychological issues are all but inevitable, and pose a serious threat to mission success.21 Future crews must adhere to a strict and demanding schedule while confined in a spacecraft, removed from earthly conveniences and daily routines. To date, no mission has been terminated prematurely due to behavioural disturbance, but this may be largely due to the current duration of flights, frequency of contact with ground control, and strict astronaut selection criteria.24 The longest prior simulated space mission lasted a mere 240 days;25 the ambitious Mars 520 project confined a multinational crew of six healthy males to a 550m² chamber on Earth for 520 days.26 While unable to mimic the effects of microgravity, radiation and real threat to life, the project isolated participants from Earth’s light-dark cycles, limited their access to consumable resources, simulated communication delays, and assigned daily maintenance work, experiments and exercise identical to that predicted on a real mission to Mars. Investigators noted disruptions to circadian rhythm and modest increases in depressive symptoms and psychological distress, but arguably the most interesting observation was an increase in crew-perceived conflicts with ground control as the mission progressed.24 The development of an ‘Us vs Them’ attitude is a well-documented form of displacement during space flight: the team transfers intra-group tension onto a remote individual.27,28 The most extreme case of frustration resulted in crew cutting contact with mission control entirely for over 24 hours.24 Longer-duration flights are expected to increase stress and the severity of the displacement response. Proposed countermeasures include allowing more autonomy in planning work schedules, and greater involvement of mission control in pre-flight training exercises.24,26 This may also help to address the frequently reported feelings of sedentariness and monotony resulting from hypostimulation and restricted social contacts.29 The consensus is that more emphasis needs to be placed on personality and identification of behaviour predisposing to certain adaptations to prolonged confinement. Individuals’ insight into their own capabilities, mental endurance, and response to stressors must be taken into account.29 Biological markers such as polymorphisms involved in sleep-wake cycle, circadian rhythm and cognitive regulation should also be used to identify those at increased risk of neurobehavioural vulnerability to sleep restriction.24,30 Encouragingly, not all psychological changes experienced by astronauts are negative. Numerous astronauts report experiencing a “transcendental, religious experience or sense of the unity of mankind” while in space.31 This positive phenomenon enabled astronauts to experience change as normal and beneficial, and to believe that events would work out as well as could reasonably be expected.29 However, this salutogenic phenomenon is, in the majority of cases, related to the perception of Earth from space.29 With the longer duration flights to Mars, the inability to see Earth could have detrimental effects on psychological well-being.

**Surgery in microgravity**

Life-threatening surgical conditions that may arise without warning in healthy crew members include traumatic injuries, appendicitis, diverticulitis, cholecystitis and pancreatitis.32 As missions move further from Earth, telemetric medical support and traditional communications travelling at the speed of light will be greatly delayed. For example, two-way contact on Mars would take a minimum of 44 minutes, which will pose great challenges to real-time robotic surgery and support from mission control in medical emergencies.33 While no surgeries have yet been performed on humans in space, the first animal laparotomy was performed in 1967 and since then haemorrhage, large vessel repair and wound closure were not found to be significantly more difficult than during terrestrial procedures.34,35 However, restricted resources and limited crew medical training, including inability to provide basic perioperative and postoperative...
care, which still pose significant challenges. Immune dysregulation and the documented increased pathogenicity of bacteria in space could also greatly increase the likelihood and severity of postoperative infections. If significant operative complications occurred requiring critical care support, there would almost certainly be loss of mission or of life. Support for prophylactic appendicectomies and cholecystectomies is growing. Appendicitis and cholecystitis are common conditions and prophylactic appendicectomy has been mandatory for the Australian Antarctic Programme for those spending winter in Antarctica since 1950. No cases of cholecystitis or appendicitis have been documented in space thus far, but this is largely due to the relatively young age and lower BMIs of crew members, combined with intensive medical screening; future astronauts will likely be in less optimal condition and will undergo more lenient screening. Arguably, prophylactic surgery could be beneficial and necessary in preventing the catastrophic loss of mission or life; however, this is fraught with significant ethical issues. Having the surgery may become a significant advantage for candidates being considered for a position on a flight, leading to peer, corporate and public pressure to comply. Conversely, suffering operative complications may disqualify a candidate entirely from the flight. Regardless of whether this becomes mandatory, changes will need to be made to medical and surgical protocols to ensure mission success. Currently, one crew member receives limited medical training and has some minor surgical skills (such as suturing). At the minimum, future flights will need a physician astronaut with basic surgical skills and the ability to manage acute illness. Emergency physicians are likely the most suitable candidates for this position.

Conclusion
This past year proved monumental for space exploration, imparting an even greater sense of urgency to efforts to extend our habitat boundaries beyond Earth’s limits. The Mars Reconnaissance Orbiter identified hydrated salt minerals on Mars and SpaceX continued their success in developing fully and rapidly reusable launch vehicles that will drastically lower space flight costs. Perhaps most significantly, International Space Station astronauts consumed the first ever meal of space-grown lettuce, bringing the possibility of self-sustainable astronauts closer to reality. The uniquely challenging medical setting that space flight presents will undoubtedly further terrestrial medicine through spin-off technologies, such as telemedicine, and greater understanding of human physiology. However, if future missions are to be successful, it is clear that current medical protocols must change. At a minimum, emergency physicians must be included in all crews, prophylactic surgeries must be seriously considered, and greater efforts need to be directed into truly effective and affordable radiation countermeasures.

References
15. Cavanagh P, Licata A, Rice A. Exercise and pharmacological...


Introduction
Amidst the furore surrounding ‘anti-vaxxer’ campaigns, and the issues surrounding public funding of healthcare, the overworking of junior doctors, and the use of medical marijuana, a 15-year war has been fought behind the scenes in the world of science and medicine. The issue of access to and sharing of scientific research has become divisive. The open access (OA) movement advocates for freely accessible and reusable research, while traditional publishers claim copyright on the material they publish, since they absorb the costs of maintaining online repositories and expert review boards. Now, as more and more government grants require free and open access to the information provided by these articles, the issue is receiving more public focus. The OA movement has extended to medicine, focusing notably on science research and pharmacology, but also on the education of trainee doctors, with a surprising Irish influence.

For the scientist: open access research
The key battle that is being fought focuses on whether the sale of scientific knowledge in the form of journal subscriptions is valid despite reduced costs due to digitisation and the fact that much of this research has direct benefits to the public. One answer to this problem has been the advent of the OA philosophy, which espouses unrestricted access to research articles along with the rights to re-use these articles.\(^1\)\(^2\) Publishers assert that their subscription fees are legitimate because they provide the resources to publish these articles widely, they ensure high-quality research via a free-market approach, and they provide a long-standing reputation, conferring legitimacy to any papers published in their journals.\(^3\)

However, OA journals argue that restricting access to academic research that is already being funded from public grants is not only disingenuous, but also impedes progress and discovery. By putting information behind a paywall, only those individuals or institutions that can afford a subscription can use that article for their own research, creating a social hierarchy of access to information.\(^3\)

The OA movement has extended to medicine, focusing notably on science research and pharmacology, but also on the education of trainee doctors, with a surprising Irish influence.
Further complicating the situation, journal subscription fees have risen by more than three times the inflation rate over the last 30 years, despite a reduction in operating costs due to digitisation. In fact, the average annual price for a health sciences journal subscription is $1,694 USD, which is still far below the average for a chemistry journal subscription, which will cost an individual on average $4,942. It seems that the current journal publishing elite – only five companies, which publish 50% of all research – are taking advantage of their privileged status. Thus, in an effort to provide freely-accessible quality research to everyone, OA journals like PLoS and BioMed Central (as well as thousands of others) have sprung up and not only offer this information for free, but allow anyone to use the research, figures or data freely under Creative Commons licenses. This movement has also encouraged the development of OA-friendly research tools and platforms like Mendeley, ResearchGate, Overleaf, Figshare and others, which allow not only the free sharing of this information, but an OA approach to collaboration, leading to thousands of articles that would not otherwise have been produced.

In 2008, the US National Library of Medicine in the National Institutes of Health developed ClinicalTrials.gov, a repository of the results for every trial performed on every drug that is approved by the Food and Drug Administration in the US.

Of course, someone must cover the costs of OA publishing, so most OA journals charge publishing fees to the authors, thus putting the onus on the producer of the research (known as “Gold OA”). While this has the benefit of ensuring that OA journals are not inundated with requests to publish, it can at times be predatory, leading to exploitation of authors. For example, a number of vanity presses have popped onto the scientific landscape, leading to largely unreviewed papers and articles being published under the name of OA, but in fact lacking the necessary scrutiny that is required of quality scientific research. It also means that even if the OA journal is legitimate, well-reviewed and well produced, the Gold OA approach can limit what an early-career scientist or student can realistically publish because of a lack of funding.

For example, Elsevier, the third largest OA publisher, has fees ranging from $500 to $5,000 for its Gold OA journals. Further complicating the issue is that many OA journals accept manuscripts from a broad range of disciplines, leading to questions about the quality of the editorial process and how likely the ‘peers’ are to be from the same specialty.

The saving grace is that those OA journals which are well-established and have instituted legitimate peer-review systems are considered to have the same scientific quality and impact as subscription journals, especially in the field of biomedicine. In short, while OA is far from perfect, it provides a tenable and credible alternative to traditional subscription journals.

For the physician: open access pharmaceuticals

This push for open access is not isolated to the publishing of scientific research, but has also spread to the world of drug development. The information garnered from drug trials has always been the property of the development company, giving them the prerogative to disclose that information as they see fit. Of course, pharmaceutical companies will suppress or minimise the trials they perform that do not support the adoption of their drug, as this makes financial sense. However, the problem that arises is that these unpublished trials may have direct benefit to the general public and the scientific community. In 2008, the US National Library of Medicine in the National Institutes of Health developed ClinicalTrials.gov, a repository of the results for every trial performed on every drug that is approved by the Food and Drug Administration in the US. Even then, only 13.4% of all drug trials in the US were reported to ClinicalTrials.gov in a span from January 2008 to September 2012. The purpose was to provide OA for all trials, with complete reporting of side effects and complications, not just those that were most common, as decided by drug companies.

The need for this repository is clear – despite OA in the repository, the negative side effects of drugs are reported in published articles only 45% of the time. Although compliance with laws to submit data to ClinicalTrials.gov has improved, it is still far from ideal, especially considering that only summaries of the trials (not actual patient-level data) are submitted to the repository.

Pharmaceutical companies have a responsibility to provide any and all information to those to whom they advertise and sell, especially those physicians who will prescribe and recommend their drugs. In fact, there are additional benefits to providing the information in an open fashion. Jay Bradner of the Bradner Lab at the Dana-Farber Cancer Institute at Harvard Medical School developed JQ1, an anti-BRD4 chemical, which targets large solid tumours. However, rather than keep the molecule to himself and seek financial gain, he sent it out to his colleagues – up to 70 labs throughout the world.

Their contributions were small at first: one group performed crystallography to reveal the chemical’s structure; another recorded the chemical converting tumour cells back to normal cells. At this time, over 450 labs have used JQ1 in their own research and the amount of literature published about JQ1 has doubled every year for the seven years since they began sharing the molecule, leading to eight human clinical trials and more knowledge about their own chemical than could have been achieved by their own lab in that time.

Of course, the downside has been that in openly sharing both information and the chemical probes themselves, the venture has been an expensive lesson in sharing (since Dr Bradner’s lab covered the costs of distribution), despite the benefits that have been received from that sharing.
For the student: free open access medicine

Finally, the movement towards OA has even invaded the world of education, with a unique Irish influence. Free OA medical education (or medication), also known as FOAM, was first conceived in Dublin in 2012 (over a pint of Guinness) with the purpose of providing both an online curriculum and medical education that is freely available to all. It hearkens back to the Hippocratic Oath, which advocates for freely teaching medicine to all interested parties. It has been bolstered by the unique progress afforded by social media, with blogs, YouTube videos, Twitter feeds and Facebook pages dedicated to giving students the opportunity to access sophisticated resources providing asynchronous learning without having to spend anything (except a monthly internet bill). In fact, FOAM resources have become some of the most frequently visited medical websites on the internet, with KevinMD, Medscape and iTeachEM ranking among the top medical education websites, and blogs like Burnt Orange Scrubs, Life in the Fast Lane, and The Presenting Complaint among some of the most visited websites for medical students in the world. Conferences focused on FOAM have even begun to thrive, with the Social Media and Critical Care Conference (SMACC) now in its fourth year and being hosted in Dublin this year. In short, the OA approach has now made positive impacts in the world of medical education, providing quality resources to facilitate student learning and further entrenching the OA movement in a younger generation of physicians.

Conclusion

There are still some significant hurdles to completely adopting a free and open approach to research and medicine, especially when it comes to funding the publication of research. However, the benefits far outweigh the detriments; most notably, the increased rates of discovery, the provision of medical information to the public, and the delivery of high-quality education resources to any student hoping to improve their learning. As medical students, we have a duty to consider and ultimately adopt an OA approach, where we consider sharing our own research and investigation. It is only with this perspective that we can advance our professional development and improve the quality of care of our patients.

References


3. Marincola E. Elizabeth Marincola: Advance science with open-access publishing [Internet]. TEDMED. 2013. Available from: https://www.youtube.com/watch?v=9ztwFtF-lgA.


Empathy is the new black

AMELIA REID examines changing attitudes to the art of communication in medicine.

In medical practice today, increasing attention is being given to the art of communication, to expressing (and better still, feeling) empathy, and viewing a person as more than their physical or psychological presenting complaint; that is, moving from a dehumanising approach – as exemplified by describing a patient as ‘the appendicectomy in bed 4’ – to an understanding and acknowledgement of the person and his or her experience, values, feelings and personal situation.

There has been a trend away from the paternalistic approach of the doctor, to a more collaborative, ‘patient-centred’ approach to consultation. A more egalitarian approach encourages the physician to see patients as having agency and a legitimate role in decisions about their treatment, to follow their lead, and to appreciate experiences and problems from the patient’s point of view – including understanding their expectations and life circumstances more broadly.1,2

Communication is especially sensitive and difficult in the context of palliative and end-of-life care for the physician, the patient and the patient’s family. For this reason, discussions about dying, and the patient and family’s wishes, occur infrequently.

Malpractice in medicine

With medicine becoming increasingly litigious, malpractice claims provide one window into the impact of poor communication. Levinson et al. have found that physicians who have not had legal claims made against them are more likely during their consultations to use humour, ask patients for their opinions, spend more time
with patients (than their sued colleagues), educate patients about what to expect with a given diagnosis and treatment plan, and encourage them to ask questions. Similarly, the emotional states of patients are just as important as their physical states, with individuals citing a lack of clear explanations, sympathy or honesty, or a reluctance to apologise, as further reasons for pursuing legal action against a doctor. There has been a shift, at least in principle, in many major hospitals from defensive denial and legal protection to admission of fault, apology, and compensation.

Similarly, levels of depression have been shown to decrease when the doctor communicates clearly and sympathetically the severity of a diagnosis, the life expectancy, and the impact a diagnosis is likely to have on someone’s life. This is partly because a protracted legal battle is not only traumatic for the patient or family, but also very expensive and distracting for the hospital. Taking a non-punitive approach also creates an environment in which a doctor is more likely to disclose an error, rather than trying to conceal or deny it. The majority of patients and physicians favour knowing what has gone wrong and why. Additionally, many hospital policies advocate full disclosure, investigation, explanation, apology, and some form of compensation. Unfortunately, however, these approaches are still uncommon.

Assessing patient satisfaction by way of malpractice claims is, however, focused on reputational and financial risk. It is one means of retrospectively assessing a person’s psychological state, and level of comfort and satisfaction with consultation and treatment, but is by no means ideal. It is the result of a failed procedure or medical error and/or poor handling of a case, and does not necessarily speak to the ethical dimensions of honesty and the physician’s care for the patient.

A more appropriate measure is to examine the person’s emotional state and responses during or immediately following a consultation. Evaluation of this approach suggests that patients experience lower levels of anxiety when they are prepared for a diagnosis, have the people they want with them when they are told the diagnosis, receive written information as well as clear verbal communication on the day of the consultation, have time to ask questions and discuss how they are feeling, and to be reassured.

In one study, even one minute of compassion shown by the physician in a consultation was shown to decrease the levels of anxiety participants felt. Similarly, levels of depression have been shown to decrease when the doctor communicates clearly and sympathetically the severity of a diagnosis, the life expectancy, and the impact a diagnosis is likely to have on someone’s life.

Communication at the end of life

Communication is especially sensitive and difficult in the context of palliative and end-of-life care for the physician, the patient, and the patient’s family. For this reason, discussions about dying, and the patient and family’s wishes, occur infrequently. When they do, there are serious shortcomings. Multiple studies have identified key themes of importance to dying patients by interviewing the patients themselves, their family members and physicians. These focused on what was important to patients and whether the same concerns applied equally to their doctors and other caregivers. These themes included being straightforward with all the information imparted, using clear and understandable language, having a willingness to discuss dying and to use the words ‘death’ and ‘dying’ as opposed to using euphemisms, delivering news sensitively, choosing an appropriate time and place to break bad news, listening to patients, and encouraging questions. This requires the physician to balance the need to give honest and distressing advice without broaching a discussion of death when the patient is not ready, and potentially causing greater distress or hopelessness.

Apart from the emotional and psychological effects, poor communication has ramifications regarding the choice a patient makes about their treatment. When a patient has an accurate understanding of their diagnosis and prognosis, they are more likely to choose a therapy that focuses on comfort and palliative measures rather than life-extending interventions. The latter patients often accept aggressive and distressing interventions, which, when controlled for known prognostic factors, do not increase their survival rate.

A programme of purposefully driven cultural change, involving everyone from the consultants to the cleaners, drove expectations of professional behaviour using evidence, videos, workshops and other strategies.

Teaching communication and empathy

Most medical schools now supplement the academic record and the standardised aptitude tests with some form of interviewing in an effort to identify those candidates who have, or at least exhibit, qualities such as motivation, ethical values, resilience, maturity, and social and communication skills. Variations such as the ‘multiple mini interview’ (MMI), which use multiple stations to better assess a candidate’s ‘soft skills’, are becoming more common. A typical MMI might use a series of trained interviewees or actors from diverse backgrounds, and videos, which candidates are asked to interpret. All of these measures are designed to select for high-demand courses those students who it is hoped will be well-rounded, empathetic and collaborative practitioners.
However, notwithstanding these efforts to filter out unsuitable applicants and select those with the most promising interpersonal as well as academic skills, effective and empathetic communication is not guaranteed. In fact, it has been shown that levels of empathy decline as medical students progress through medical school, jeopardising the quality of care they are likely to be able to offer as practising doctors.\textsuperscript{12}

Reaching a consensus on the definition of empathy has been difficult. However, most agree that to be empathetic one must possess interpersonal sensitivity and be able to put oneself ‘in the patient’s shoes’.\textsuperscript{13} There is, however, no consensus on whether empathy should be defined as an emotional or a cognitive quality, and whether it is a skill that one can acquire or is an attitude one possesses. Some view empathy as an innate quality, an aspect of personality, and therefore difficult to teach or to predict.\textsuperscript{14}

A well-known effort to increase ‘patient satisfaction’ is that of the Cleveland Clinic in the USA. Of the range of patient satisfaction scores, communication was particularly poor: 14% for doctor communication skills and 16% for nurse communication skills. In the author’s words:\textsuperscript{15}

“Patients did not want to be in the hospital. They were afraid, sometimes terrified, often confused, and always anxious. They wanted reassurance that the people taking care of them really understood what it was like to be a patient. Their families felt the same way. Patients also wanted better communication: they wanted information about what was going on in their environment and about the plan of care; they wanted to be kept up to date even on minute activities. And they wanted better co-ordination of their care. When nurses and doctors did not communicate with one another, patients were left feeling that no one was taking responsibility for them”. (p 3)

A programme of purposefully driven cultural change, involving everyone from the consultants to the cleaners, drove expectations of professional behaviour using evidence, videos, workshops and other strategies. The intention was to ‘make everyone a caregiver’ and to redesign the operations around patient needs rather than organisational efficiency or clinicians’ convenience. From 2008 to 2012, the hospital’s ranking on a US government patient survey of 4,600 hospitals rose from the 55th to the 92nd percentile.\textsuperscript{15} A caution, however, is needed. The risk in teaching communication strategies and skills is that the health professional simply learns some new phrases and uses them without feeling, either because the feeling is lacking – that is, they are not able to show empathy (which, in itself, raises some serious questions about their suitability to practise) – or because time, exhaustion and practical demands override their inclination to communicate well.

References


The current migration to Western Europe is unparalleled. In the summer of 2015, Europe experienced the highest influx of refugees since World War II. In 2015, an estimated 60 million people were displaced globally, with approximately 50% of these people under 18 years of age. The main reason for this large influx is that Syria has become the world’s top source of refugees as a consequence of the Syrian Civil War. In addition to the Syrian refugees, large waves of migrants and refugees from other countries in Asia, Africa and the Balkans are migrating to Europe in the hopes of escaping conflict, bad governance and poverty.

Response in the European Union

In response to this large wave of refugees, many European countries have agreed to accept migrants and refugees. The number of asylum applications received in 2015 by European Union (EU) nations more than doubled compared to 2014. In 2015, there was an estimated total of 1,117,890 asylum applications from stateless people across the EU. The majority of applications are from people originating from Syria and Afghanistan. Germany is currently the recipient of the largest number of asylum applications – with 476,620 applications received in 2015 – followed by France, Sweden, Italy and the United Kingdom. This influx of migrants and refugees to Europe has, however, created tension within the EU. Many countries do not agree to what extent Europe as a whole should respond to the refugee crisis due to the political and economic implications of taking in large numbers of migrants and refugees. While many nations support the EU quota plan to relocate refugees currently in Italy and Greece, other countries like the Czech Republic, Slovakia, Romania and Hungary have rejected the plan (Figure 1). Ireland has taken a more moderate approach, reflecting its size and means. The Irish Government has established an Irish Refugee Protection Programme, in which Ireland has agreed to accept up to 4,000 displaced persons in response to the current migration crisis. However, Ireland estimates the cost of hosting migrants to be €12 million per 1,000 migrants. Therefore, taking in large numbers of migrants and refugees could potentially put enormous strain on economic resources.

A global responsibility

JESSICA SUDDABY examines the challenges and opportunities involved in refugee and migrant healthcare in Europe.

FIGURE 1: EU Resettlement Plan. NB: The UK and Denmark are not taking part. Source: Dept. of Foreign Affairs, European Commission.
In addition to the Syrian refugees, large waves of migrants and refugees from other countries in Asia, Africa and the Balkans are migrating to Europe in the hopes of escaping conflict, bad governance and poverty.

Migrant and refugee healthcare
In addition to political and economic concerns, migrant and refugee health has become a growing issue. Its importance on the global health radar has become evident: the “right to health of refugees and other displaced people” was declared one of five key areas of global health on which the M8 Alliance, a collaborative network of academic institutions with 23 members from 16 different countries, called for action at the 2015 World Health Summit (WHS) in Berlin. In the statement, the M8 Alliance determined that the immediate health problems of refugees, and the long-term mental health and well-being of these millions of men, women, and children, were neglected areas of global health that must be addressed in co-operation with refugee agencies and the humanitarian sector. The following discussion is based on major topics discussed at the Migrant and Refugee Health workshop at the WHS 2015.

Infection and disease in refugee camps
One major concern associated with the overall health of migrants and refugees is disease in refugee camps. The United Nations High Commissioner for Refugees (UNHCR) was not prepared for a refugee crisis of this scale. Thus, many refugee camps are crowded and undersupplied, providing conditions for the onset of chronic malnutrition and the spread of infection. Measles, hepatitis A, leishmaniasis, poliomyelitis, meningitis and scabies, diseases that have been virtually eradicated in developed countries, have spread through vulnerable populations in Syria and refugee camps in neighbouring countries. In addition, migration itself contributes to higher infection rates as vectors move further, faster, and in greater numbers than ever before. One route often used by migrants is from East Africa, through Sudan and Libya, to North Africa and eventually to Europe. This has led to the introduction of microbes rarely seen in developed countries such as *Borreliac recurvata*, *Rickettsia prowazekii*, and *Bartonella quintana*, which cause infectious diseases such as louse-borne relapsing fever (LBRF), epidemic typhus, and trench fever, respectively. Thus, it is important to address the issues of crowding and poor hygiene in these camps to reduce the spread of infectious diseases.

Cultural barriers to healthcare for migrants and refugees
Informal barriers to health for migrants and refugees are largely cultural and include inadequate language services and cultural training. For instance, in Ireland there is a translation service called Rotext; however, many healthcare professionals are not even aware of it. A great deal can be done on a healthcare professional level to improve language services for refugees and migrants by having translators who can aid in the communication between the physician and the patient. It is important that the translator does not merely translate literally, but attempts to communicate some of the feelings and nuances that would otherwise be lost in translation, so that the physician can better serve the patient. It is also critical to provide cultural training for healthcare professionals working directly with migrants and refugees. The awareness of the cultural determinants of health – including shared conventions, understandings, practice, ideas, symbols and artefacts of a given culture – has impacts on clinical care and informs clinical practice. In addition, by providing language services and cultural training for migrants and refugees, informal barriers to healthcare can be reduced. In Germany, the government spent €2 billion on
language training for migrants and refugees, a significant step in reducing cultural barriers.\textsuperscript{21}

Although the current refugee crisis presents many challenges for European health systems, in many ways it can be viewed as an opportunity for European nations to test the strengths and weaknesses of their own health systems. At the WHS 2015, the M8 Alliance took clear stances on the issues of migrant and refugee healthcare in Europe. The M8 Alliance asserted that refugees should have access to healthcare services equivalent to that of the host population.\textsuperscript{10} Refugee policies should prioritise the integration of new refugees into the new country’s health and social systems.\textsuperscript{31} In addition to the immediate health concerns discussed, they also declared it critically important to be aware of the long-term mental health and well-being of the millions of men, women and children that have been displaced. This will require action from a healthcare perspective as well. Ultimately, the M8 Alliance feels that the migrant and refugee crisis in Europe is a global health issue that requires the co-operation of the international community and humanitarian sector at large to respond in a co-ordinated manner.

References


THE FUTURE OF SURGERY OR
a robotic waste
of money?

SAMY BESHAY wonders if robotic surgery is here to stay, or just an expensive surgical white elephant.

Introduction
The past few decades have seen extensive advances in surgical techniques as technology adapts to the ever-demanding needs and expectations of patients. One such medical advance is the use of robotic arms and devices to assist in surgery, including one of the most common surgical robots used in gynaecological surgeries, the da Vinci® Surgical System (Intuitive Surgical, Inc.; Sunnyvale, CA, USA). The Mayo Clinic defines robotic surgery as the “use of advanced surgical tools to perform minimally invasive surgery for complex procedures with increased precision, flexibility and control compared to traditional surgical methods”. Initially, robotic surgery was introduced to compensate for limitations in human dexterity and to reduce surgical complications. However, a majority of the potential benefits of robotic surgery are not being realised to the fullest extent in Ireland as a result of the lack of acclimatisation into surgical theatres. The high cost of operating and maintaining a robot, as well as the extensive training involved, have often outweighed the potential benefits for its utilisation in the wider context of surgery. Therefore, the question arises as to whether the use of robots in surgery is here to stay for the long term or is a waste of money.
**Cost-effectiveness analysis**

The Health Service Executive (HSE), which runs the public healthcare system in Ireland, has determined that the clinical benefits of robotic surgery compared to traditional methods are negligible and not cost-effective. Performing surgery using the da Vinci® Surgical System has been found to consistently cost more than traditional laparoscopic procedures, operating at an approximate cost of €1.45 million with hundreds of thousands more in annual maintenance fees and licensing agreements. In addition to these high fixed costs, robotic procedures are marred by increased operating times, which increase the overhead costs of a hospital.

In the United States, the surgical system is used for a wide range of operations in both urology and gynaecology. However, for nearly all operations, robotic surgery consistently costs several thousand dollars more when compared with local best practice. A recent study published in the *Journal of the American Medical Association (JAMA)* found that robotically assisted hysterectomy was not more efficient compared to the traditional laparoscopic methods, and the only notable variation between the two was the substantially increased cost associated with the robotic technology.

In a prospective cohort study by Desille-Gbaguidi et al., robotic surgery was shown to cost 2.6 and 2.7 times as much as laparoscopy for endometrial and cervical cancers, respectively. The significant increases in cost associated with robotic surgery were attributed to the time and labour of preparation, anaesthesia, incubation and equipment set-up, which increased overhead costs and reduced the availability of the operating room, with a non-significant reduction in average hospital stay. However, upon performing further analyses, it was shown that reducing hospital stay duration by one day in a given patient, and performing two daily operations using the robot, may allow robotic surgery to be the most cost-effective treatment option.

The increased cost of robotic surgery is echoed in a case-control study by Sarlos et al. in the context of hysterectomy. Another study found that robotic surgery increased operating time, leading to an increase of approximately €2,000 when compared to laparoscopy. While Desille-Gbaguidi et al. reported set-up time to be a major contributor to the cost of the da Vinci® Surgical System, Sarlos et al. determined that preparation time at their practice had decreased with each successive surgery. With improved training, costs associated with set-up may be minimised. The robotic system reportedly offers surgeons better ergonomic control and a wider range of motion when compared to current gold standards, and greater perceptual awareness, but it was disadvantaged by preventing access to the patient during the procedure.

**Surgical training involved with robotic technology**

While experienced surgeons cannot readily use a robotic system, training curricula that integrate didactic and experiential sessions exist for all surgical disciplines, particularly within gynaecology and urology. Expertise-based trials have shown that the learning curve for experienced open and laparoscopic surgeons is approximately eight to 12 cases, assuming a completion of 100 previous surgeries. For a naive surgeon, it is estimated that 80-100 cases are needed before sufficient expertise is achieved with the robotic system. Hanly et al. had also demonstrated that with more experience, set-up time decreased by 30% and operative time lowered by 20% at their practice, minimising the elevated overhead costs associated with a robotic surgical system. Moreover, specifically training an Irish surgeon on the robotic technologies is arduous and tedious, often requiring a visit overseas to the United States for training in multiple facilities. The surgeon will also require mentor supervision during his or her first 15 to 20 procedures with the robot to gain the essential knowledge and expertise, after he or she returns to Ireland, a process that can take several months or even years. This not only decreases the amount of surgeries that an Irish surgeon will perform, but also increases waiting times and limits the amount of surgeons available at a given hospital.

**Context of Irish healthcare – integration into Irish hospitals**

The implementation of robotic surgery has been severely limited in Ireland where there are only three systems in the entire country: one actively used in the public healthcare system at the Cork University Maternity Hospital and two in the private sector. These surgical robots are primarily used in gynaecological care in hysterectomy procedures. Regardless of whether or not the use of a surgical robot has improved patient outcomes in gynaecological surgeries, it is undoubtedly a heavy burden on the publicly funded healthcare system in Ireland. A study by Teljeur et al. found that in Ireland, the cost of a robot-assisted hysterectomy is nearly €3,300 more than the existing mix of both open and traditional laparoscopic surgery. In countries such as the United States, where the da Vinci® Surgical System is thriving with over 2,000 robots in use, it is simple to maximise a robot’s use. A high volume of patients ensures that the substantial investment cost of the robot and its lifespan are capitalised upon and that the costs of licence agreements are compensated for. However, in smaller countries such as Ireland, where the demand is much lower and there are significant constraints...
on the public healthcare system, it is much more difficult to capitalise on the investment in a surgical robot. The single surgical robot in the Irish public healthcare system is used primarily for hysterectomies and averages around 100 cases per year, a quarter of the number of cases a typical robot in the United States would see.12

Robotic surgery in Ireland has not fully developed and there is very little infrastructure to support its development.

Possible suggestions to increase this number would include allowing the robot to perform non-gynaecological procedures, or putting a referral system in place that allows tertiary facilities to access the robot. In either sense, robotic surgery in Ireland has not fully developed and there is very little infrastructure to support its development.7

Conclusion

Although robotic surgery may improve the functional design and visualisation for surgeons, in the patient-centred world of medicine, if it does not equate to more efficient outcomes, it is not practical to use in the wider context of surgery. Moreover, in times of scarce resources, healthcare investments should be directed towards interventions that demonstrate both positive patient outcomes and cost-effectiveness. As Prof. Lord Darzi, an RCSI graduate and world-renowned surgeon and inventor of surgical methods, once stated regarding the efficiency of robotic surgical techniques: “Healthcare systems all over the world are facing completely different pressures compared with 20 years ago ... the whole way in which we provide healthcare has got to change. The world is crying out for low-cost, high-impact technologies that can be employed widely across the globe”.10 For the time being, it is evident that more research is required before robotic surgery is fully integrated into the Irish healthcare system. As it stands, robotic surgery is, indeed, a waste of money.

References

Introduction
In an ever-evolving healthcare environment, industrialised countries are constantly faced with new and difficult challenges. Foremost among these is the changing age profile of western populations. Against this backdrop, there is a strong argument for a single specialty assuming the role of perioperative physicians, a concept much discussed in anaesthetic conferences. There are pros and cons to anaesthetists filling the role – from a healthcare perspective and from the perspective of the specialty of anaesthesia. However, their unique skillset makes them ideal candidates, if certain practical barriers can be overcome.

An ageing population
In most industrialised countries life expectancy is increasing, while the number of live births is decreasing, with the result that in these countries the population is ageing. The most recent census showed that Ireland is no exception, with an increase in the number of over-85s and a relative decrease in the under-14 category. The United States faces a similar situation. Because people are living longer with existing chronic conditions, the ageing patient tends to have more comorbidities, making their management more complex. Patients who are higher risk due to their age or comorbid diseases have the highest mortality rates.
This results in a rise in the number of high-risk patients presenting for surgery. To complicate matters further, there is increasing pressure to reduce the number of surgical inpatients and to perform more surgical procedures as day cases. Postoperative complications have been shown to negatively impact long-term survival more than either comorbid disease or intraoperative adverse events; therefore, it is imperative that perioperative care also extends for a period beyond discharge. In this context, it is clear that patients need optimal preoperative management in order to maximise their chances of a positive outcome.

On this background, there is a strong argument for a single physician taking the lead in the care of the patient, from the decision to undergo surgery until a specified time postoperatively. Mantz et al. (2010) observed that “perioperative care may have a major impact on long-term postoperative mortality and major complications in surgical patients by decreasing the rate of individual decisions”. This is the proposed realm of the perioperative physician.

Streamlining of medical practice in the perioperative period is reported to improve “co-ordination and management of surgical patients and has been shown to increase quality, reduce complications, ... and improve the patient’s perception of the surgical experience”.

The perioperative physician

The perioperative physician takes charge of the patient from the time of the decision to have surgery, managing the patient through the preoperative phase, in which the health of the patient is optimised and comorbidities are controlled as best as possible, and then through the surgery. The same physician follows up after discharge to monitor recovery, ensuring that day cases do not become re-admissions and that postoperative complications are kept to a minimum. This specialist is not a lone doctor, but the co-ordinator of a multidisciplinary team, membership of which will vary based on individual patient needs. There is evidence that a single co-ordinator for the perioperative period improves the co-ordination and management of surgical patients, and has multiple benefits to the patient and hospital in terms of cost reduction, positive outcome and patient satisfaction. In addition, a single specialty performing the role leads to standardised practice, which results in fewer mistakes. This streamlining of medical practice in the perioperative period is reported to improve “co-ordination and management of surgical patients and has been shown to increase quality, reduce complications, increase the efficiency and cost-effectiveness of perioperative care, and improve the patient’s perception of the surgical experience”.

An example of this process in practice is the American Society of Anesthesiologists’ Surgical Home model, in which a single physician co-ordinates a patient-centred, multidisciplinary team to guide the patient throughout the entire surgical experience. Reviews of this model of care are heartening in that they report positive outcomes in many areas, including patient satisfaction and cost reduction. Longer hospital stays increase the healthcare burden in a number of ways. The longer a patient remains in hospital, the higher their chances of developing a hospital-acquired infection, which in turn increases mortality. Increased length of stay for an individual patient reduces the amount of bed space available for new patients, as well as increasing the financial burden on the healthcare system. Limiting the amount of time patients spend in hospital by proactively avoiding preventable complications reduces the financial burden on healthcare systems, as patients require fewer re-admissions and, ultimately, fewer hospital days. Various specialties have already offered their services privately as perioperative physicians. Here we will discuss the merits of the anaesthetist performing the role.

The anaesthetist as a perioperative physician

The anaesthetist already takes part in perioperative medicine. While the surgeon’s primary concern is dealing with the disease process, the anaesthetist’s concern is keeping the patient alive for the duration of surgery and managing the patient’s physiological response to the insult, both intra- and postoperatively. The anaesthetist already needs to be intimately familiar with the patient’s medical history in order to provide optimal analgesia and to predict possible complications during surgery; becoming involved in the care of the patient from an earlier stage and taking responsibility for their management heightens pre-operative knowledge of the patient and their medical history. This in turn aids the anaesthetist in avoiding complications intra- and postoperatively, while making them the most suitable physicians to undertake post-surgical follow up. Anaesthetists’ roles as intensivists make them ideal candidates. On a daily basis they manage very ill patients with multiple comorbidities, with the result that they have a wealth of experience managing complex cases and optimising physiological function in patients who require intricate medical management. As part of this role they liaise with members of virtually every specialty in the hospital, managing patients as part of multidisciplinary teams. The perioperative physician is merely an extension of this role. In addition, some feel that the unique training, skills and experience of anaesthetists mean that they are natural candidates for the role, more so than any other specialist. They already have crucial experience in risk assessment and quality improvement, areas vital to the field of perioperative care; the importance of risk assessment in particular cannot be overestimated, and has been highlighted as a means of minimising surgical risk through anticipation of patient-specific complications and optimisation of organ function prior to surgery. Advocates for the concept of anaesthetists expanding to the role of perioperative care feel that they should embrace the role, and that not to do so would be to limit the scope of practice and sphere of

RCSI | Smj perspective
influence of the anaesthetist in the medical environment. On the other hand, if anaesthetists were to take on the role of perioperative physician, it could mean a loss of focus in their current role as anaesthetists, intensivists and pain managers, potentially detracting from care in those areas. Compounding this, a recent report by the College of Anaesthetists of Ireland revealed significant shortages of manpower at all levels, from specialist anaesthetist trainees to consultant, and an over-reliance on non-training NCHDs to run services. Expanding the role of an already stretched service to include broader perioperative care may place too much strain on an already overloaded specialty. Anaesthetists would add significant value to the healthcare service as perioperative physicians, but only if sufficient resources were made available to make further positions available at all levels.

**Practical issues**

There are a number of practical issues that could come into play in expanding perioperative care. Clear definitions of where the role begins and ends would need to be agreed upon in order to optimise patient care. Follow-up of patients postoperatively by the perioperative physician is also a difficult question, particularly in the ambulatory setting, as the speed of recovery is bound to be quite variable. This could create an unsustainable care burden if a large number of patients required extended postoperative management. The importance of developing objective criteria and the need to develop evidence-based guidelines in order to receive certification, are crucial to developing the role. Currently, there is no training scheme or college that covers the full scope of the perioperative physician. It is necessary to define what core knowledge, skills, and experience are expected of the perioperative physician, and at what stage of the training, from basic to advanced, the competencies should be achieved.

**Conclusion**

In the context of an industrialised country with an ageing population and pressure to increase the number of surgical procedures as day cases, there can be little doubt as to the value a perioperative physician would provide to all parties involved. There are compelling arguments for anaesthetists to take on this role, not least as it would be an expansion of their current role in surgical care. There are a number of practical issues that would need to be resolved in order to facilitate incorporation of the role into the perioperative process, but it is certainly an idea that merits further exploration.

**References**

THE BLUNT TRUTH: can marijuana fund better healthcare?

HUGH McGOWAN looks at the financial and ethical implications of legalisation of marijuana.

Introduction
Marijuana, also known as cannabis, consists of dried leaves, stalks, flowers and seeds of the *Cannabis sativa* plant.\(^1\)

\(\Delta^9\)-Tetrahydrocannabinol (THC) and cannabidiol are the primary active components in cannabis and are thought to act on cannabinoid receptor sites CB\(_1\) and CB\(_2\) to produce psychoactive effects on mood, perception and psychomotor performance. Cannabis plants contain over 60 cannabinoids, which act additively, synergistically, or antagonistically with THC and cannabidiol, modifying the drug’s effects.\(^1,2\) To determine whether legalising marijuana could provide adequate funding for addiction services, this paper discusses available literature pertaining to the financial benefits, health implications and societal impact that legalisation has, paying particular attention to Colorado, USA, where the effects of legalisation can be observed and used to estimate the effect it would have in Ireland.

Medical uses
Claims exist that cannabis can effectively treat numerous diseases; some of the potential uses include treatment of muscle spasticity in multiple sclerosis (MS), as a neuroprotective agent against neurodegenerative diseases, in the treatment of chronic pain, in the treatment of cancer, and in a palliative setting.\(^3,12\) The illicit uses of marijuana are thus not the only considerations when looking at the issue of legalisation.

Reducing spasticity in MS sufferers with cannabis has had positive results in placebo-controlled trials, but is accompanied by acute cognitive effects as well as dizziness, nausea, headache and fatigue.\(^3,5\) Studies of patients with MS using cannabis also showed a decrease in cognitive performance compared to non-users.\(^6,7\) In an attempt to circumvent side effects and enhance therapeutic effects, oromucosal and oral preparations of THC and cannabidiol have been developed to treat muscle spasticity in patients with MS, and have shown positive results clinically.\(^8\) In Ireland, MS advocacy groups successfully campaigned for a change in the Misuse of Drugs Act 1977 to allow cannabis-based drugs to be made available by prescription.\(^9,10\) Using cannabinoids as neuroprotective agents has shown potential *in vivo* and *in vitro* for epilepsy, and may be effective in treating neurodegenerative diseases, including Huntington’s, Parkinson’s, and Alzheimer’s diseases.\(^4,11,12\) Use of cannabidiol and other cannabinoids that act as CB\(_2\) receptor agonists could inhibit the inflammatory processes involved in neurodegenerative diseases.\(^13\) In Alzheimer’s disease, there is evidence that cannabidiol prevents degenerative pathways that lead to neuronal death; however, these patients may be concerned by the prospect of cognitive decline as seen in MS trials.\(^6,7,14\)

The use of cannabinoids as anti-proliferative and apoptogenic agents has shown promise against a variety of tumour types. There is some evidence that cannabinoids can specifically target tumour cells, making them exceptionally desirable for use as anti-cancer agents. Palliative uses of cannabinoids in cancer and other life-altering conditions increases the profile of cannabis-based drugs as potential therapeutic agents.\(^15\) Studies investigating the use of marijuana to treat pain are subject to intense scrutiny.\(^16,17\) Some conclude that there is little or no benefit in using cannabis over conventional pain medication and that the psychological side effects are unacceptable;\(^18\) however, cannabinoids have the potential to act synergistically with opiates and benzodiazepines to allow for a reduction in doses, limiting the associated side effects of these drugs.\(^4\)

Although not a comprehensive list of the possible medical indications of marijuana-based medicines, the above examples illustrate the potential benefits that may exist. Further research is needed to isolate and fully develop selective molecules targeting the endogenous cannabinoid system to balance therapeutic effects with side effects.\(^4,11,12,18\)
Impact of substance use

In Ireland, arguably the most important public health concerns are associated with the use of alcohol and tobacco, both legally available to the adult population. The cost of alcohol to Irish society is in excess of €3.5 billion per year, including €1.2 billion across a range of healthcare services. Alcohol is the most common substance for which addiction treatment is sought in Ireland. Just as with alcohol, driving under the influence of cannabis is associated with a riskier driving style and increased reckless behaviour; therefore, legalisation of cannabis could easily result in an increase in dangerous driving and road traffic accidents, with an associated increase in hospital admissions. The use of tobacco and marijuana are strongly linked in young people, with use of one increasing the likelihood of use of the other. Smoking is a major cause of morbidity, costing those who smoke an average of 10 quality years of life, and is responsible for one in 10 deaths. The average treatment cost in Ireland for a smoking-related illness is €7,700, with an estimated health expenditure on smoking-related illness of €500 million in 2009. Studies show that young adults perceive quitting smoking tobacco preferable to quitting marijuana, and that the desire to quit one does not correlate to the desire to quit the other. The likelihood of smoking tobacco is increased if one’s mother smoked while pregnant, and there have been suggestions of increased probability of marijuana use due to enhanced receptor expression in the foetus, which contributes to addiction in later life. The propensity for users to continue using cannabis, and for this use to increase the likelihood of future generations using cannabis, is a cause for concern, as it could potentiate a rise in consumption levels over time. Studies show that of those who experiment with marijuana, 9% become addicted, increasing to almost 17% if marijuana use begins in the teen years, and up to 50% if it is smoked daily.

Quitting is made more difficult due to the low cost and high availability of the drug, even though withdrawal is less severe than with other drugs. A survey of young people aged 15 to 24 in Europe discovered that 42% of Irish participants had used cannabis, with an EU average of 31%. Some 72% of Irish participants considered it easy to obtain cannabis, and 25% believed that regular cannabis use posed no health risks. Marijuana use has been shown to influence the academic achievement of users and is linked to impaired cognition, memory, and problem solving, lower levels of life satisfaction, lower IQ (with frequent adolescent use), and increased risk of chronic psychosis where predisposition exists. Although it is difficult to ascertain the far-reaching effects that some of these impairments could impose, it is certain that there would be direct demand on the healthcare system as a result of increased prevalence of psychosis in the population.

Current addiction treatment

In Ireland, the three substances for which addiction treatment is sought most are alcohol, marijuana and heroin. In 2011 cannabis overtook heroin as the second most sought addiction treatment. Treatment for alcohol addiction consists of multi-tiered intervention strategies, ranging from identification of the problem and providing advice to reduce harm, to provision of specialist healthcare from multidisciplinary teams. Due to the complex nature of alcohol addiction, and high levels of comorbidity that accompany it, treatment costs escalate as severity increases. However, there is evidence that alcohol addiction treatment results in savings to the healthcare system of five times the amount that is initially invested. Quitting marijuana without formal treatment is associated with increased use of alcohol and tobacco, but not with uptake of new substance use. Simple interventions such as motivating users to quit by highlighting usage-related problems has been shown to significantly increase the chances of a permanent change in behaviour in a study of young women aged 18 to 24, particularly where there have been previous attempts to quit. It is reasonable to assume that such interventions would produce similar effects in males. The potential for this form of intervention to have low associated costs, and for it to be available from frontline services such as GPs and addiction helplines, has considerable appeal.

Potential revenue

Financially, there is the potential benefit of tax revenue from the legalisation of marijuana. In 2012, cannabis herb, plants, and resin received by the forensic science laboratory in Ireland for testing was valued at €71.8 million, accounting for over 60% of the value of controlled drugs reported by the laboratory. Annual costs for tackling drug crime in Ireland are approximately €30 million, only a fraction of this being spent on marijuana. In the 2014 tax year, the state of Colorado generated $34.8 million USD through application of sales taxes and licensing fees for medical and retail marijuana. In 2011 Ireland had a population of 4.5 million people; similarly, in 2010 Colorado had an estimated population of five million. The comparable demographics in terms of population, age and gender profiles mean that it could be possible to generate similar revenue in Ireland.
Results of legalisation

Direct observation of the effects of legalising marijuana is an invaluable tool in determining whether it is advisable to legalise marijuana in other areas. Since the legalisation of marijuana in Colorado, the perception of risk associated with the use of marijuana has decreased compared to states where medical marijuana is not available. The changing attitudes towards risk are seen in the increase in levels of risky use, particularly among males. Availability of the drug legally has increased the odds of use to 1.92 times the usage seen in prohibition states. Before legalisation of marijuana in Colorado, the number of fatal car crashes where the driver tested positive for marijuana was decreasing, but it began to increase after legalisation. No equivalent increase was seen in prohibition states. In Colorado the use of marijuana increased after commercial legalisation; however, introduction of medical marijuana resulted in no significantly increased use due to limited patient numbers qualifying for prescriptions. The usage by adolescents was also seen to decrease where medical marijuana was available, possibly due to an association with the chronically and terminally ill.

Conclusion

Legalising marijuana to pay for addiction treatment is a stopgap measure. Development of cannabis-based drugs that minimise psychological impairment and psychoactive properties has considerable appeal, and creating avenues for research and regulation is preferable to legalisation permitting herbal preparations of unknown concentration. Legalising marijuana for recreational use introduces an addictive and intoxicating product, which impairs cognitive function, to the general public. Significant costs are already incurred by society due to the use of alcohol and tobacco, and as such the introduction of a new addictive agent makes little sense. Factoring in the rising requests for cannabis addiction treatment, which is already the second most requested addiction treatment in Ireland, arguments for legalisation are significantly undermined, with the prospect of commercial availability threatening to further exacerbate the problem. Although the revenue that would be generated is potentially significant, a fine balance would be required to prevent the associated health and safety concerns, rendering any income generated obsolete.

References


Committed to sport

DANIEL O’REILLY interviews Dr Michael Webb, Medical Director of Ulster Rugby.

Dedicated to the team

Dr Michael Webb is the Medical Director of Ulster Rugby and an assistant team doctor to the Ireland senior rugby team. He is the current Chairman of the Pro12 Doctors Group and has worked extensively as a team doctor within rugby for both the Ulster and Ireland teams at all levels since 2000. He is also a part-time general practitioner in Newtownards, Co. Down.

How did you get involved in sports medicine in the first place?

I suppose sport has always been a passionate interest; it’s something I have always wanted to work in. I studied in Trinity and at the time our anatomy professor, Moira O’Brien, was one of the pioneers of sports medicine in Ireland. At that stage there was no real run-through sports medicine training so her advice to me was to choose something else – be that orthopaedics, emergency medicine or general practice – and to do sports medicine on top of that. So that’s what I did: general practice training, and then parallel to that I did my sports medicine training in Bath University. After I stopped playing rugby I started helping my local club, then the Ulster U21s, then the Ireland U18s. Things have kind of just snowballed as the years have gone on. I suppose I now have what would be called a portfolio career; I still do some general practice, but sports medicine has become an ever-increasing part of my job.

So you played rugby until you were finished with your GP training?

Yeah, I trained in England and then came back to Northern Ireland and was doing locum GP work for a couple of years, and at that stage, well, the rugby packed me in as much as I did it. It became too difficult managing the demands of the job, training and most of all the pain post games!

What makes sports medicine different from other fields you might also have an interest in, such as general practice?

It’s a relatively new discipline. I think we are still finding our feet a bit on how we position ourselves. What’s happened in the UK is that a lot of what developed as sports medicine is now repositioning itself as ‘exercise medicine’, because I think that’s where we will have the population benefit. The benefits of exercise are so well documented, and similarly, lack of physical fitness is associated with so much morbidity, that that is where the big ‘vins’ are to be had. The difficulty is influencing those in decision-making positions because it probably seems less pressing than a lot of other health priorities. I think that to have a cohort of well-qualified doctors there to advise not just on sports injuries and musculoskeletal medicine, but also on the wider picture, such as exercise in people with chronic conditions such as diabetes, asthma, or cardiovascular disease, is essential.

So you think it’s moving in a health promotion kind of direction?

Yes, health promotion, but also for someone who has a chronic medical condition: what are they able to do? How do they fulfill their potential? Similarly then, in terms of exercise for the nation: how do we advise on that? Just simple things like the fact that girls reach peak bone mass by age 13/14 and that is done through skeletal loading, so should we have primary school children bouncing up and down on their feet for five minutes every morning? Simple little interventions like that. ... It essentially covers all of medicine. Then you have team medicine, which covers everything as well, so even within sports medicine there are loads of specialist areas, which is an attraction.

What do you think about the issues surrounding concussion?

It’s changed unbelievably quickly. I would have had a keen interest dating back to 2007/2008 but a lot of that was watching what was happening in the States – they are probably three or four years ahead of us in what they’ve experienced with regard to concussion. In many ways the explosion in interest has been a really good thing because the media interest has driven the public interest in it. We have been able to do a huge amount of work trying to educate people and I think it’s now on people’s radar and they are willing and interested to learn more about it. When we started our education initiatives back in 2009, really very few people came along to anything we tried to do while now, regularly, we’ll have one hundred plus people at our workshops, so that’s been great! The evidence would say that we’ve become very much better at ‘recognise and remove’, and our threshold for diagnosis has dropped significantly. Players are now reporting symptoms earlier because they realise how important it is that they report any symptoms they are experiencing – even seemingly trivial or short-lasting ones. Also, coaches, parents and teachers are becoming more vigilant, looking out for signs of concussion and picking these up, so we’re becoming good at that. And I think we
have also gotten really good at keeping people out for the requisite period of time. Actually, one of the issues we’ve come across now is the medical clearance to go back to sport, and as a medical community we are lagging behind a little bit. One big concern is that concussion doesn’t become such a divisive topic that children or their parents get put off participation in sport. Because the benefits of contact sport so far outweigh any potential risks. It would be very sad if people were turned away from sport because of a perceived risk of long-term problems that in real terms is relatively low. And certainly the risk now would seem to be lower than it was five years ago because the condition is likely to be managed so much better now than it was even then.

Do you think it will change how contact sports are played?
We are already seeing a change in how these sports are played. It’s interesting – Brian McLaughlin (Ulster Head coach 2009-2012) took a session in my local club this year with U12s/U14s and he was talking about how guys came to the ruck, and he was talking about injury prevention. He was saying: “You lead with your shoulder and your hip and keep your head well out of the way”, so that was really fascinating for me to see. Coaches are already taking it on board. That is one big positive thing.

I also think there is an onus on the lawmakers of sports to remain aware of trends and keep on top of that, and implement good evidence-based rule changes. I am sure that all sport will continue to evolve with regard to safety. In fairness, sports realise that for the PR side of each individual sport, player welfare is key.

Do you think rugby is at risk of diminishing popularity?
Rugby is still a contact sport, and that’s why a lot of people like watching it. It’s also why a lot of people like playing it as well. I don’t think you need to disbar contact completely but there is no point in having any needless risk. I think how you prepare for games is important, certainly how you train. I don’t think there is any point doing hours and hours of pointless contact training – straight away you can drop your exposure to risk of injury way down there. There are lots of interventions you can introduce that, when put together, can make a big difference.

Do you think strength and conditioning has changed the nature of injuries?
Statistics would actually show that serious injuries in rugby haven’t gone up, which almost belies the public perception. I think over the past 10-15 years we have become better at managing injuries, and perhaps if we hadn’t done that then maybe the injuries incidence would have risen a bit. There’s no doubt that players have become bigger and faster, but that’s probably maxed out now. The World Cup has taught us a lesson – if you look at New Zealand, they have taken the view that they are looking to be a little bit more mobile and lose a bit of the excess weight. For me, that’s really exciting and that’s the way rugby should go.

With the doping scandal in the IAAF, do you think that’s changing the way you do your job as someone who is involved in sports medicine? Do you think it is going to be more of an issue?
It’s a big part of our job. My biggest fear with our professional players isn’t deliberate doping, it’s guys making an inadvertent mistake over something or another – taking a supplement, or taking a cough or cold remedy with pseudoephedrine in it. That’s a bigger concern. I think within rugby in Ireland there is no evidence of any sort of systemic doping. However, you’d need to be naïve to say there’s no risk. We know that within the general population there is quite a prevalent use of anabolic agents for aesthetic purposes. These are not professional athletes. Clearly if there is a lot of this in local gyms, the fear would be that 16-, 17- or 18-year-old kids, who want to be bigger to be a bit better at rugby, could make poor life choices and be tempted to take anabolic or other banned agents. It’s so important that this cohort are well educated about all the potential risks of getting involved in this, so that they understand why it would be a huge mistake to do so.

What do you think is coming down the line as far as sports medicine as a career is concerned?
I think a lot of it is probably hampered by health economics and the problem is that, for example here in Northern Ireland, the health budget is going up every year but it’s not keeping pace with inflation and currently the NHS is really struggling. It’s hard to position yourself against cancer services or children’s heart services, and there is an endless list of very deserving medical causes, who are all fighting for the same piece of the pie. There is a problem there for sports medicine to develop in any big way. I think hopefully it can continue to steadily evolve. We need policy makers who have the vision to see the benefits of prevention that will come with a fitter population.

And are you involved in any research yourself at the moment?
We have a schools injury audit running up here where we are following all our senior rugby-playing schools. This is the second year of the study. The research group encompasses some orthopaedic surgeons and sports medicine doctors in Belfast and researchers from the University of Ulster. Ulster Rugby and the IRFU are part funding it along with support from the MITRE charity. It’s an injury audit of schoolboy rugby players – and again, we talked about it earlier – and the aim is to establish the injury patterns within the game so that we can use good, objective evidence to inform lawmakers who want to make the game as safe as possible. It’s one of the biggest studies of its kind that’s ever been done in the world and already we’ve gleaned some really interesting information, which is very exciting.
In April of 2015 an earthquake struck the small mountainous country of Nepal, killing over 9,000 people. The government was going through a political upheaval and the $4.1 billion USD earthquake reconstruction fund sat in the bank, while thousands of families faced the winter with nothing more than a sheet of plastic for shelter. Although the Nepali people are resilient and resourceful, the situation was bleak for many. Nepal was my home for 12 years while my dad worked as a missionary doctor in a rural hospital. In May, I had the opportunity to go back for two weeks with my dad and brother to lend a hand in the rebuilding process.

Rebuilding
When we arrived in Kathmandu, we met with friends who work for an NGO, Human Development Community Services (HDCS), which my dad used to work with. HDCS had been working on earthquake relief for several weeks, so they were able to offer insight into the current situation. Later that morning, we headed off toward Besi Sahar, a town eight hours from Kathmandu, close to the epicentre of the quake. When we got there we met with the HDCS hospital administrator and the mayor of the district. They advised us to go to a village close to the epicentre, where 30 houses had been completely destroyed.

Two weeks after the earthquake, there was not a large need for medical aid or food; the main issue was shelter. The earthquake destroyed over half a million homes. Families slept under tarps, in chicken coops or anywhere that provided shelter from the elements and fast-approaching monsoons. My former high school track and field team had raised some money for earthquake relief, with which we bought roofing tin and building supplies for all 30 houses in the village. This all took several days, but soon we were able to load up a truck and head off, arriving after several hours on dirt roads. The destruction was widespread and devastating, and although the newer brick and cement houses had survived, almost all of the mud and stone houses had collapsed. Distributing the supplies took all day, but everyone in need got enough to build a temporary house. The next morning a man asked for help to build a home that would survive the monsoon and the winter. Until then, his wife and 12-year-old daughter had been sleeping under a tarp. It took us two days to put up his bamboo house, which will last several years until they can rebuild their own house.

Reflection
Being able to give back in a small way to the place that helped to shape who I am today was an amazing opportunity. It reminded me why I want to be a doctor, and of the great needs of many around the world.

Reference
Turkey is one of the biggest hosts for Syrian refugees, with 1.9 million people seeking refuge there in 2015.1 This became very apparent to me in August 2015 when I was on holiday there. I contacted a humanitarian NGO that is very active in aiding Syrian refugees, the International Blue Crescent (IBC) Relief and Development Foundation. I was assigned to a city called Gaziantep, where many child-friendly spaces (CFS), and primary and secondary schools, have been opened for Syrian refugees. Together with its German partner Malteser International, IBC is running a temporary field hospital (TFH) in Kilis, a town 3km away from the warzone in Syria.

Growing up in Gaziantep
I accompanied a Syrian psychologist to a CFS in Gaziantep. This particular programme ran a morning and afternoon shift five days a week, with approximately 40 children in each, divided based on age. Learning exercises with a focus on psychosocial support were organised to educate these children, whose education had been interrupted by the devastating civil war. Group activities and games focused on expressing emotions, making new friends, building self-confidence, and showing artistic skills and other talents. The teachers attempted to convert the fear and anxiety these children were experiencing into hope for the future. Although interacting with children was a tremendous experience, it was also an emotionally challenging one.

Crisis in Kilis
Initially, I took a public minibus from Gaziantep to Kilis, but due to the proximity to the Syrian border the IBC arranged for a car to drive me to the hospital. The TFH, with a capacity to accommodate 48 inpatients, receives conflict-affected patients for postoperative care. Intensive physiotherapeutic care of war-injured patients is provided, in addition to psychosocial support for patients and relatives. The determination and faith of patients, particularly in the physiotherapy room, was truly admirable and eye opening.

Patients were surprisingly open to sharing their stories. One woman had been injured by barrel bombs dropped by air forces. She lost one of her three daughters when her house collapsed, but was miraculously able to deliver her fourth baby at the TFH despite injuries to both her legs. The TFH provided her with much-needed medical and psychosocial support in the form of daily consultations and stress-relieving exercises. Another story that was particularly touching was that of a 10-year-old boy who had lost his arm in the war. This extremely smart and sociable young boy was attending school to learn to write with his left hand in order to fulfil his dream of becoming a doctor, but expressed a desire for a prosthetic arm to be able to play with his siblings again.

Reflection
Apart from getting a closer view of the hardship associated with such crises, and an opportunity to help where possible, this was also a valuable learning experience, as I had the chance to practise in my mother tongue of Arabic, improve my communication skills, and be supervised in performing some basic medical procedures. This experience also opened my mind to Turkish culture and the generosity of Turkish people and, importantly, emphasised the role medical professionals play in such trying conditions.

Reference

AMENAH DHANOON travelled to Turkey to volunteer with Syrian refugees.
The mass approach

DANIELLE WUEBBOLT spent some time in Shanghai seeing how medical teams there managed breast cancer care.

When I first considered travelling to Shanghai, with its population of 14.35 million people,1 I wondered how the medical system coped with the massive population. Given that breast cancer is one of the world’s top ten causes of death for women and, together with cardiovascular and cerebrovascular disease, contributed to 70% of all female Chinese fatalities in 2010, I decided to observe breast cancer patient care.2,3

I was placed in the Comprehensive Breast Health Center at the Ruijin Hospital in Shanghai, where I had the opportunity to shadow the chief resident of breast cancer surgery team one.

**Multidisciplinary team meetings**

Each morning began with patient rounds, followed by multidisciplinary team meetings, where – to maximise efficiency and deal with time constraints – each physician used a tablet to cast a vote for the next treatment for the specific patient case. Treatments receiving the highest number of votes were employed.

**Operating theatre**

The Ruijin Hospital has an entire floor of operating theatres dedicated to breast-related surgery, ranging from mastectomies to central line insertions and breast reconstructions using silicone implants. Surgeons performed up to five to six procedures per day and discharged patients back to the ward, where medical students (including myself) performed dressing changes and monitored for postoperative infections or drainage tube complications. Typically, patients remained for up to three days before being discharged home.

**Outpatient clinic**

The chief resident and I worked in a small room with connections to other rooms, facilitating communication with other physicians. Patients returning for bandage changes saw a nurse or medical student, then had a consultation with the physician. As the patients came into the room, they handed the physician their medical and payment card before quickly explaining their medical concern. Breast examinations were completed while the patient was standing and lifting their shirt, not lying down. The entire hospital visit often lasted less than five minutes.

**Reflection**

Seeing how the Shanghai physicians efficiently handled an overwhelming number of patients (and their families) was an incredible experience. During a consult, other patients or family members often waited just outside, or even entered the room and bombarded the physician with questions and concerns. I was not accustomed to this sort of interaction, but the chief resident was extremely patient with the women and often handled multiple appointments at the same time. Additionally, the physicians and students all spoke English and were eager to teach and answer any questions, demonstrating an abundance of grace, patience and understanding, which I wish to emulate in the future.

**Reference**


Neurosurgery is often seen as an impossibly technical and emotionally distant specialty. Two surgical memoirs produced on either side of the Atlantic give an insight into the challenges and rewards of a neurosurgical career. Do No Harm: Stories of Life, Death and Brain Surgery by British neurosurgeon Henry Marsh describes his meandering career in hindsight as he prepares to retire. When the Air Hits Your Brain: Tales from Neurosurgery by Frank Vertosick Jr is an autobiographical take on becoming an American neurosurgeon, from his time as a medical student through to the end of his residency. While both books address the same central theme, their tone and approach could not be more different.

**Matter-of-fact**

In Do No Harm the style is matter-of-fact and anecdotal. Each chapter is named after a different neurosurgical condition, wherein Marsh outlines his own experience with managing the disease and weaves elements of his personal and professional life into his factual accounts of each case. These can be harrowing, hilarious or, more often, a mixture of both, as Marsh recounts struggles against disease, discusses bureaucracy in the NHS, and muses on a surgical life. As a narrator Marsh is a painfully honest, sharing both his triumphs and his failures. In a notable exception to the condition-oriented titles of his chapters, ‘Hubris’ recounts an early experience with the consequences that can arise from major neurological surgery and shows how profoundly affected a doctor can be by a case gone wrong. Marsh’s journey into neurosurgery is certainly not typical, with a prior degree in politics, philosophy and economics, a short stint as a porter, and an early diversion into anaesthetics all featuring in his portfolio. This contributes to his likeability as a narrator, as he displays the myriad of experiences and how they brought him to the profession he finally entered.

**The trainee’s perspective**

When the Air Hits Your Brain is from the beginning more jovial in tone. Written from the perspective of Vertosick as a trainee, it betrays the naivety and immaturity of his early coping mechanisms with difficult cases. Vertosick writes with a distinctly American voice, outgoing and with an ascerbic wit, describing his younger self as confident to the point of arrogance. His description of medical students as falling into three categories – “Slackers, Keeners and Wild Cards” – may strike close to home for many a student in our own College, while his rules of neurosurgery may compete with the famous rules of Samuel Shem’s ‘House of God’ as the finest medical guidelines committed to print. His own pursuit of what he views as perfection, “the surgical psychopath”, is described in detail, and his description of his reaction to an unsuccessful aneurysm surgery performed by one of his senior colleagues may make even the most hardened, cynical student cringe. However, as the book develops, his professional goals are altered by a number of cases. When one finally emerges from the book it is with a sense of how Vertosick developed as both a surgeon and a person through his training.

**Something to offer all readers**

So why compare these two memoirs? Beyond the profession of the men writing them, do these books have anything in common? I have already underlined the differences in tone and perspective that make both books intriguing reads in very different ways. Ultimately, both books stress the importance of compassion in the pursuit of a medical career. Both describe the self-doubt that can emerge from managing difficult cases, the consequences of one’s actions as a medical professional, and working in a high-stress environment. In spite of both narrators’ chosen niche, there are lessons in these books for readers in both medical and non-medical careers, and both are engaging from front to back. When the Air Hits Your Brain is rightly regarded as a medical classic, while Do No Harm has featured on scores of non-fiction writing awards lists. As a final note, one other reasonably famous neurosurgeon, Harvey Cushing, remarked: “I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least of the work”. Upon finishing both these books, the reader comes away with the impression that there is a great deal more to surgery than performing procedures, and that almost eight decades on from Cushing’s death, his thoughts are as true as ever.

References

Oestrogen receptor gene mutations in endocrine-resistant breast cancer

Benjamin Lau
RCSI medical student

Introduction
Breast cancer is the most common form of cancer in females. The majority of breast cancers express the oestrogen receptor; oestrogen exposure drives cell growth and division in the breast, and is therefore a major risk factor for tumour development. Tamoxifen, a selective oestrogen receptor modulator (SERM), is effective in treating oestrogen receptor positive breast cancer due to its anti-oestrogen actions in mammary tissue. However, metastatic disease may recur after the tumour develops drug resistance. Mutations in the ligand binding domain of ESR1, the gene coding for the oestrogen receptor, have previously been found in metastatic breast tumours. This experiment explored the possibility of resistance due to mutations in ESR1.

Methods
Genomic DNA was extracted from tamoxifen-resistant LY2 cells and cells of their parent cell line MCF7, which are tamoxifen sensitive, using a DNeasy Blood & Tissue Kit (Qiagen; Manchester, UK). Specifically designed primers were used to target each of the eight exons in the ESR1 gene, which were amplified by polymerase chain reaction (PCR). Agarose gel electrophoresis was used to confirm that the PCR products were the correct size. The PCR products were then purified using a MiniElute PCR Purification Kit (Qiagen), quantified by a Nanodrop 2000 Spectrophotometer (Thermo Fisher Scientific; Wilmington, USA) and sent to GATC Biotech for sequencing. The results of sequencing were compared using the bioinformatics tool BLAST.

Results
All exons were amplified by PCR with the exception of exon 1, which did not yield a specific PCR product even after redesigning primers. Sequencing was successful except exon 4, which was not sequenced accurately. A heterozygous point mutation at nucleotide 336 resulting in an alanine to guanine substitution at amino acid 112 was detected in exon 8, changing the codon from ACA to ACG. However, both codons encode the amino acid threonine, and therefore the mutation was non-functional.

Conclusion
There was no functional mutation found in the ESR1 gene of the LY2 cells. Experimentation with alternate methods is needed to produce a suitable PCR product for exon 1. Further investigation into alternate mechanisms, such as cross-talk between the oestrogen receptor and other growth factor receptors or ligands, is needed to determine the cause of endocrine resistance in breast cancer cells.

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References
**Fig 1.** Heart attack

**Fig 2.** Cardiac arrest