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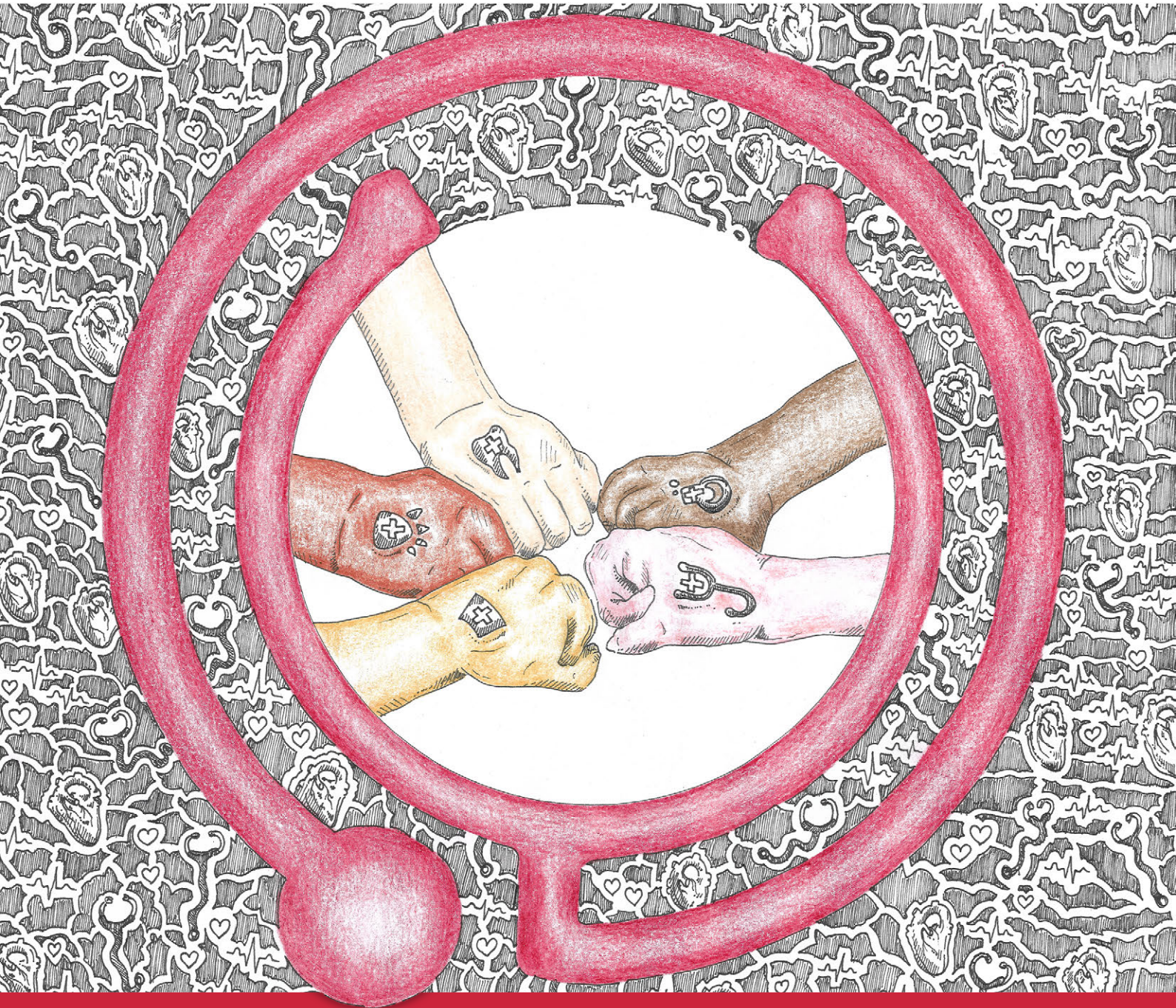

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Student Health Sciences Research Journal

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Welcome to the third issue of the INSPIRE Journal: created by students for students

After a little break, we are very pleased to introduce you to the third issue of the INSPIRE Student Health Sciences Research Journal. As the brainchild of the INSPIRE leads in four medical schools in Bristol, Cardiff, Exeter and Plymouth universities, in 2015 the INSPIRE Journal was created as part of the INSPIRE scheme to provide a platform for medical, dentistry and veterinary students to show the world what research they have been up to and to share their knowledge. The INSPIRE scheme aims to provide students in medical schools across the UK with an opportunity to experience research and to encourage them to incorporate research into their chosen career paths. The INSPIRE Journal aims to support this goal by allowing students to experience a very important part of research: publication.

This issue is written and peer-reviewed by students and the whole Editorial Board is composed of students, making this a true student journal. The issue that you are currently looking at has taken over a year's worth of hard work by all of those involved, and what a year it has been. We are aware that many of our readers will have been affected by the COVID-19 pandemic in one way or another and we hope that you are all keeping safe and well. We are extremely grateful for the healthcare workers (some of whom include the students that have contributed to this issue) who are currently working on the front line. We hope that this issue inspires student doctors, dentists and vets to carry on during this challenging time, highlighting the importance of their work. We are very proud of everyone who contributed to this journal, despite having to work around the ever-changing environment, making this issue even more special to all of us.

Within this issue, you will find a wide variety of articles that span a range of disciplines within health sciences. From a very topical review of strategies for global eradication of infectious diseases and an interesting debate on the use of zoos for animal conservation, to research on the prevention of vicarious trauma in prison healthcare professionals and useful information on how to conduct a dental elective, we really hope there is something in here for everyone. Finally, please don't forget to check out our blog pieces at **www.inspirestudentjournal.co.uk/resources.**

We really hope that you enjoy this third issue of the INSPIRE Journal and promise we won't leave it so long next time!

Best wishes,

The INSPIRE Student Health Sciences Research Journal Senior Editors

FRONT COVER
The central image of the cover represents the interconnection between the three healthcare disciplines (medical, dental and veterinary sciences), whilst encompassing the diversity of student culture, background and career aspirations. The black and white background was originally designed as part of an SSC project by Hannah Walter.

Cover credit:
Concept: Hannah Walter (Year 2, Medicine, University of Plymouth) and Nirmal Jayakrishnan (Year 3, Medicine, University of Plymouth)
Design: Hannah Walter

Contents

The rise and fall of mesh in urogynaecology surgery: the impact of inadequacies in the surgical device approval system

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Introduction

Mesh is a synthetic material used to reinforce a weakened area **(Figure 1)**.[1] It was first developed in the 1950s for the surgical repair of inguinal hernias.[1] It proved to be superior to conventional suture repair, making it incredibly popular in general surgery.[2] This led to mesh also being adopted in urogynaecology surgery in the 1990s,[3] including in the treatment of pelvic organ prolapses (POPs).[4] A POP is the descent of the bladder, uterus or rectum, from their normal anatomical position, into the vagina.[5] Symptoms may include a bulging sensation in the vagina, urinary incontinence and increased urinary frequency.[6] POP is a common condition; it is estimated that it affects 50% of women who have had children.[5] The aim of using a mesh implant in conditions of POP is to reinforce and support the weakened pelvic tissue.[5]

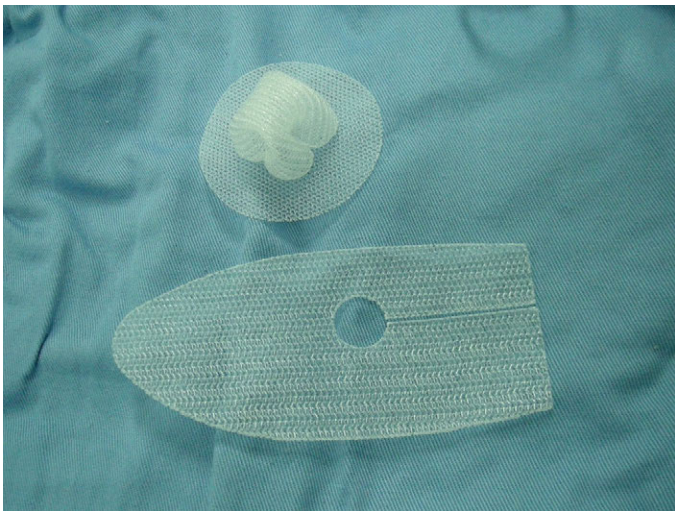

Figure 1: Mesh implant. Image reprinted from[7], under the terms of the Creative Commons Attribution-ShareAlike 3.0 Unported License (https://creativecommons.org/licenses/by-sa/3.0/)

Between July 2018 and April 2019, the use of mesh for POP was temporarily halted pending further investigations.[8,9] Years prior to this, women were reporting severe side-effects from mesh implants. A meta-analysis by Feiner et al in 2009 (n = 2653) found that mesh erosion through the vaginal tissue was the most common post-operative complication, with the incidence ranging from 4.6–10.7%.[10] Another post-operative complication includes dyspareunia (painful sexual intercourse), which affects 1.7–5.5% of patients.[10]

The long-term implications following mesh surgery have also been devastating for some patients. An independent review by the Scottish government enquired about patients' post-operative experiences. Some patient excerpts included:

"I have had four separate surgical procedures with no avail and now I have been left with severe problems."[11]

"I am now 46 years old and the last 6 years of my life have been hell since being implanted with this device."[11]

Whilst only a small proportion of patients were negatively affected by the mesh implants, these concerns were first raised decades ago.[12] Furthermore, there have been many litigation cases, worth millions of pounds, against mesh manufacturers.[13] However, the inadequacies in the approval system of such surgical devices meant that these problems went unbridled.[13]

This issue raises the question: is the current system for the approval of surgical devices adequate to ensure positive patient outcomes?

Issues with the approval system

It is difficult to comment on the details of the approval system of mesh in the United Kingdom, as this is managed by the Medicines and Healthcare Products Regulatory Agency (MHRA), which is not subject to Freedom of Information requests.[14] However, this is not the case for surgical devices in America. Although differences exist between the American and the UK medical-device approval system, the American system can provide some insight on the approval process of mesh implants and shed light onto the inadequacies that precipitated to the mesh scandal.

The Food and Drug Administration (FDA) are responsible for surgical-device approval in America. They classify medical devices into class I (low-risk), class II (moderate-risk) and class III (high-risk) categories. The higher the risk classification, the more stringent the approval process.[13]

Class II devices can gain approval if manufacturers demonstrate that the device is 'substantially equivalent' to a previously approved product, and no new clinical investigations are required.[13] Mesh was originally classified as a class II device.

The ProteGen sling (Boston Scientific) was approved in 1996 for use in urogynaecology surgery after it was deemed to be equivalent to a type of mesh used in hernia repair.[11] It was recalled after 3 years due to its high failure rates.[12] However, due to its moderate-risk classification, subsequent mesh models were approved on the basis of being 'substantially equivalent' to the 1996 ProteGen Sling, despite its removal from the market **(Figure 2)**.

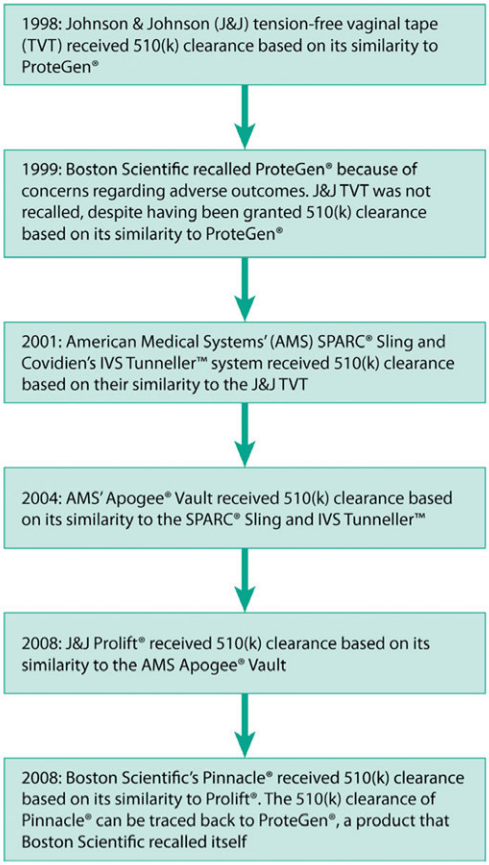

Figure 2: Cascade of mesh approval after the recall of the 1996 ProteGen sling. Image from Campbell et al[4], published with permission from John Wiley & Sons. ©2018 Royal College of Obstetricians and Gynaecologists

Future changes

Certain amendments have been implemented in an attempt to rectify the aforementioned problems associated with mesh implants. In January 2016, the FDA reclassified mesh as a class III (high-risk) device, now requiring more stringent tests prior to approval.[15] The European Parliament also followed suit and, in September 2017, it declared mesh as a high-risk device and instructed that new devices must be held under greater scrutiny.[3]

In April 2019, the temporary ban on mesh in England was lifted and recommendations were made for future practice. One particular recommendation was the introduction of a national registry for all mesh surgeries in England. Hospitals are now required to disclose information, such as the type of mesh used in each surgery. In addition to this, they must also monitor each patient's outcomes for at least 5 years.[9]

The implementation of such a registry may prove to be very helpful in the future. Any implants that are consistently associated with poorer outcomes can be swiftly recognised and removed from clinical practice. Hopefully, this could curtail and prevent such issues from arising again.

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How should hyperbaric oxygen therapy be utilised in the management of osteoradionecrosis of the mandible?

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Background

Osteoradionecrosis (ORN) of the mandible is a severe non-healing condition, which involves irradiated necrotic bone becoming exposed through ulcerated skin or mucosa.[1] It usually arises 6–12 months following radiotherapy in patients with head or neck cancer.[1] Patients present with pain and trismus (spasm of jaw muscles) as the most prominent symptoms.[2]

Risk factors for mandibular ORN include previous dental extraction, oral mucositis and smoking.[3] However, the most significant risk factor is exposure to a radiation dose of greater than 60 grays (Gy). Radiation-induced injury to the inferior alveolar artery and its branches ultimately leads to ischaemic necrosis of the mandible.[4]

Hyperbaric oxygen therapy as a treatment

The Notani staging system can be used to classify the severity of ORN based on clinical and radiological findings.[5] The stage of disease ultimately determines what treatment is given. Treatment of early-disease ORN involves the use of local wound irrigation and antibiotics, whereas surgical reconstruction is often performed in more severe cases, i.e. grade III ORN **(Figure 1)**.[6]

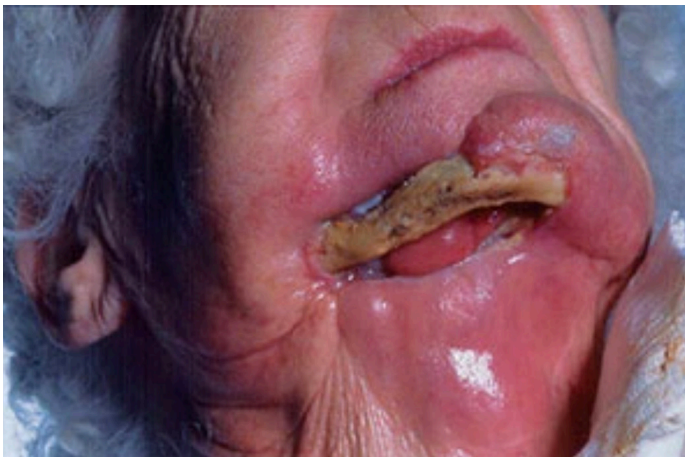

Figure 1. Grade III mandibular ORN. Image from Thomson et al[14], reprinted by permission from Springer Nature.

Hyperbaric oxygen therapy (HBOT) involves inhaling 100% oxygen at 3 atmospheres pressure in an enclosed body chamber. This results in a considerable increase in the concentration of oxygen dissolved in blood plasma (and percentage saturation of haemoglobin).[7] Despite oxygen levels returning to normal after 10 minutes of HBOT, a greater supply of oxygen reaches tissues during the session.[7] Although HBOT is utilised in all stages of ORN, the literature remains unclear as to whether HBOT is more effective when used as a standalone treatment, or as an adjunct to surgery.

Standalone treatment An unblinded randomised trial by Tobey and Kelly concluded that HBOT improved the recovery rate for patients with ORN by improving the likelihood of complete mucosal covering.[8] This is supported by a systematic review, which supported the application of HBOT for a select number of patients.[9] However, this systematic review focused more on HBOT use as prophylaxis, as opposed to treatment once ORN had developed. Moreover, the use of an unblinded trial introduces an element of bias, as patients with less severe ORN could have been favoured in the selection criteria.

A double-blind study carried out by Annane et al evaluated HBOT therapy without the use of surgery or any additional treatment methods in comparison with a placebo group. Nineteen per cent of the participants in the experimental group made a full recovery as opposed to 32% in the placebo group. This trial suggests that HBOT should not be used as a standalone treatment for mandibular ORN.[10] A limitation of this study is that HBOT was used twice daily, as opposed to once, therefore differing from standard guidelines. However, the trial was of high quality since it was double-blinded and was conducted at multiple centres.

Adjunct to surgery In contrast to standalone treatment, evidence supports the use of HBOT in conjunction with surgery. A retrospective study carried out by D'Souza et al showed that HBOT was not able to cure ORN in patients with grade II or III disease if it was used alone; however, if it was administered before or after surgery to the mandible, it had beneficial effects.[11] This is supported by a recent study demonstrating that, when used alongside adjunctive HBOT, surgical bone debridement or reconstruction resulted in significant patient recovery rates. However, early surgical intervention was essential, particularly in grade II or III ORN.[12]

Furthermore, a study by Dieleman and colleagues, found that the highest cure rate for patients with grade II and III ORN was achieved with extensive surgery (a free vascularised osteocutaneous flap) alongside HBOT.[5] However, only a small sample of 27 patients was included in this study.

It is believed that HBOT can increase the success of procedures, such as local flaps or bone grafts. A critical factor for bone-graft survival is the presence of a recipient bed that is already well vascularised and has an abundance of cells capable of osteoinduction.[6] Exposure of tissue to hyperoxic levels stimulates fibroblasts to produce collagen at the site of the wound, which then enables endothelial cells to proliferate into capillary buds.[13] The focal point of HBOT is, therefore, to enhance collagen synthesis, which will, in turn, promote neovascularisation, providing the vascular bed required for a successful bone graft. Local flaps are usually already well vascularised, so do not necessarily rely on this mechanism.[13]

Conclusion

There is little evidence to support the use of HBOT as a standalone treatment for mandibular ORN. Results for its use in grade I ORN have been inconsistent and its efficacy as a lone therapy for treating grade II and grade III ORN show little to no benefit. As far as current research goes, HBOT is best utilised as an adjuvant to a surgical procedure, as this is shown to have the greatest impact on recovery rates in patients with ORN.

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Opinion

Is the glass ceiling breaking for women in health science careers?

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Definition: glass ceiling—that invisible barrier to advancement that minorities, including women, face to reach the top.

Despite the movements for female equality and empowerment, few women occupy top scientific decision-making positions and this is partly due to the many societal challenges they face during their advancing careers. Being a current female medical student, it is a difficult debate subject to write about; however, it is a very important matter for women worldwide.

Women have been battling to achieve equality for a long time in all areas of life, not only in science. In medicine, there are still some medical specialities, like academia and surgery, where it is still difficult and challenging for women to get to the top. Some studies have found that this is due to women not pushing themselves into these roles and feeling that they are not worthy of these positions.[1] Some studies have found that women will not apply for certain jobs if they have not matched all the criteria in the job description, whereas men will apply for the job even if they do not have any of the job description requirements.[1]

An example of where women seem to have a glass ceiling in medicine is consultancy. Women account for 59% of the medical workforce but they only account for just 28% of consultancy jobs.[2] This is even reflected in the BMA members, with 45% being women but only 30% taking up positions on its committees.[2] In general, it has been found that women are paid 18% less than male counterparts as the glass ceiling seems to be holding back the highest fliers.[3] This seems to suggest that the medical glass ceiling has undoubtedly not been broken. Women still seem to be held back from achieving top consultancy jobs, whether it is because women do not think they are good enough for the position, family life choices or because men seem to dominate that medical speciality.[4]

However, it is important to publish and support women who do break the glass ceiling on a global scale as it inspires so many other women to focus on their career prospects. A good example is Dr Audrey Elizabeth Evans, who was born to a lower-class family in York, England. Since the age of 5, she knew she wanted to be a doctor.[5] However, in her time, this path was never encouraged for females and, therefore, she knew it would be a difficult route. However, despite this, she managed to get a place at the Edinburgh University Medical School.[5] Unfortunately, during her time at medical school, she developed a memory problem and failed her first year. Despite this, Audrey was determined to have a career as a doctor and when she got to her clinical years, she exceeded. Her communication and empathy with patients was something others desired. She then went on to complete her residency in Boston, USA, where she was the only female doctor.[5] This did not discourage her but fuelled her desire to work hard and fulfil her dream career. She is now a world-renowned oncologist with a desire to live out her legacy as the doctor who cared. Even at the age of 92, she was still fundraising for organisations within the oncological field.[5] Her case study shows that every woman who has a career dream should not be put off, regardless of societal challenges, and that they should persevere.

On a positive note, the glass ceiling in medical schools seems to have been broken, where there is normally a higher female:male ratio (55%:45%).[6] The encouragement from other successful women is potentially now making a difference to the future health care system for women. As long as women in academic medical centres are supported and encouraged to apply for positions higher up, women's attitudes and confidence will grow and allow us to break through this glass ceiling that exists in parts of our society. As the gender ratio changes in medical schools, the number of female consultancies shall increase in the next 10–20 years.[7]

The concept of the glass ceiling can be controversial, with the

metaphor itself first being used by feminists.[8] This term may now be out of date and, in fact, in our society, gender differences are more recognised and this is something we are trying to rectify. There is a parallel phenomenon called the glass escalator. The glass escalator refers to the way men, namely heterosexual white men, are put on a fast track to higher up positions when entering women-dominated sex-segregated professions, for example, preschool teachers, childcare workers and nurses.[3]

Globally, in dental care, we are seeing an increase in female dentists.[9] There are obstacles for women once they enter a dental career path, including attitudes and practical obstacles in continuing or advancing their careers.[10] Some of these barriers have been identified, including socio-cultural challenges, dual family responsibility, workplace challenges and lack of role models. However, in some parts of the world, there is an increase in the number of women applying to dental schools.[11] Fifty per cent of dental undergraduates in the UK are female and, in 2020, more than 50% of all practising dentists will be female.[12]

In veterinary science, the issue is very similar in that it is estimated that around a quarter of leadership roles are held by women. This is despite women accounting for almost 60% of practising vets and 80% of veterinary degree undergraduates.[13] There are many and varying reasons why women are less likely to end up in leadership positions, although these are not unique to the veterinary industry. As previously mentioned, traditionally, women have been less likely to put themselves forward for leadership positions due to a lack of confidence.[14,15] However, with the increasing number of women applying to study veterinary science at university, in future there will be more females taking up leadership roles.[16]

A company development called the Athena SWAN Charter was developed in 2005, encouraging women to advance their career in science, technology, engineering, maths and medicine (STEMM).[16] This was a company advertised during my time as a biomedical science undergraduate. It was good to hear that employers were striving to recruit more women into higher positions, seeking to eliminate some of the barriers that women typically face.[16] This suggests that the glass ceiling still exists, but we are cracking the surface and if more companies like Athena SWAN are formed throughout the UK, many women will be encouraged to apply for top science jobs. The Athena SWAN Charter drives forward the systemic changes needed by institutions to continue encouraging gender equality in STEMM departments.

A major social change that has occurred in all specialities of science is that 70% of all women with younger children are now working outside the home, as compared with previous generations.[17] It is clear that child-rearing and family responsibilities have a great impact on a woman's working life.[18] The responsibilities for family caretaking continue to fall disproportionately on women, and this fact could explain why women abandon their careers in the advanced stages.[18]

In conclusion, women have broken the glass ceiling in many ways, and we have smashed the glass ceiling in many professions. However, currently, in science overall, there still seems to be a glass ceiling and we are only cracking the surface of it. It appears that the new incoming science undergraduate students are majority female and this will hopefully lead to more of them applying and gaining higher positions in their field.[19] Our society is also changing, with women working outside the home, as compared with previous generations. All these factors suggest that the glass ceiling for women in science is fading and that more women are gaining top jobs in science. It is hoped, one day, that the term 'glass ceiling' will be a term of the past.

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Opinion

#Storemysperm: a plan to freeze the clock on falling sperm counts

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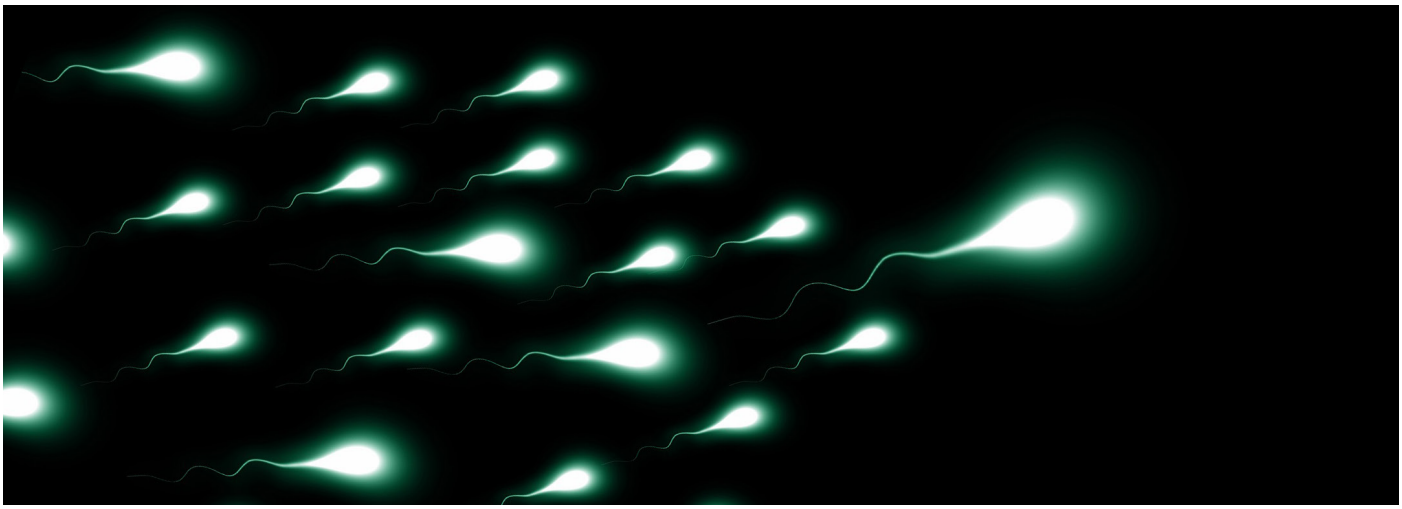

Considering recent evidence confirming falling sperm counts over the past 50 years, the future of male fertility seems more uncertain than ever. Despite this potential global health threat, the aetiology of declining sperm counts is still poorly understood. We considered the feasibility of a hypothetical public health sperm cryopreservation programme for young men. Such a programme would ensure the availability of male gametes in the eventuality that sperm counts were to approach or reach zero. A survey was distributed to students to establish willingness and barriers to engage in a sperm cryopreservation programme. Most students were willing to engage with a sperm cryopreservation programme, although ethical, religious and consent-related concerns were identified.

Introduction

The story of declining sperm counts has re-emerged into the public eye once again with conspicuous headlines[1] declaring the end of the world is nigh. Spermageddon: a dystopian future where babies are few and humanity's hopes of survival rely on assisted reproductive technology. This panic was reignited by a meta-regression analysis by Levine et al,[2] which reported significantly declining sperm counts among unselected western men between 1973 and 2011. Mean sperm concentration (SC) of western men unselected by fertility declined by 1.4% each year during the study period, resulting in an overall mean SC decline of 52.4%. This is stark, given modern medicine offers no therapeutic options to increase SC. The extrapolation of this data suggests that SC could reach zero within 34.1 (23.3–63.6) years and the current WHO reference criteria for subfertility within 23.3 (15.9–43.4) years.[3] Yet, this decline seems unique to western men (referring to studies from North America, Europe, Australia and New Zealand), with no similar decline identified among non-western populations.[2]

Changing semen parameters have been examined by many researchers before, but inconsistencies in sperm-counting techniques have limited the generalisation and interpretation of available data.[4-6] The study by Levine et al[2] is unique in that only studies reporting primary data on human SC obtained using standardised sperm counting methodology were reviewed. This standardisation in counting technique reduces bias, making findings more reliable. It is not unreasonable to anticipate that the aetiology underpinning falling SC could be uncovered in the coming decades, particularly in light of the recent calls to improve our understanding of male reproductive health.[7,8]

A theory to explain falling SC describes involvement of prenatal insults resulting in testicular dysgenesis syndrome (TDS).[9] TDS could explain falling SC and the observed rise in cryptorchidism, hypospadias and testicular cancer.[9] Additionally, environmental pollutants[10] and lifestyle factors, such as obesity,[11] may also contribute. Generating functional gametes from stem cells could be a potential solution.[12] With the assumption that SC will continue to decline, what should we do about it, if anything? Pre-emptive action, such as a sperm cryopreservation programme, could be an answer.

Freezing for the future

Efforts to elucidate reasons behind falling sperm counts have not provided a clear solution to this growing problem.[8] We suggest that sperm cryopreservation amongst young men may be a proactive strategy to ensure availability of male gametes if sperm counts should continue to fall. This strategy would primarily serve as a backup plan to 'buy time' in ensuring sperm availability should developments fail to occur within a reasonable timeframe. We expect that many of the men who may choose to store sperm will not utilise the stored specimens for themselves. It is their sons and grandsons who may be faced with azoospermia and have no other option. Additionally, such a programme may also facilitate sperm donation with appropriate consent and adequate counselling.

Would you freeze your sperm?

A short survey **(Appendix 1)** was distributed to students at the University of Dundee, under local ethical approval, aiming to establish willingness and barriers to engage in such a programme. Participants gave informed consent when partaking in this study. Participants were provided with a short summary of existing research involving falling sperm counts before proceeding to the questionnaire. Medical students of all year groups were targeted via email and social media channels. Full survey responses are available on request from the authors. In summary, most students (*n*=85/87) were aged 18–30 years. Approximately 76% of students (*n*=66/87) expressed willingness to engage in such a cryopreservation programme. Students opting not to engage (*n*=21/87) drew attention to ethical and religious concerns and a disbelief in the seriousness of the problem. Additionally, discomfort with the notion of transgenerational consent and a perceived unnaturalness pervaded throughout responses.

Final thoughts

A population-based sperm cryopreservation programme is probably not feasible at present due to limitations relating to laboratory capacity and availability of trained staff. Other issues requiring consideration include the number of sperm stored per individual, the age at which individuals are invited to store sperm, the current 10-year statutory cryopreservation storage limit[13] and achieving public engagement. However, these issues do not detract from the potential severity of the situation and fail to consolidate an argument that inaction is an appropriate response. Such a programme may appear drastic, but the need for such measures may become more obvious in coming years. Conversely, declining SC may resolve without intervention, rendering such a programme obsolete. Nonetheless, the next steps could include economic modelling to better understand how such a programme could function. Public health campaigns encouraging and subsidising elective sperm cryopreservation could be considered. We believe the greatest barrier in the implementation of such a programme is financial in nature. Considering a western 'spermageddon' could occur within the next 40 years, we urge that the potential crisis in male reproductive health is acknowledged in the wider scientific community to enable solutions, including cryopreservation, to be actively explored.

Acknowledgements We would like to thank Professor Christopher Barratt and Dr Steven Gellatly (both University of Dundee, Scotland, UK) and Dr Vanessa Kay (Dundee School of Medicine, Scotland, UK) for their guidance.

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Appendix 1: Student survey – Would you freeze your sperm?

This survey was carried out under ethical approval (SMED REC 018/18) from the University of Dundee, School of Medicine Research Ethics Committee.

Who are we?

Hello, our names are Davy, Sarah and Scott and we are undergraduate students at the University of Dundee currently undertaking a project as part of BMSc in Human Reproduction. Our supervisor is Professor Christopher Barratt who currently leads the Reproductive Medicine Group at the university.

What is the purpose of this project?

A recently published paper seemed to have confirmed prior suspicions that sperm counts in western men have fallen during the last 40 years. There are concerns about this decline not slowing down or showing any 'levelling off'. There are multiple theories to explain the falling sperm counts, but the exact reasons remain unclear. Sperm cryopreservation for all men between ages 20-24 have been proposed to be a short-term fix to provide time for scientific research to devise a long-term solution. This project wishes to gather opinions about such a public health programme by finding out the potential response rate should such a programme be implemented.

Who should complete this questionnaire?

We are hoping to collect responses only from men as this is more of a pilot and exploratory-type study. We are aware that the decision-making process behind sperm cryopreservation may be complicated at times and may involve multiple people. Hence, we are targeting this questionnaire to only men to keep the analysis straightforward and manageable. Participation in this survey is voluntary.

Question 1

Do you consent to taking part in this questionnaire?

Question 2

The fertility of western men appears to be under threat. A recent published paper seemed to confirm prior suspicions that sperm counts have fallen during the last 40 years (Levine et al. Hum Reprod Update. 2017). Men now have roughly half the number of sperm concentration as compared to 1980 measurements. There are concerns that this decline is not slowing down or stopping when examining data from the last few years. If trends are to continue there may be no sperm within the next 35 years. Although many theories exist, reasons why these sperm counts are falling remain unclear. Freezing the sperm of young men (say aged 20-24) is a possible solution as a short-term fix to ensure the fertility of the next generation. This would buy time until scientific solutions to address the problem become available. If a public health campaign offering sperm freezing for young men was to become available – would you freeze your sperm for your sons and grandsons to use?

Question 3

If you answered 'no' to Question 2, please explain why.

Question 4

What is your age?

Opinion

Nutrition science: a chronic deficiency amongst healthcare professionals?

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'Let food by thy medicine' (Hippocrates)

Since starting medical school, 3 years ago, my attitude towards nutrition science has changed rather dramatically. I certainly didn't question why we only had a single workshop discussing nutrition; in fact I thought even that hour was a bit unnecessary. A few years later, my views couldn't be more different. The aim of this article is to encourage a new perspective on nutrition's vital role in the future of medicine.

The issue I had was thinking about the bigger picture. Most of medicine, in my mind, meant treating a patient's acute and unavoidable illness and sending them on their way. However, my eyes slowly opened when I began to appreciate how the majority of what we treat is tragically preventable. The world health organization (WHO) stated in its published plans for the prevention and control of non-communicable diseases (NCDs) that 'most of the premature deaths from NCDs are largely preventable'.[1] Considering that, in the UK, approximately 89% of deaths are attributable to NCDs,[2] I was shocked to realise how little we even discuss the prevention of these chronic diseases in medical training.

The Global Burden of Disease study is the most comprehensive observational epidemiological study to date, examining the most significant risk factors for mortality and morbidity across 195 countries. Published in *The Lancet*, this study found that, in the UK, diet is the second leading risk factor for death and disability after tobacco.[3] The health implications of smoking are common knowledge, but what about diet?

I naively used to think that all we could do was tell patients to limit their intake of fast food, but as it happens there is a wealth of evidence on nutrition science, which is rarely discussed in medical training. The National Institute for Health and Care Excellence (NICE) have specific dietary guidelines for preventing our leading killer in the UK, stating that 'reducing general consumption of saturated fat is crucial' in preventing cardiovascular disease.[4] Similarly, the World Cancer Research Fund has clear advice on how to eat for cancer protection.[5] Both of these recommendations share similar dietary staples, such as whole grains and vegetables, with both bodies encouraging reductions in saturated fat.[4,5] These recommendations are made from evidence regarding the prevention and management of these diseases. However, medical students are sparsely exposed to this kind of life-changing science,[6] which suggests that patients could make simple swaps for a healthier and longer life.

Despite patients trusting their doctors to give nutrition advice,[6] I have found that there is very little formal training for healthcare professionals regarding nutrition science. This was reflected in a *Lancet*-published systematic review, including 25 medical curricula from five different continents, concluding that 'medical students are not supported to provide high-quality, effective nutrition care'.[7] We need attitudes of both patients and healthcare professionals to shift towards understanding the fundamental use of food in medicine. The solution to this mainstream ignorance regarding nutrition in health begins with addressing the issue and calling for change. The use of lifestyle medicine is vital in tackling the rising burden of NCDs, which is currently overwhelming the NHS. Organisations like Nutritank, a national student-led project, are attempting to raise awareness of the role of nutrition in medicine.[8]

However, more pressure on medical schools and public health campaigns to educate doctors and their patients is essential. I would like to see a health system where doctors are fully trained in nutrition science and even prescribe certain foods in primary care to put some control back into the hands of their patients.

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Opinion

A life in captivity: the good, the bad and the necessary

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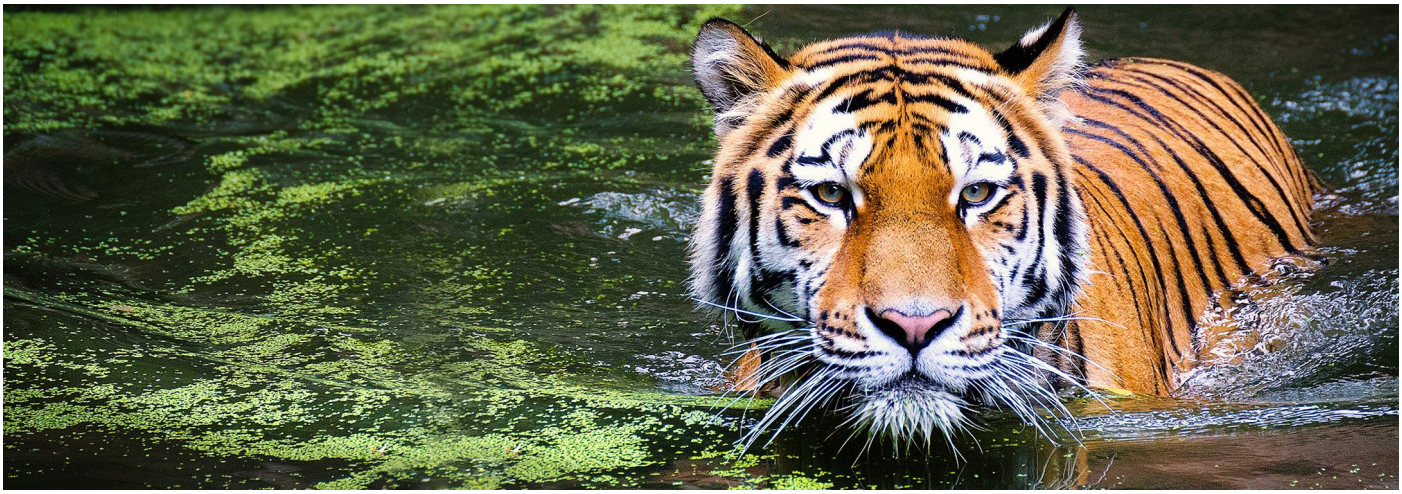

According to the International Union for Conservation of Nature's (IUCN's) Red List,[1] there are currently over 13,000 species of animal that are under threat of extinction. It is undeniable that human activity has placed a significant strain on countless ecosystems and a point has been reached where we need to protect the natural world from our own destruction.

Habitat loss due to land usage poses as the main direct threat to 85% of all species on the IUCN's Red List, with the illegal wildlife trade coming in second place.[2] Poaching drove the Western Black Rhino to extinction in 2011, a fate that is swiftly becoming the reality for a number of other subspecies.[3] The list goes on, with climate change, pollution and over-hunting also meaning that many species are no longer safe in their natural environments. But what about animals in captivity?

The world's zoos are currently fighting to restore some of the most vulnerable animal and plant species, but such a complex and challenging task inevitably comes with its pitfalls.

The good

Although not the only motivator for zoos, a huge philosophy for most is conservation. Conservation can generally be divided into "in-situ" and "ex-situ".

In-situ conservation aims to enable wild populations to maintain themselves, by restoring habitats, minimising threats and monitoring genetic diversity, among many other things. This is considered to be the mainstay of conservation and is supported by ex-situ conservation.[4]

Ex-situ means "off-site" and refers to breeding programmes that take place outside of the natural habitat, often in captivity. The aim of these programmes is to allow animals to breed in a secure and controlled environment in order to produce viable and genetically varied species populations that may one day be released back into the wild.[5]

According to the 2014 IUCN/Species Survival Commission (SCC) guidelines,[6] ex-situ management has previously been successful in preventing the extinction of some threatened species, for example the California Condor,[7] and there are a growing number of species that would benefit from its application.

However, ex-situ breeding is not appropriate for all species and comes with its limitations: failure can occur at the level of the breeding itself, due to a number of physiological, psychological and environmental factors, or at reintroduction. With captive breeding, there is a risk of creating populations that cannot sustain themselves in the wild as they are often not required to exhibit instinctive behaviour in captivity.[7]

It is vital that the initial threat to a species is addressed prior to their reintroduction into the wild, demonstrating how in-situ and ex-situ conservation should be integrated to provide a species with the best chance of survival.

The bad

A 2007 study of 13 UK zoos showed that less than 25% of species held were classed as threatened.[8] So, what are the implications of caging wild animals unnecessarily?

The Animal Welfare Act 2006[9] outlines the five needs of animals that should always be met:

- Suitable environment
- Suitable diet
- Ability to exhibit normal behaviour
- Housed with or apart from other animals (where applicable)
- Protection from pain, injury, suffering and disease

The vast majority of zoos strive to provide animals with a suitable diet and protection from suffering and ensure they are grouped appropriately. However, the promise of a suitable environment and the ability to express normal behaviour cannot feasibly be met. Limitations with enclosure space often means that animals are unable to exhibit their natural behaviours as they would in the wild. They are unable to roam freely, escape confrontation or hunt or forage as they instinctively would. Despite best efforts by keepers to provide animals with appropriate mental and physical stimulation, they can develop what is described as "stereotypic behaviour" or, more colloquially, "zoochosis". This term describes a vast array of repetitive and aimless behaviours exhibited by animals in captivity that have previously been theorised to arise due to stress or deprivation.[10] A well-documented example of such behaviour is pacing in carnivores, such as large felids and bears.[11,12] Reportedly due to the inability to express natural instinctive behaviours, it has been suggested that up to 82% of wild carnivores in captivity suffer with this behaviour. The cause behind the development of these abnormal behaviours is not fully understood and the correlation with poor welfare is disputed.[10,13] Research is still being conducted in this field and the understanding of stereotypic behaviour will play a significant role in improving animal welfare in the future.

The necessary

As humans, we must take responsibility and reduce the impact that we have on other species. Ex-situ management is certainly a viable option for the restoration of some species, but for most, it can only be successful if their natural habitats are also restored. In the meantime, zoos and aquariums can provide a safe environment in which animals may survive, but not necessarily thrive.

Whilst the welfare implications of life in captivity are significant and must be addressed, for many species it is the only viable option to secure their future.

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Conference Report

Inspiring the future of clinical academia: INSPIRE National Intercalators' Research Conference

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The fourth INSPIRE National Intercalators' Research Conference took place in the Wills Memorial Building, Bristol, in 2018. This one-day conference saw over 150 delegates attend from across the UK, including Cardiff, Exeter, London, Ireland and more.

Over 80 posters were presented (**Figure 1**), with a further 30 oral presentations by students. The themes of the presentation sessions included dentistry, surgery, neurology, cardiology, paediatrics and population health. Delegates voted on presentations according to their content, presentation style and research impact, with the top-rated presenters being awarded prizes.

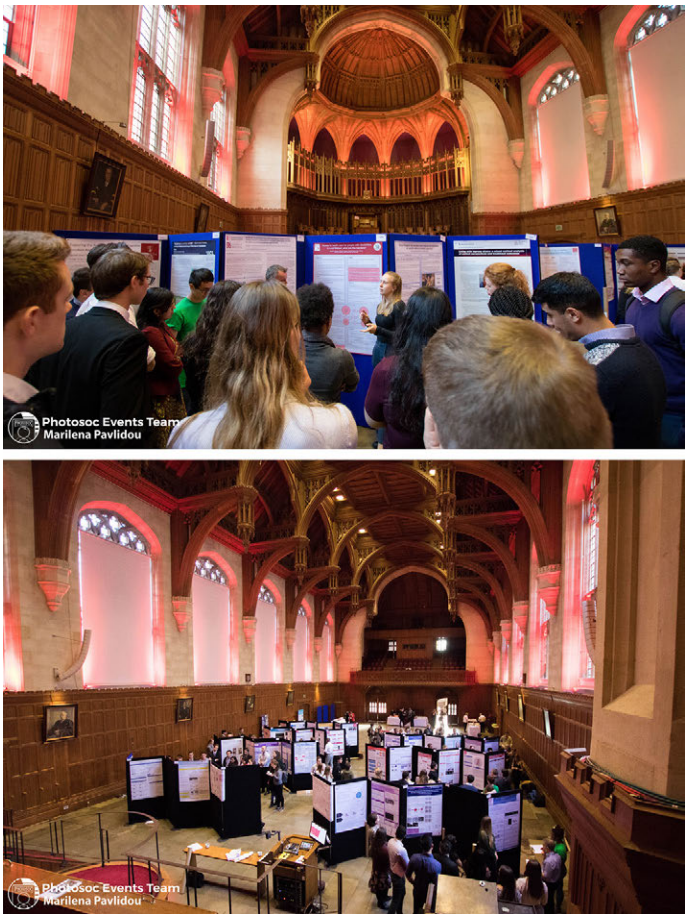

Figure 1. Poster presentations in the Wills Memorial Building. Image credit: Marilena Pavlidou.

The keynote speech from Professor Sadaf Farooqi, FRCP, FMedSci, was an inspiring insight into her time as a medical student and how she entered the world of research (**Figure 2**). A series of clinical academics of different training levels also gave talks on their careers and the challenges they have faced. It was clear that there is more than one route into research and it is always possible to start at any stage in your career, whether as a first-year student or core trainee.

Figure 2. Professor Sadaf Farooqi delivering her keynote address. Image credit: Marilena Pavlidou.

The conference showcased the many opportunities of intercalating, such as moving to a different university, carrying out master's degrees and the chance to conduct longer projects, boosting your CV and future possibilities of research success.

Overall, it was impressive to see medical, dental and veterinary students presenting such high-quality research. Presenting and networking with fellow academics at a national conference gave students a taste of the research world.

A great accomplishment was the £750 raised through delegate's donations for the Bristol Children's Hospital's charity, 'Above and Beyond'.

We are grateful to the University of Bristol and the Association of Physicians of Great Britain who sponsored this superb event. We look forward to the next conference.

Interview

Professor Oliver Hanemann: a nexus between clinician and scientist

Consultant Neurologist
Chair in Clinical Neurobiology
Associate Head of Peninsula Medical School (Research)

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Introduction

For the modern clinician, in addition to exercising one's clinical repertoire, evidence of research enterprise has become a cardinal pillar in their portfolio. It is increasingly important for medical students to obtain a holistic understanding of a career in research alongside clinical practice. The aim of this article is to provide an appreciation of the benefits of research, including top tips on how to get involved. To this end, a face-to-face interview was conducted with an eminent researcher who has achieved the delicate nexus between being an insightful clinician and an enterprising scientist: Professor Clemens Oliver Hanemann.

Prof. Hanemann trained at medical schools in Hamburg, Glasgow, Baltimore (Johns Hopkins) and Cambridge, USA (Harvard). Following a Deutsche Forchungsgemeinschaft (DFG) research fellowship, he undertook clinical and academic posts, including working as a consultant neurologist and senior lecturer at Duesseldorf and Ulm University, Germany, all whilst continuing to exercise a voracious appetite for conducting neuroscience research. Over the years, he has acquired an extensive portfolio, including a multitude of publications, and has been a senior reviewer for more than 17 international journals. He built and was founding director of the Institute of Translational and Stratified Medicine (ITSMED) in the Faculty of Medicine and Dentistry at the University of Plymouth. He also leads a national centre of excellence for brain tumour research.

Questions

How did your journey into research begin?

So, I guess it was different from when I went to medical school. If you wanted to get a good job after medical school, you were almost expected to do research. If you wanted to go to the best training centres, there was no way you could train there without doing any research. I started off with a research fellowship in the same hospital I trained in afterwards. It allowed me to establish an idea of the research field, getting addicted to it, and to establish working relations with a research group, which I could then re-join during my clinical training. After starting with two years of research, I went into clinical training where there was a mechanism where you could buy yourself back into research if you got some grant funding. This became possible and I knew where to go back to as I had my projects and collaborations going.

What do you think are the benefits of undertaking a PhD alongside clinical work?

It is very important that you get a deeper systematic and scientific insight into a specific area, be it brain tumours or neuroscience or cancer. Especially here in the UK, the medical training is very clinical- and practical-orientated. So, a very thorough understanding of a specific topic is a very complimentary approach to the current teaching, and scientific thinking is different from thinking. Clinical thinking is very practice-based and guideline-following. Scientific thinking is different; it is problem solving. You have a bit of intellectual freedom. You design an experiment, you fail, discuss it with colleagues, read a bit, try it again, fail again, you finally succeed, you build a story, present it at meetings… So, it is a process of systematic in-depth working and intellectual freedom.

What is the subject of your current research interest?

My current interest is in brain tumours and we are a centre of excellence for low-grade brain tumours. As I see patients with brain tumours, I run clinics for low-grade brain tumours, so that gives me the motivation to research biomarkers and therapies. But I'm fully aware, as I have been doing research for a while, that this is not a question of just going back into the lab for a couple of days, weeks, months and then I find a cure. No, it takes a long time. But I'm confident that finally I myself, or people I have trained with or colleagues, will succeed. So that's why I'm doing research.

I drifted into brain tumour research as I was doing neuromuscular research earlier on Schwann cells. So, my current field is a mixture of serendipity, drifting into it, and then the conscious decision from seeing patients with it.

How do you manage to combine clinical work with research?

It's a constant battle. During my career I've always asked myself, should I stop this one or the other? You must reserve time for both research and clinical practice in an appropriate way. I don't think you can do a day research a week; you must block time to do research or clinical work, otherwise you lose your focus. There is no doubt that it's difficult to combine it but it's worth it – it's worth the suffering!

What would you advise a student interested in undertaking research?

I would probably advise to do research earlier. In the UK, commonly the tendency is to do it when you reach specialist training but then it's probably too late. I would advise to do it well earlier and preserve some time for it.

What are the three most valuable skills you have learnt from undertaking research?

1. Scientific thinking. It's different from what you do in the clinical routine. It's a different kind of approach.
2. Openness to discussions and other ideas.
3. Not a skill precisely but being part of a scientific community is a thing which I value greatly.

What would you advise students when selecting a research project?

You need to get more information about what you like, try to taste what research is like and what you personally like. You could do clinical research projects, for example, in functional MRI of the brain and that is totally different from doing brain tumour research in the lab. For some 4 year PhD studentships, for example, you do taster research work in different groups to then make an educated decision to study what you like. Similarly, with the Inspire scheme, you can volunteer in the summer, and there are also other possibilities where you can get a taste of research, discuss with your potential supervisor and then make a semi-educated decision. But you need to taste to make an educated decision.

Contribution statement The author of this article has substantially contributed to the conception, design, drafting and editing of this work. Final approval of the version has been provided by the author (and the interviewee)

Advice for dental electives

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What is an elective and why should I do one?

A dental elective is a clinical placement where you can experience different sides of dentistry, from working in developing countries with the bare minimum of materials and equipment, to working in specialist fields with state-of-the-art technology. Going abroad for an elective is a great way to open your eyes to dentistry in different countries. It provides experience working within different cultures and learning the limitations that some countries face on a day-to-day basis. It is also a great way to keep your brain in 'dental mode' during the summer!

When should I do an elective?

This is very much dependent on your degree and dental school. Some will incorporate an elective as part of their programme, but this was not the case for my course and, so, it was something I went about organising myself during the summer of my third year. By this time, I had completed all my practical competencies and felt I was well equipped with the skills and experience needed to get the most out of my elective.

I spent 4 weeks of my summer in Zambia; this allowed enough time to familiarise myself with the hospital and city in which I was working, to get to know the people I was working with and to explore the country, learn about the culture and ultimately be a 'tourist'. It also meant I had time before and after my elective for some 'R&R' at home before heading back to university in September.

Where should I go and who should I go with?

Here are some things you may wish to consider to help you make your decision on where to go and which provider to go with.

How long is the travel time? There are many different locations and opportunities for electives. Where you choose is dependent on which part of the world you want to see and explore. It's important to consider how long it is going to take you to get there. If you are only on placement for a short while, you may not want to spend the best part of 24 hours on a plane. Don't forget to factor in transfer times from the airport: for some locations you may have a long bus/car journey the other side.

What to organise yourself and what will be organised for you The company I went with was Work the World (www.worktheworld.co.uk). Luckily, they did almost everything for me: transport from the airport, accommodation, hospital/city orientation and work visas. This was great as it took a lot of the pressure off. All I really had to think about were flights and immunisations. (On a side note, don't forget to get your travel vaccines sorted early – I left mine quite late and ended up having one in each arm on the same day, which is not comfortable!). You can check what vaccines you need on the NHS website (www.fitfortravel.nhs.uk/destinations).

There are many different companies offering elective packages as well as Work the World, including:

- Elective Africa (www.electiveafrica.com/program/dentistry_electives)
- Floating Doctors (www.floatingdoctors.com/programs/dental/)
- One-2-One (http://one2oneworld.org/)

How much is it going to cost me? Dental electives are not cheap. It's important to consider the length of time you wish to go for and research different travel options. Make sure you know the full breakdown of costs when looking at the different companies. Some will cover accommodation, airport transfers and meals, whilst others will consider these extra costs. Don't forget to budget for spending money too: a big part of your elective will be exploring and experiencing a new country and culture! Keep a look out for bursaries or grants from professional bodies to help fund your trip, for example, the British Medical and Dental Students' Trust–Royal Society of Medicine (BMDST-RSM) Student Elective Awards (www.rsm.ac.uk/prizes-and-awards/travel-grants-and-bursaries/).

Is the company a non-profit organisation? This is something I didn't consider when I organised my trip. I thoroughly enjoyed my elective and got a great deal of experience. Being in the hospital allowed me to see lots of different cases, such as general dentistry, maxillofacial surgery and acute trauma patients, such as road traffic accidents and Ludwig's Angina. However, friends who completed an elective with a charity organisation also had a great experience; they found it very rewarding being in a position to help those with little or no access to any other dental care.

Will I get hands-on experience or will it be more observational? If you want to get 'stuck in' assisting in clinics, a more observational placement isn't going to be for you. However, you want to make sure the placement you choose has suitable supervision. As students, there are things we haven't seen or done before and you do not want to get yourself into a situation you cannot handle.

What other departments are available to visit? I had the opportunity to visit the maxillofacial team for part of my elective; observing in theatre and assisting with their clinics was a great experience. This isn't something that will necessarily be advertised, so it is important you ask questions about possible opportunities beforehand.

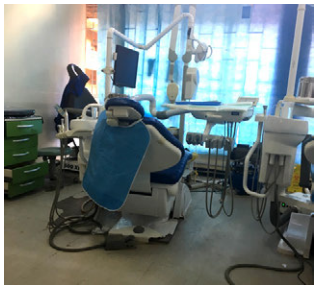

Figure 1. Dental Unit, University Teaching Hospital, Lusaka, Zambia.

What type of clinic will I be based in? Working in a busy city hospital is completely different to working in a rural clinic and so it's important to find out what environment you'll be placed in. Luckily, I had the opportunity to spend time in the hospital in the capital of Zambia as well as spending time in a rural village living with a host family. These were completely contrasting experiences and it was fantastic to see both sides. The hospital had the standard set-up of dental chair **(Figure 1)**, dental equipment and access to radiographs, whereas in the rural village there was no facility for dentistry at all. I was seeing patients who had been experiencing problems for years and had to do the best I could for them with the little equipment that was available **(Figure 2)**.

Figure 2. Examination of patient in pain in a rural village outside of Chirundu, Zambia.

What activities/sights are there in the area? Although a lot of your time will be spent working in the clinics, evenings and weekends are your time to explore the country you have chosen to visit. It's wise to research this before you go: plan what you want to see and do whilst you're away. I visited Victoria Falls **(Figure 3)**, which was beautiful, and went on multiple safaris **(Figure 4).**

Figure 3. Victoria Falls, Livingstone, Zambia.

What language is spoken locally? Will there be a language barrier? Remember English may not be the dominant language where you are going, therefore, you may want to think about learning some of the language before you go. Luckily for me, English is the official language of Zambia, so it was easy to converse with both dentists and patients in most situations. Bear in mind that the professionals you are working with will be busy, so if you don't speak the language, it may not be possible for them to translate every conversation for you.

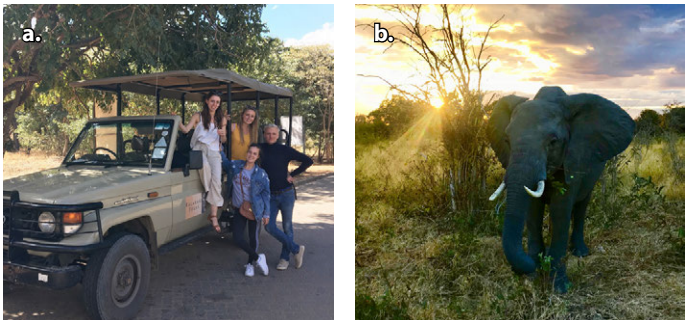

Figure 4. Safari excursions. (**a**) Ready for our overnight safari, Chobe National Park, Botswana. (**b**) Elephant at Sunset, Chobe National Park, Botswana.

What's the risk? Travelling to an unfamiliar country can be dangerous for a number or reasons: there may be unrest in the country, high crime rates, as well as health risks, such as common diseases or high rates of blood-borne viruses. The gov.uk website on travel advice (www.gov.uk/foreign-travel-advice) is a good place to start as it gives information on safety and security, terrorism, law and health. It will give a good idea of what the country is like as a whole and how safe you will be. It's advisable to ask about where you'll be staying and how you'll get to and from your place of work. Is it a secure compound? Will you be on public transport or walking? Don't forget indemnity insurance for whilst you're away; you can easily contact the Dental Defence Union (DDU) or Dental Protection, who can advise how to acquire this and it is usually free in most instances (https://www.theddu.com/for-students/your-elective/electives-guide/2018-electives-guide/how-we-can-help-you and https://www.dentalprotection.org/uk/benefits-renewal/student-dentist/your-elective). Like all trips abroad, you'll need to consider travel insurance. I purchased a comprehensive package from the company I went with, which covered extra things such as cancellations for exam failure, exposures to biological fluids, HIV needle-stick injuries, medical equipment cover and student loan cover for injuries limiting study. If you use an independent company you will need to ensure that they will cover you for these things, which may be additional costs.

The lowlights?

With all trips there are going to be ups and downs along the way.

• Location: although I managed to get out and do a lot of fantastic things, it took a lot of travelling and organising as most activities were quite far out from where I stayed in Lusaka. This is why it is really important to thoroughly research where you will be staying and what there is to do in the local area.

• Physically and emotionally draining: I experienced some challenging sights whilst away. Witnessing a young boy who had recently been involved in a road traffic accident to patients who had passed away on the wards. Make sure you get some downtime to recuperate after the long days and that you have people around you to speak to if you have a particularly challenging day.

Despite this, all these challenges add to the overall experience of the elective.

The highlights?

• You'll get to see another part of the world and experience life from another perspective. Working in another country, alongside some wonderful, experienced people and learning how dentistry works in a developing world is a privilege.

• You'll meet people from all over the world. I made friends who I am still in contact with now and hope to be for a long time.

• By immersing yourself into that country's way of living, you'll be able to experience the culture in a way you wouldn't by travelling there on holiday.

Take full advantage of the sights whilst you're away. We flew to Livingstone to see Victoria Falls, which is a must – it's clear to see why it is one of the natural wonders of the world! From there, we took a boat across the river to Botswana and spent 2 days in the African bush on safari, getting really close to Africa's big five and eating dinner around a campfire! It really was one of the best experiences of my life so far.

By going with a company, I had people who I could contact and ask all these questions to during the run up to my trip. They were on hand via phone or email when I needed them, both whilst in the UK and abroad. For me it was the best way to make organising a trip like

this the easiest and most convenient experience. If you decided to organise an elective independently, I would advise you to thoroughly research where you are going and get help and guidance from as many people as possible with experience in this area to ensure nothing gets forgotten. I would highly recommend doing an elective to anyone, it has really been one of the most memorable parts of my degree. You get to put into practice everything that you have been taught and get to see dentistry in a whole other light.

Review

Prevention of ventilator-associated pneumonia in ICU: chlorohexidine plus toothbrushing vs chlorohexidine alone—a critical appraisal

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Abstract

Aims Ventilator-associated pneumonia (VAP) is one of the most common infections that occurs in the intensive care unit (ICU). It has significant risks of morbidity and mortality, alongside increased care costs and length of hospital stay. Unfortunately, the current guidance to prevent VAP does not correspond with the most recent evidence available regarding oral care methods in the prevention of VAP. The aim of this appraisal was to investigate the efficacy of oral hygiene interventions for the prevention of VAP, specifically comparing use of chlorohexidine (CHX) alone and with toothbrushing.

Methods This appraisal investigated whether toothbrushing plus CHX, an antimicrobial mouthwash, more efficiently prevents VAP vs CHX alone. A search was conducted using Medline, the Dentistry & Oral Sciences Source (DOSS) and the Cumulative Index of Nursing and Allied Health Literature (CINAHL). The search was limited to randomised control trials (RCTs).

Results Two RCTs were included in the study. One of the RCTs showed a significant reduction in the mean time on ventilation (p=0.018) in the toothbrushing plus CHX group vs the CHX only group. However, overall, there was no significant difference in VAP occurrence in either of the studies when toothbrushing was added to CHX vs CHX alone.

Conclusion Well-designed RCTs with larger sample sizes are needed in the future to establish the significance of oral care in the prevention of VAP. Holistic care is crucial in ICU and oral hygiene could play an important role in reducing mortality associated with nosocomial infections, such as VAP.

Introduction

Mechanical ventilation gives critically ill patients the ability to keep breathing when they are unable to do so on their own. However, this comes with the risk of developing ventilator-associated pneumonia (VAP), a hospital-acquired infection that can be fatal.[1] According to the Oxford Handbook of Clinical Medicine,[2] 20% of patients admitted to the intensive care unit (ICU) and in need of ventilation for 48 hours (or longer) develop VAP. Some reports even show that up to 67% of patients admitted into intensive care will develop VAP.[3] This can potentially increase a patient's hospital stay, mortality risk and care cost.[4] Therefore, an effective VAP prevention bundle **(**see **Text box)** is crucial for increasing the chances of saving more patient lives.

Humans are composed of more microbe than human cells, being outnumbered 10:1. The oral cavity, alone, contains over 700 different microbe species, including viral, fungal and bacterial microbes. In addition, the oral cavity provides various surface types, such as mucosa and teeth, and aerobic and anaerobic environments.[3] Therefore, with a complex habitat that allows microbes to form biofilms, the oral cavity is essentially a harbour of opportunistic infection, which could be deadly for the already unwell patient in ICU. Oral care is, thus, included in the VAP prevention bundle, with the aim of decreasing the microflora load and reducing the risk of aspiration of potentially virulent species into the lower respiratory tract.

Dental plaque has been shown to have a population of over 100 million bacterial cells.[3] Plaque is composed of complex biofilms made by oral bacteria. The bacteria form extracellular polysaccharides (EPS), providing an armour-like housing and nutritional source.[3] Chlorohexidine (CHX), an effective antiseptic that can be used as a mouthwash, has been proven to be effective at reducing plaque. However, CHX may not be able to fully remove and penetrate plaque. An effective way to remove this structure is by brushing, thus, not allowing stagnation to occur in the mouth (hence the dental recommendation of brushing twice a day).[5]

CHX can cause anaphylaxis (all be it rare), and a study carried out by Klompas et al in cardiac patients has brought into question the efficacy of CHX vs its risk.[6] Current guidelines from The National Institute for Health and Care Excellence (NICE) have since withdrawn the recommendation of use of CHX for the prevention of VAP,[7] and the Intensive Care Society (ICS) is in agreement.[8] However, a Cochrane review that was carried out in 2016 concluded that the inclusion of CHX in oral care significantly decreases VAP occurrence from 24% to 18%, saving up to one in 17 patients.[9] However, this review also reported more research was needed to assess the significance of toothbrushing in the prevention of VAP. The BMJ Best Practice indicates that CHX is still commonly used in ICU.[10] Moreover, the Australian Guidance for Infection Control in Healthcare (2019) states that, where indicated, the use of CHX is appropriate for the prevention of VAP in ICU.[11]

With the oral cavity being the major gateway to the respiratory tract, it is important to review these guidelines and form definitive, clear instructions for practitioners and nursing teams. This appraisal accepted the effectiveness of CHX and investigated if toothbrushing alongside CHX increases the efficacy of oral care to reduce the incidence of VAP in ICU vs CHX alone.

Key components in the VAP prevention bundle

- Head elevation
- Sedation interruption
- Subglottic drainage
- Deep-vein thrombosis and gastrointestinal-bleed prophylaxis
- Oral hygiene

Components are examples that have been extracted from Chacko et al[12]

Methods

A search of the literature was conducted using Medline, accessed via Ovid. In addition, a combined search of the Dentistry & Oral Sciences Source (DOSS) and the Cumulative Index of Nursing and Allied Health Literature (CINAHL), accessed via EBSCOhost, was also carried out. The search was limited to randomised control trials (RCTs) in the English language that compared CHX and toothbrushing oral hygiene methods, excluding those published before 2016. The search was carried out in November 2018 (see **Figure 1**).

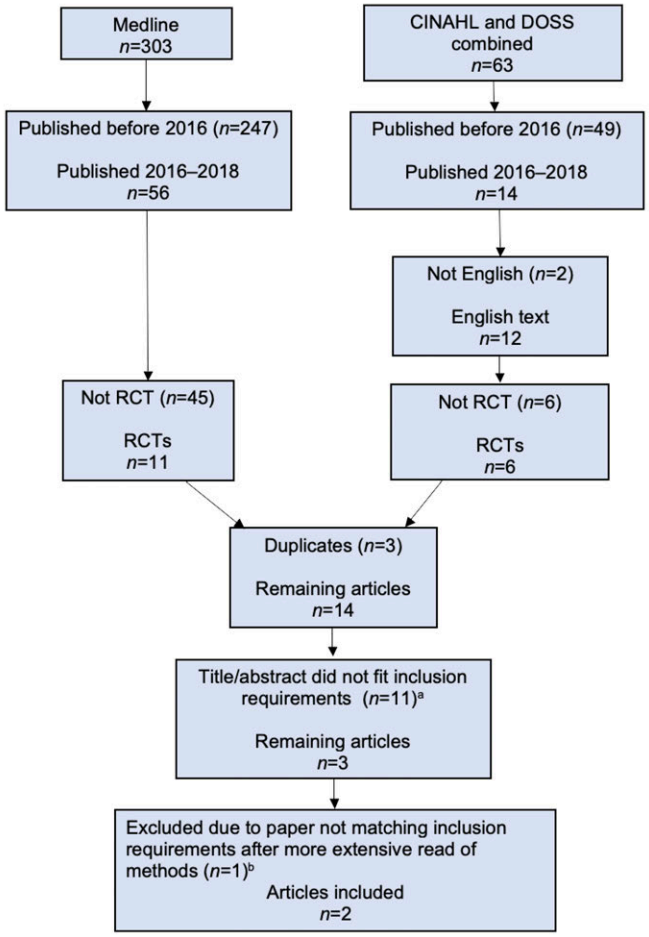

Figure 1. Flowchart of database search. Numbers excluded at each step are shown in brackets. [a]Oral hygiene methods differed to those being investigated. [b]Article did not allow the comparison of tooth brushing in addition to CHX use with CHX use alone.

Results

RCTs included Two RCTs were included in this appraisal: de Lacerda Vidal et al[13] and Chacko et al.[12] The relevant findings from each RCT are shown in **Table 1**.

Table 1. Summary of RCT results: toothbrushing plus CHX vs CHX alone.

Variable measured	Findings from de Lacerda Vidal et al13	Findings from Chacko et al12
VAP occurrence	Reduced (p<0.084)	Whole cohort: no change (p<0.82); males: reduced (p<0.01)
Mean time on ventilation	Reduced (p<0.018)	Reduced (p<0.001)
Mortality	No change (p<0.064)	No data
Time spent in ICU	No change (p<0.064)	Reduced (p<0.001)
Risk of bias	High	High
Applicability	Low	Low

Findings The results in **Table 1** demonstrate that the addition of toothbrushing to CHX treatment, vs CHX alone, significantly reduces the mean time a patient needs ventilation. Chacko et al[12] carried out a multivariant regression analysis showing VAP risk increases by 1.3 times with every day a patient is mechanically ventilated, which may support the use of brushing alongside CHX. However, overall there was no significant reduction in VAP occurrence between the two groups. There was a non-significant reduction in mortality and length of ICU stay for those receiving toothbrushing in addition to CHX as compared to those receiving CHX alone.

Risk of bias and applicability During the appraisal, it was found that the risk of performance bias in both studies was high **(Table 1)** because the nursing teams could not be blinded as they would have had to have known what method of oral care they were carrying out (toothbrushing cannot be concealed). Therefore, the strength of applying the results to real practice is limited, since it is hard to determine if the lack of blinding influenced the results and, thus, the true effect of the intervention.

Discussion

Extensive research and debate regarding oral care has occurred recently, leading to both NICE[7] and the ICS[8] retracting advice to use CHX. However, evidence has suggested that CHX use may help to reduce the risk of developing VAP. However, even with evidence suggesting benefits to CHX application, it has not yet been reintroduced to guidance, yet still seems commonplace.

Biofilms can increase bacterial resistance to antiseptics due to the protection offered by the complex EPS matrix.[14] This supports the theory that incorporating toothbrushing into oral care with CHX use may offer more benefit than use of CHX alone. With the additional mechanical removal of biofilm/plaque, it is thought that VAP incidence would be further prevented when toothbrushing is added to CHX. Both studies included in this appraisal suggested that toothbrushing may be used in combination with CHX to prevent VAP; however, the findings were not significant and larger studies are needed to detect any true significance.

Although no significant difference was found in the occurrence of VAP with the addition of brushing to CHX in oral care vs CHX alone, a holistic approach to mouth care is still important. Patients who are mechanically ventilated have an inhibited cough reflex and are more prone to dry mouth. Therefore, due to the decrease in saliva, the patient's oral environment experiences less buffering and protection, leaving the teeth and soft tissues more prone to infection. These environmental changes lead to an imbalance of the oropharyngeal flora, which is suspected to increase the likelihood of developing VAP.[13] Therefore, as oral health deteriorates, the risk of VAP increases.[12]

The appraised articles showed significant decreases in time spent on mechanical ventilation with use of toothbrushing plus CHX vs CHX alone. This could lead to greater applicability of the results because, according to Chacko et al's multivariant regression analysis,[12] VAP risk increases by 1.3 times with every day a patient is mechanically ventilated. The studies also showed a non-significant reduction in length of stay in ICU with combined toothbrushing and CHX vs CHX alone, which could decrease the cost of patient care. Moreover, this could free ICU beds, potentially relieving some pressure on an already strained healthcare system.

Additional advancements in the prevention of VAP With current oral care guidance on the prevention of VAP conflicting with the most-recent evidence regarding CHX use,[9] and with the addition of toothbrushing to CHX showing non-significant reductions in VAP occurrence vs CHX use alone, it may be time for new innovative protocols to be implemented to help decrease the number of patients developing VAP, such as photodynamic therapy.[15] This therapy uses a combination of a photosensitiser dye, light and oxygen to decrease

the bacterial microflora. It has the advantage of not being limited by antimicrobial resistance (unlike CHX) and is less invasive than brushing, decreasing the collateral risk of introducing a transient bacteraemia and the possibility of aspiration, limiting the risk of introducing potentially virulent species into the lower respiratory tract.

Conclusion Control of the oral microflora remains a crucial part of the VAP prevention bundle. Therefore, further development of the guidance for oral care in the prevention of VAP is needed. In doing so, more lives in the ICU could be saved. Providing up-to-date evidence on decreasing bacterial load within the oral cavity should be carried out, creating the most effective guidance. In the future, well-designed RCTs with larger sample sizes may help to establish the correlation between the different oral care methods and the incidence of VAP. Holistic care is crucial in ICU and oral hygiene care can contribute to reduced mortality associated with nosocomial infections, such as VAP.

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Review

Whodunnit? When the question finally turns to science and medicine

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What is Mendelian randomisation?

Mendelian randomisation (MR) is an increasingly popular observational epidemiological method that uses genetic variants combined with the principles of randomised controlled trials (RCTs) to examine whether a causal association can be found between a given risk factor and a disease. The validity of the results rests on assumptions that, although cannot be directly tested, can be scrutinised by methods to check for violations. This article discusses the main principles in MR and its most common applications.

Medicine has often been described as a spider web of associations between different diseases and risk factors. Almost every research article ends with the statement "correlation does not prove causation" and ends with the comment "more research is needed." So, the question arises: how are we able to really understand causative factors in associations?

RCTs are recognised as the highest form of evidence in the hierarchy of evidence. However, this method is also limited; for ethical reasons, we cannot simply assign one group to interventions such as drinking alcohol or smoking.

This is where MR can contribute to research. Unlike conventional observational studies, this method can be used to find the causal association between risk factors and disease using genetic variables. MR makes use of the random allocations of genes that naturally occur at conception.[1] Most commonly, single nucleotide polymorphisms (SNPs), which are differences of a single nucleotide in a sequence of nucleotide bases, are used as the independent variable. Just as a change in one letter can change a word and its meaning, likewise, a difference in a nucleotide base can change the SNP and what it codes for **(Figure 1)**. Some people may inherit one version of the SNP and therefore a particular gene variant, or allele, and others may inherit another variant. Thus, conveniently, the population is randomly and permanently sorted into groups.

Mendelian randomisation rests on several assumptions for the analysis to be valid:[2,3]

1) the instrumental variables (SNPs) are associated with the exposure (risk factor);

2) the instrumental variable is not associated with confounding variables related with the outcome variable;

3) the instrumental variables are associated with the outcome (disease) only through the exposure variables.

Apart from the first assumption, which can be empirically tested, these assumptions are difficult to test, and may not always be completely met. However, many MR analysis methods and sensitivity analyses can be used to test if any of these assumptions have been violated.[1] Some MR methods allow specific assumptions to be violated to some extent but can still return a valid outcome.

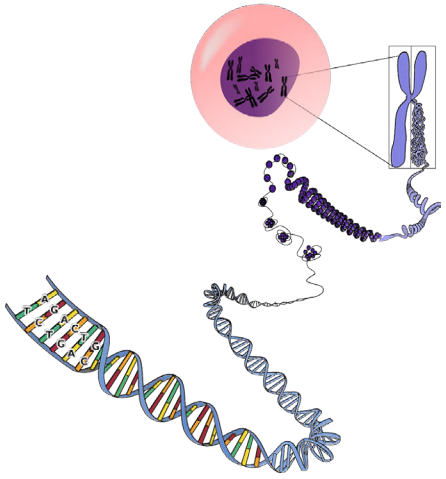

Figure 1. The nucleus of a cell with several chromosomes inside. One chromosome has unravelled to show nucleosomes, which in turn unravel to show DNA, with its double helical structure. The two DNA strands are composed of nucleotides, and a sequence of several nucleotides make up an allele, or gene variant. A difference of one nucleotide base in the sequence is termed a SNP. Image from https://pixabay.com.

A fictitious example can demonstrate the randomisation of SNPs: SNP1 has a T nucleobase and SNP2 has an A nucleobase in its place. Thus, both are different SNPs and can lead to two different outcomes. A part of the population may inherit SNP1 and others may inherit SNP2.

SNP1: AAGGTTCC → disease A = 44%
SNP2: AAGGTACC → no disease = 56%

In the example above, 44% of the population have SNP1, resulting in 44% of the population also having an increased risk for developing disease A. Likewise, 56% of the population have SNP2, which means they have a reduced risk of developing disease A.

Surprisingly, beyond disease risk, our DNA, genes and SNPs may be responsible for many of the decisions we make,[2] even ones such as whether we are likely to drink alcohol or are an early riser. One's genes and DNA are fixed at conception and so there is no chance of external factors influencing or changing the DNA after this moment.[3,4] This avoids the problem of figuring which came first, the disease or the risk factor causing the disease, and thus whether the risk factor caused the disease, or the disease caused the risk factor.

The fundamental idea of MR is to find SNPs associated with the risk factor we are testing to see if they are related to the disease. This SNP must not be related to other confounding factors associated with the disease, or even directly with the disease itself, except through the risk factor. If we then find that the SNP is associated with the disease, this must be due to the risk factor causing the disease.[1]

In the most commonly conducted MR analysis, risk factor (exposure variable) data and the outcome variable data are obtained from different samples. This means data from publicly available giant consortia can be used, resulting in large sample sizes for the analysis **(Table 1)**. As there are many consortia, it is possible to test for causal associations between different pairs of risk factors and outcomes.[5] There are many applications and limitations to a MR study, some of which are shown in **Table 1**.

Table 1. The applications and limitations of MR analysis and studies.

Applications	Limitations
MR analysis can be cheap to conduct if data are available from publicly available Genome- Wide Association Studies (GWAS).	Data consortia for the relevant risk factor or outcome may not be available.
MR studies allow triangulation and the use of many methods to test for potential violations of MR assumptions.	There may not be updated GWAS studies in the relevant field. Thus, only very few and weak SNPs may be available for analysis.
MR analysis is less likely to be affected by reverse causality compared with other types of studies, like case-control, cross sectional and cohort studies.	The GWAS studies may have a small sample size.
MR results provide a stronger form of evidence compared with observational studies.	The analysis will not be correct if the assumptions for MR methods are not met.
MR studies are increasingly common, and the methods are now widely recognised.	The second and third MR assumptions are difficult to test empirically.

Previously, MR studies have been used to establish a causal association between obesity and smoking behaviours,[6] triglycerides and cardiovascular disease incidence,[7] and many other important associations.

By using MR we may be able to develop a greater understanding of some of the toughest questions facing medicine today, including a better insight into diseases and how to deal with them.[2] It could thus allow us to better inform decisions and government policies, and ensure we are providing correct advice.

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Review

The use of multi-omic approaches to study the microbiome during disease states paves the road towards comprehensive understanding of disease processes

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The human microbiome encompasses the microorganisms (also known as microbiota), their genomes[1] and the surrounding environmental conditions of where they are found throughout the body.[2] The microbiome is highly varied in the population,[3] affected by genetics, dietary changes and mode of delivery at birth.[4,5]

The integrative Human Microbiome Project (iHMP) is the second phase of the Human Microbiome Project (HMP). The HMP sought to examine taxonomic and metagenomic elements present in the microbiome of healthy individuals and those in specific disease states. It concluded that more nuanced studies looking beyond microbiome composition are needed to fully appreciate the host–microbiome interplay during good health and diseased states due to significant inter-individual compositional variation.[3] The iHMP sought to use multi-omics, the study of analytes such as metatranscriptomes, metabolomes, microbiome composition and cytokine profiles, longitudinally to study host–microbiome interactions during three specific states: inflammatory bowel disease (IBD), preterm birth (PTB) and prediabetes. This article aims to explore and summarise the findings and conclusions of the three flagship studies conducted as a part of the iHMP.

Multi-omics in IBD

Lloyd-Price and colleagues looked at identifying potential multi-omic changes in participants with and without IBD.[6] They found cross-sectional differences, such as decreased metabolome diversity and the lack of vitamin B5 and B3 in the guts of individuals with IBD compared with those without. Analyte variation corresponds more with dysbiotic periods than with IBD phenotype, making it difficult to determine whether dysbiotic changes were a cause or a result of IBD. Extensive taxonomical shifts were observed in both groups, but IBD cases had a slightly higher rate of shifts and the species undergoing the greatest change in relative abundance differed between groups. The study chose to forgo collecting samples from patients selected for active disease and instead focused on subsets of inactive and relatively more active IBD. This may have caused the lack of significant difference in metagenomic species (species genomes recovered in samples) between participants, a result that contradicts existing studies.[7-9] This is because these subsets of IBD cases may be metagenomically closer to non-IBD controls than to active IBD. Therefore, future studies must compare metagenomes of all four subsets (active IBD, inactive IBD, relatively more active IBD and non-IBD patients) and establish a consensus. The multi-omic approach enabled the analysis of how each analyte varied in IBD, allowing for closer study of cross-sectional changes during the disease course. Studies with homogenous methodology and larger cohorts are necessary to understand the aetiology of IBD, leading to development of management and therapeutic strategies.

Preterm births and the vaginal microbiome

Building on previous studies to find population-specific effects of the vaginal microbiome composition on the risk of PTB, Fettweis and colleagues[10] compared the vaginal microbiome between two groups of mothers experiencing either term birth (TB) or PTB delivery. Throughout longitudinal analysis, taxa abundance and transcription activity varied differentially and, in some cases, similarly between PTB and TB women throughout pregnancy. For example, women who had PTBs experienced large decreases in *Sneathia amnii* during pregnancy as compared with those who had TBs, but both groups experienced decreases of *Gardnerella vaginalis*. Interestingly, the

changes differed by women's ancestry, suggesting that ancestry possibly influences pregnancy taxa dynamics. PTB-associated taxa decrease throughout pregnancy, therefore, samples from early pregnancy are more useful for predicting adverse outcomes. A model based on four taxa in samples taken at 24 weeks' gestation was produced to predict the risk of PTB delivery using vaginal microbiome profiles. It had 5–7% greater sensitivity and specificity but a slightly lower area under receiver operator characteristic (AUROC) curve (0.723 vs 0.764) than a purely clinical model, meaning that the clinical model is slightly better at predicting risk of PTB. With some improvements and refinement, this microbiome model's remit can extend to all populations, showcasing the model's impressive potential. The formulation of a sensitive and specific model in the study demonstrated that the vaginal microbiome has an impact on the risk of PTB. Improving our understanding of the underlying mechanisms will help to improve health outcomes in the estimated 15 million PTB deliveries that occur worldwide[11] through preparation and, potentially in the future, therapeutic intervention.

Prediabetes

Zhou et al examined the microbiomes of healthy individuals and those with prediabetes or diabetes aiming to better understand associations of biological processes at the earliest stage of these conditions.[12] Individuals were categorised by measuring HbA_{1c}, fasting glucose and annual oral glucose tolerance. Sixty-six of the 106 participants underwent insulin suppression tests and were classified as either insulin sensitive or insulin resistant using steady-state plasma glucose (SSPG) measurements. Following adjustment, multi-omic measures strongly correlated with SSPG. Known associations of SSPG, such as with inflammation, were also confirmed. Both insulin-resistant and insulin-sensitive groups had unique and significant associations between analytes and gut microorganisms. Correlations seen in insulin-sensitive individuals were absent in insulin-resistant individuals; the findings suggested that insulin resistance affects the interaction between gut microorganisms and host cytokines. Respiratory viral infections (RVIs) were found to dysregulate molecular pathways, including insulin receptor signalling and neuroinflammatory signalling, which were not previously shown to be affected by RVIs. The differences between the insulin-resistant and insulin-sensitive groups (e.g. the affected pathways) were attributed to the elevated baseline inflammation and impaired immune response seen with insulin resistance. Surprisingly, immunisations inversely correlated with type 1 diabetes and type 2 diabetes signalling and downregulated insulin receptor signalling. The fact that strong interpersonal differences exist and that variations in profiles can be contained within 'healthy' reference ranges in the disease states was highlighted by the study,[12] and demonstrates the need for large population studies in this field. Further studies are required to identify patterns present in healthy individuals and in those at risk of type 2 diabetes on a population level that would help to predict outcomes despite the significant interpersonal differences and variation. The impact of insulin resistance on the microbiome and how that culminates in the dynamics between RVIs, immunisations and the risk of developing metabolic disorders in insulin-resistant individuals was explored by this study, undoubtedly contributing to improving the treatment of insulin-resistant individuals.

Conclusion

The microbiome's far-reaching influence on health outcomes is just being appreciated through the findings of pioneering studies, like iHMP. Future studies must establish causal links between host–microbiome interplay and disease processes to open up new avenues for diagnosis and clinical interventions. Multi-omic studies will have a key role in this process because they facilitate the comprehensive study of the microbiome, as seen in the three studies discussed in this article. It is clear that the coming years will be exciting for the study of the microbiome.

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Review

Macrophages in gut disease

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What are macrophages?

Macrophages are innate (non-specific) immune cells that are the body's first line of defence.[1] Major organs in the body have their own native population of macrophages, deposited during embryonic development, including Kupffer cells (liver macrophages) and glial cells (brain macrophages).[2]

Macrophages in the gut

Recent insights have extended the characterisation of macrophage populations within the gut. Classically, macrophages can be activated to acquire one of two functional roles: M1 inflammation-causing macrophages and M2 anti-inflammatory macrophages. While M1 macrophages are in charge of attacking foreign bodies (such as disease-causing bacteria), M2 macrophages are responsible for wound healing.[3] Recent research shows macrophage function is less binary, with macrophage cells having a spectrum of different functions within the gut. For example, a transcriptomic study by Xue and colleagues, in Bonn, Germany, found that ten unique macrophage signatures were present, each occupying a different functional niche within the gut.[4] Imbalances in these macrophage populations in the gut have been thought to contribute to the underlying pathology of certain diseases, such as colorectal cancer and types of inflammatory bowel disease, such as ulcerative colitis (UC) and Crohn's disease.[5]

What makes macrophages in the gut different to others?

Macrophages in the gut have a unique transcription profile that can be dynamically influenced by molecular signals in their micro-environment.[6] Interestingly, saturated fats increase M1 polarisation of macrophages in the gut, and it is suggested that mice fed high-fat diets have a much larger M1 macrophage population in the gut when compared with lean mice, potentially leading to greater gut inflammation.[7] In addition to being one of the largest macrophage reservoirs in the body, the gastrointestinal (GI) tract is also one of the most microbe-rich organs, containing several trillion 'healthy' microbes, called the microbiome.[5] This environment is highly adaptive, being influenced by everything from diet to pathogens.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) refers to autoimmune dysfunction characterised by chronic inflammation of the colon and rectum. There are two major classifications of IBD: UC and Crohn's disease. In UC, the innermost lining of the large intestine is subject to inflammation and ulcers/sores.[8] Crohn's disease consists of inflamed patches that can occur anywhere within the intestinal tract, but commonly develop in the small intestine (**Figure 1**).[9]

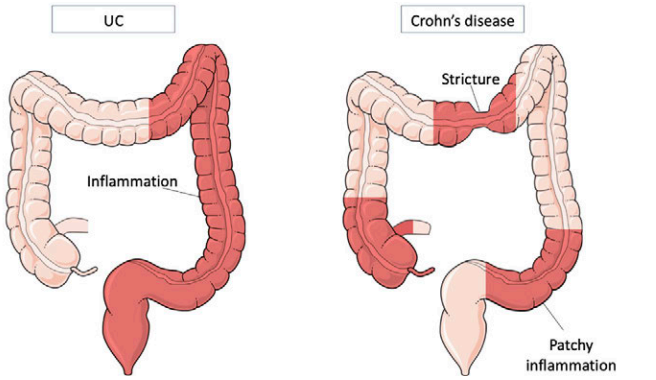

Figure 1. Summary of the pattern of disease in Crohn's disease and UC.[9]

Normally, M2 macrophages make up the majority of the gut macrophage population. However, a recent study found that the proportion of these macrophages decreases greatly in Crohn's disease, due to infiltration of M1 pro-inflammatory macrophages. Macrophages can be polarised from monocytes to the M1 or M2 state (**Figure 2**).

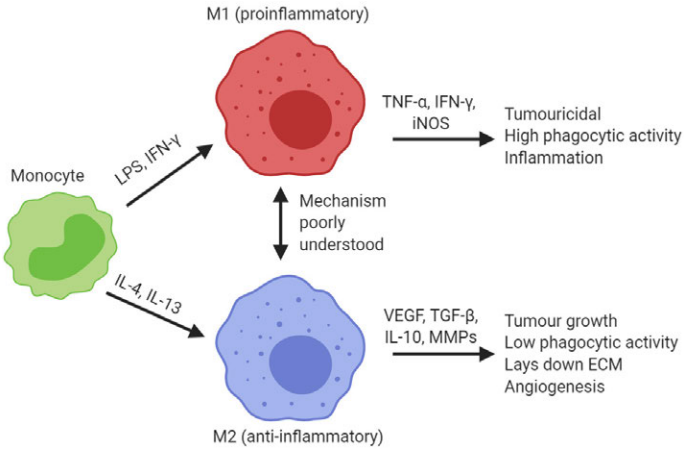

Figure 2. Binary polarisation model. M1 and M2 macrophages both derive from monocytes and their fate is decided by different stimuli. Due to their high plasticity, M1 macrophages can polarise into M2 macrophages and vice versa; however, the molecular mechanisms behind this are not well understood. M1 macrophages are pro-inflammatory and M2 macrophages are anti-inflammatory.[10] ECM, extracellular matrix; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; TGF-β, tumour growth factor-β; TNF-α, tumour necrosis factor-α; VEGF, vascular endothelial growth factor. Figure adapted from Hidalgo-Garcia et al,[11] distributed under the terms of the Creative Commons Attribution License (CC BY). Created with BioRender.com.

Treatment of Crohn's disease and UC depends on severity of the disease.[12] Treatment rationale is mainly based on targeting pro-inflammatory molecules, with surgery also being an option for patients, as stated in the National Institute for Health and Care Excellence (NICE) guidelines.[13,14] However, surgical intervention can bring about big declines in patient quality of life and may only provide temporary relief.

As previously stated, compounds in certain foods alter macrophage subtype populations in the gut. For example, genistein (a soya compound) was found to attenuate colitis through its induction of M2 macrophage polarisation.[15] Therefore, dietary modification could provide therapy for individuals with chronic gut disease. Additionally, it has been found that vitamin D supplementation decreases M1 macrophage-associated cytokine levels in IBD; however, it has not been found to induce M1 to M2 polarisation.[16] Use of therapeutic antibodies, such as infliximab, which targets the inflammatory mediator tumour necrosis factor α (TNFα), has proven to be controversial due to the unpredictable adverse response that patients with Crohn's disease have towards them. While most are probably influenced by multiple factors, it is thought that the patient's metabolism is the main determinant for lack of a beneficial response to anti-TNFα.[17]

Colorectal cancer

Colorectal cancer is the third most common cancer worldwide. Unlike IBD and its associated disorders, it is the polarisation of macrophages to M2 macrophages that contributes to colorectal cancer pathology. M2-like polarisation of tumour-associated macrophages (TAMs) seems to be linked to improved tumour blood flow through promoting expression of vascular endothelial growth factor, which initiates blood vessel formation.[18] TAMs also play an important role in tumour progression through inhibiting T cell anti-tumour responses. Most clinical investigations of macrophage subtypes in colorectal cancer have aimed to identify biomarkers that could aid clinicians in monitoring disease progression. In a recent study, levels of M2-like TAM were found to be correlated with distant tumour metastases through M2 TAM-driven release of circulating tumour cells. Monitoring these circulating tumour cells may help clinicians determine if post-operative chemotherapy is required. In addition, M2 macrophages seem to play a role in drug resistance in cancer therapy through expression of specific transporters (secreted protein acidic and cysteine rich [SPARC] and mannose receptor [MR]). This further highlights the diverse roles that gut macrophages can fulfil in different pathological states.[19]

Conclusions

Given the involvement of macrophages in chronic gut diseases, future research may benefit from developing therapeutics that alter macrophage behaviour in order to cure, or at least prevent exacerbation of chronic gut diseases. Regarding colorectal cancer, further research must be done and a description of standard M2 TAM levels and the establishment of reference ranges for clinicians must occur in order to enable the use of M2 TAM cells in diagnostic oncology as a predictive and/or prognostic biomarker.

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Review

Strategy for the global eradication of poliovirus: a model for infectious diseases

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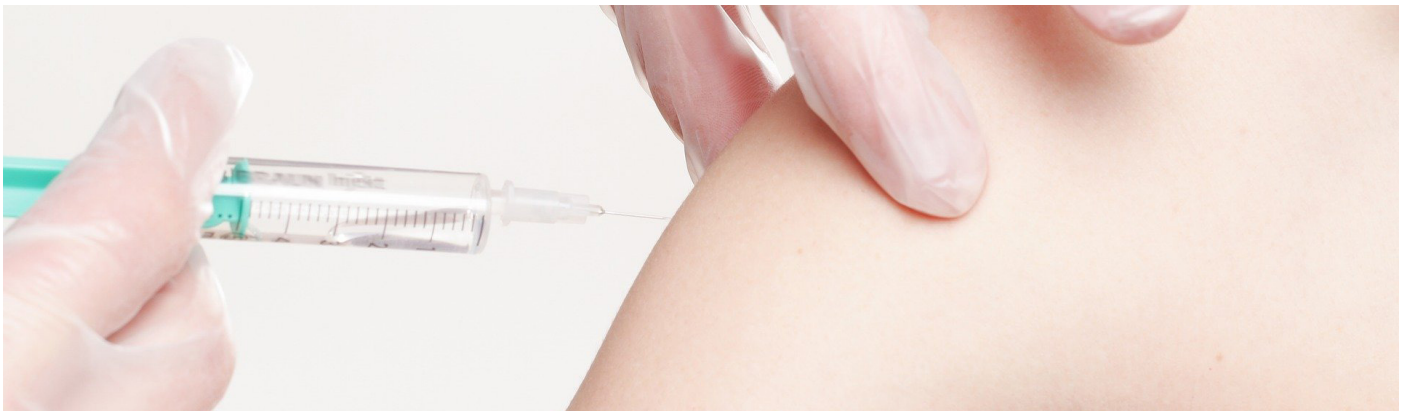

The past two centuries have witnessed a tremendous reduction in the rates of mortality and morbidity as a result of communicable disease. These changes are fundamentally due to an improved health infrastructure, increased availability of intervention tools, such as vaccines, and amended hygiene-related practices. The global eradication of poliovirus has been a crucial issue on the public-health agenda for several decades. If polio is successfully eradicated, it will represent the third disease in history to be fully eliminated (preceded by smallpox and rinderpest, respectively). This forms the discussion of a much greater narrative with an increase in global outbreaks of vaccine-preventable diseases. The aim of this article is to consider the challenges that complicate eradication efforts, using poliovirus as a model. An understanding of global strategies will inform future efforts to eliminate infectious diseases.

Background

There have been numerous outbreaks of poliovirus, with cases recorded as early as the eighteenth century.[1] Transmission occurs both directly, through aerosols and faeces, and indirectly, via contaminated food and water sources.[2] Whilst asymptomatic in the majority of cases, infection with poliovirus may lead to debilitating paralysis with no curative treatment available.[3] Effective vaccinations include the inactivated polio vaccine (IPV) and the oral polio vaccine (OPV).[4]

Considerations of eradication programmes

Vaccination against infectious diseases introduces several benefits: (1) the ability to control spread; (2) elimination of disease; and (3) the possibility of eradication. Eradication represents a permanent reduction and is possible once the reservoir of the causal agent has been identified, control measures are in place to interrupt transmission and surveillance has been implemented.[5]

To formulate an effective eradication strategy, it is important to consider the factors that encourage viral dissemination. For example, poliovirus has been shown to survive in soil for many months.[6] Contamination may occur through unsanitary conditions, ineffective sewage systems and lack of irrigation.[7] In such conditions, the virus exists in abundance, increasing disease prevalence and making eradication efforts systematically harder.[8]

The success of an eradication campaign is also heavily reliant on social and political commitment. From a political standpoint, it is imperative to note that, in the developing world, where nations are vulnerable to civil war and other disturbances, eradication programmes may not be a national priority.[9]

Strategy in practice and problems faced

In 1988, the eradication strategy put forth by the World Health Organization (WHO) was based on four key stages: maintaining routine immunisations, supplementary immunisation, global surveillance and 'mop-up' campaigns.[10]

Numerous features contribute to the recrudescence of a virus, including the failure to vaccinate and inability to institute control measures. In the developing world, the cost of manufacturing and the availability of technical facilities makes vaccine development difficult to sustain.[11] The added pressures of climate and a deficit in refrigeration resources contribute to the concern of preserving vaccine efficacy and potency.

Since efforts began, recorded cases of polio have decreased by 99%.[12] Today, polio remains endemic in three countries (Nigeria, Afghanistan and Pakistan).[13] Despite a robust eradication programme, there have been many challenges to the eradication of polio. For example, eradication in Nigeria has been difficult due to political instability and insurgency.[14] Furthermore, the northern district of Nigeria is curtailed by illiteracy, with a population that regards the government as corrupt and untrustworthy.[15] In 2003, vaccinations in the metropolitan district of Kano, Nigeria, came to an abrupt halt when rumours circulated between tribes that the vaccine was associated with sterility.[16] Convincing local leaders that these rumours had no foundations was not easy and by the time health officials had been able to do so, the virus had dissipated beyond Nigeria's borders. The virus spread to countries where poliovirus had been previously

eliminated and the cost of rectifying the consequences amounted to more than $500 million.[17]

In densely populated regions, campaigns have been created to target sanitation habits (i.e. regular hand washing), as poor sanitation contributes to viral dissemination. However, monitoring such practices is impossible. Furthermore, in developing countries, more vaccine doses may need to be administered to elicit herd immunity.[18] This means sourcing and distribution becomes an issue and keeping track of those in need of vaccines is logistically difficult.

In Afghanistan, incidence is closely linked to instability and uncertainty; in some cases, this is a lack of trust towards the vaccine itself and its production in the United States.[19] Levels of migration are often high, with individuals moving due to natural disasters, financial struggle and violence. Porous borders in countries of political–economic fragility further exacerbates spread.

Conclusion

The task to declare the international community polio-free is taking longer than expected. Whilst variables beyond international jurisdiction may complicate efforts, vaccine hesitancy plays a significant role in disease resurgence. In 2019, the WHO listed refusal to vaccinate as one of the top ten threats to global health. With vaccination being a cost-effective strategy in disease prevention, understanding underlying reluctance to it will be imperative to eradication efforts.

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Review

Is it ethically justifiable for oncologists to deny female breast cancer patients of fertility preservation options prior to cancer treatment based on their pre-conceived concerns?

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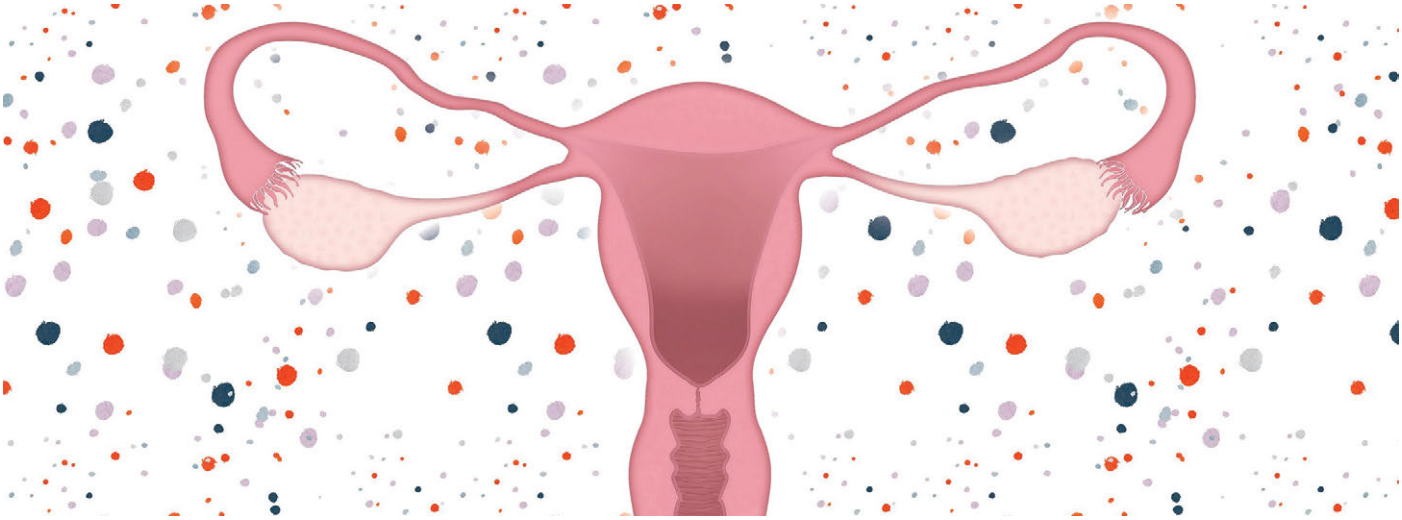

Recent advances in cancer therapeutics has led to an exponential rise in the number of female cancer patients in reproductive ages surviving cancer, which raises the issue of post-treatment quality of life (QOL). Reports reveal that some oncologists have not been adhering to guidelines set out by the National Institute for Health and Care Excellence (NICE) in supporting routine fertility preservation consultation (FPC) prior to these patients undergoing gonadotropic cancer treatments. From current research, some clinicians' presumptions and lack of knowledge of medical advances are hindering them from informing patients of the risks gonadotropic therapeutics have on fertility and the various fertility preservation options available. This is impeding patients' right to autonomy, thus going against the principle of non-maleficence. The aim of this paper is to analyse the reasons why some clinicians do not provide crucial information about fertility to female cancer patients and whether the ethical implications it has on patient safety are justifiable.

Introduction

Improvements in early diagnosis and therapeutic options in the last 40 years has led to an increase in survival rates, including those of female cancer patients of the reproductive age. Thus, adequate post-treatment quality of life (QOL) is increasingly significant.[1]

Cancer therapy, including chemotherapy, can cause off-target gonadotropic effects leading to premature ovarian failure and, in some cases, permanent infertility.[2] Several international studies have recommended that an additional decision-making process, called fertility preservation consultation (FPC), is added in order to improve QOL.[3] As a result, the National Institute for Health and Care Excellence (NICE) have published guidelines that ask for oncologists to discuss ways of improving long-term QOL for cancer patients, such as fertility preservation, before the commencement of gonadotropic cancer treatment.[4] There are several fertility preservation options currently available, including embryo cryopreservation and oocyte cryopreservation.[5]

Despite the evidence and guidelines, many cancer patients of the reproductive age still do not receive adequate information about fertility preservation options or undergo FPC.[6] A UK survey on breast cancer patients found that up to 88% were not referred to fertility reproductive specialists and were uninformed of the adverse effects that chemotherapy would have on fertility.[7] In addition, a recent systematic review found that only 41–44% of adult breast cancer patients felt that their fertility concerns were adequately discussed.[8] Research indicates that these unmet needs have led to psychological distress in patients.[9]

The aim of this article is to highlight the reasons why some oncologists are not adhering to NICE guidelines on counselling female cancer patients on the side-effects of their treatment on fertility or referring them for fertility preservation treatments, and to discuss the ethical implications this has on patients.

Methods

A comprehensive search was performed using PubMed, NICE evidence and google scholar to find articles and journals published between 2009 and 2019. The following search terms were used: "fertility preservation", "female breast cancer patient", "ethical

communication" and "oncologists". Reference lists of chosen studies were screened for other potentially relevant publications.

Studies included were prospective, retrospective, randomised controlled trials (RCTs), population studies and meta-analyses. To minimise selection bias, studies that did not focus on breast cancer patients were excluded. In addition, generic google searches using the same inclusion criteria stated above were also carried out to find suitable websites and news articles to obtain information on patient perspectives.

Results

Concerns associated with fertility preservation

Delay of cancer treatment UK guidelines emphasised that at the time of diagnosis, clinicians should discuss the potential risk of infertility caused by cancer treatment.[4] However, this is not being consistently adhered to.[6]

In line with the principle of beneficence, which is to act in the best interest of the patient, several clinicians believe that it is justifiable to withhold information from women about fertility preservation options so that it would not cause delays in cancer treatment.[10] A recent survey carried out in doctors from across the world found that over one-third of clinicians have never consulted the guidelines on this topic.[11] One study found that the reason behind these types of actions by clinicians was owing to their beliefs that fertility preservation procedures would be time consuming and that initiation of treatment should be the priority instead.[12]

Recent literature has aimed to tackle this apparent time pressure to complete fertility preservation.[13] A novel treatment regime, called random-start ovarian stimulation, has been developed, which reduces the duration of ovarian stimulation, from 4 to 2 weeks, with the same success rates.[14] Similarly, a recent study by Kitano et al in 2019, with the largest sample of cases to date, found that undergoing fertility preservation was not associated with treatment delay in breast cancer patients.[15] Researchers have emphasised that early referral for fertility preservation is paramount for the procedure to occur in a timely manner. Therefore, this evidence should reduce concerns about perceived delays in cancer treatment, enabling more female cancer patients to undergo fertility preservation.[16]

Breast cancer reoccurrence or proliferation As breast cancer is the most prevalent cancer among reproductive women in the UK, many ethical concerns surround fertility preservation in this population of patients.[17] Previously, for fertility preservation, high levels of oestrogen were required for controlled ovarian hyperstimulation (COH) before oocyte and embryo cryopreservation can occur. Clinicians have speculated that these high levels of oestrogen may have negative consequences for ~60% of breast cancer patients who are 'oestrogen-receptor (ER)-positive'. This means that their cancer cells grow in response to the hormone oestrogen, potentially leading to cancer reoccurrence.[18] Therefore, some doctors believe that allowing this to occur goes against the principle of non-maleficence as it may be deemed as unsafe practice.[19]

In a new study, novel protocols for fertility preservation that contain aromatase inhibitors, such as letrozole, in combination with gonadotrophins decreased the high levels of oestrogen previously observed during COH, whilst still allowing the collection of multiple oocytes. However, there were several limitations to this study, including small sample size, short time of monitoring and methodological issues, such as failure to report data on demographics.[20] Data from larger cohort studies showed promising results in that there was no difference in cancer reoccurrence in patients who did not undergo COH using aromatase inhibitors alongside gonadotrophins in comparison with those who did. Based on this evidence, the above method is now routinely used for ER-positive breast cancer patients undergoing oocyte cryopreservation.[21,22,23] However, recent alternative methods, such as retrieval of immature oocytes after in vitro maturation, which requires no treatment to stimulate the ovaries, could pave the way for a preferable method for fertility preservation in breast cancer patients.[24] With implementation of these novel protocols being deemed safe based on recent evidence, doctors' concerns over patient safety (non-maleficence) associated with COH should be reduced, promoting FPC to take place.

Poor prognosis Data from a survey revealed that oncologists found discussions related to the risk of infertility and fertility preservation options challenging and uncomfortable to have with female cancer patients who have poor prognosis for survival.[25,26]

In certain cases, a female cancer patient may die before the use of her stored gametes or ovarian tissue. With her consent, fertility preservation may be used to conceive a child following the death of the patient, otherwise known as posthumous assisted reproduction (PAR). Some doctors have raised concerns about whether it is ethically justifiable to allow a child to be conceived in these circumstances, knowing that the parent has a decreased life expectancy and may die prior to the birth of the child.[27]

PAR may be a legitimate procedure under the ethical principles of beneficence and autonomy. The European Society for Human Reproduction and Embryology (ESHRE) have stated that PAR is permitted within the conditions that: (1) written consent is collected; (2) the surviving partner is notified and thoroughly informed of possible future implications; and (3) treatment is initiated within a 5-year span after death of the parent. These outlines are useful; however, they do not mitigate how very challenging this topic is.[28] Therefore, each individual case must undergo considerable ethical analysis to weigh up the advantages and disadvantages of PAR, without any preconceptions from the doctor preventing key discussions with patients and their families.[26] More research is needed on the outcomes of PAR in children born as a result of PAR and their families, as limited data is available on this crucial topic.

Conclusion

In conclusion, pre-conceived beliefs held by some oncologists, which hinder them from abiding to NICE guidelines, go against the ethical principle of autonomy. There is strong evidence that denying FPC to female cancer patients is correlated with a further decrease in QOL and psychological distress, which may affect their compliance to future treatment, leading to patient safety risks.[9] Data from several systematic reviews highlight the critical need for clinicians to provide timely, detailed and accurate information on the side effects of cancer treatments with regards to fertility, and the options for fertility preservation available to female cancer patients of reproductive age.[8,9,20]

Clinicians should be encouraged to continuously keep up to date with knowledge surrounding current protocols available for fertility preservation. This will aid them in supporting patients' overall decision making and maximise opportunities for patients to have more cycles of COH prior to gonadotropic treatment plans.[29] Future research should aim to use larger sample sizes, novel methodology and longitudinal monitoring to analyse the concerns and experiences of female cancer patients with fertility preservation, which may lead to a deeper understanding of this crucial subject area.[30]

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Review

Folic acid in pregnancy: a need to obtain universal coverage

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Neural tube defects (NTDs) are conditions in which the central nervous system has an opening from early development, and they have been known to be prevented by adequate intake of folic acid during the early stages of pregnancy. Due to this evidence, many countries have implemented mandatory fortification of staple foods with folic acid to reduce the number of preventable NTDs. This paper aims to evaluate some of the current methods in place to achieve better/universal coverage of folic acid and to make recommendations on how to widen the coverage of folic acid use in pregnant women. This literature review concludes that the current Healthy Start programme used by the UK government to promote folic acid intake during pregnancy is wholly inadequate in preventing NTDs and mandatory fortification should be implemented to follow the success of other countries.

Introduction

The evidence for increased folic acid intake in pregnancy to reduce the number of neural tube defects (NTDs) in offspring has been known since the Vitamin Study by the Medical Research Council (MRC) in 1991.[1] Yet 2000 preventable NTDs were estimated in the UK from 1998 to 2012, and it is predicted that this number will continue to rise at a rate of 150 deaths per year.[2] Folic acid is a naturally occurring compound in healthy diets and is found in a variety of foods, including dark leafy greens, avocados, lentils and nuts.[3] The National Institute for Health and Care Excellence (NICE) guidelines state women should take 400 µg of folic acid daily during pre-conception, and should continue to take folic acid tablets until the twelfth week of pregnancy.[4] Women who are at higher risk of having offspring with NTDs are advised to take 5 mg of folic acid daily before conception and to continue to do this until the twelfth week of pregnancy. These recommendations are to prevent children being born with NTDs, such as spina bifida and anencephaly, which affect 5 in every 1000 births in the UK.[5]

How is folic acid intake promoted in pregnancy in the UK?

To investigate the approaches taken by the UK to promote folic acid intake in pregnancy, a literature search was conducted in November 2017 using the PubMed database (www.ncbi.nlm.nih.gov/pubmed) for primary research articles. Phrases such as 'folic acid', 'United Kingdom' and synonyms were used for the search. Articles included were limited to those with full-text availability and those written in the English language to ensure full comprehension. For basic definitions and government information, appropriate search engines and websites were used.

This search revealed that the current method used in the UK is targeted supplementation under the 'Healthy Start' programme. This programme was introduced in 2006 and is a statutory nutritional safety net for pregnant women and children under 4 years of age. It provides milk, fruit/vegetables and vitamins (A, C, D and folic acid), which are exchanged for vouchers.[6] However, substantial evidence suggests that this scheme is inadequate and has many shortcomings; these are discussed in more detail below.

Factors affecting the efficacy of the Healthy Start scheme

The uptake of the Healthy Start programme is extremely poor (estimated at 3–10%).[7] Barriers to uptake include the delay associated with the application process, as well as the strict eligibility criteria, meaning that vulnerable individuals, such as asylum seekers and prisoners, have been excluded from the scheme, limiting its benefits and overall impact.[8] Furthermore, women are expected to re-register subsequent pregnancies with the programme, instead of being retained in the system.[8]

In addition, NICE guidelines state that women should be taking folic acid before conception and up to 12 weeks after; however, the Healthy Start scheme only provides vitamins to women after 10 weeks of gestation, which means that the foetus is unprotected from abnormalities in the development of the central nervous system and spinal cord, which could lead to NTDs, and the supplements provided by the scheme have limited effects.[9]

Studies show uptake is lower in younger women, women for whom English is a second language and those from a low socioeconomic background.[7] Moreover, the helpline that handles queries relating to the Healthy Start programme is associated with a charge, which may serve as a barrier for those seeking additional help.[8]

Regarding initial exposure to the scheme, women reported it being mentioned briefly in the first prenatal visit to their healthcare practitioner but complained that, due to the vast quantities of information given, they often forgot about it or remembered the scheme when it was too late.[10] Furthermore, when healthcare professionals were asked if they mentioned the Healthy Start programme to pregnant women or during family planning conversations, many said that they did not, giving reasons such as lack of awareness of the scheme, uncertainty as to where women can access the supplements and, sometimes, a negative attitude towards use of supplements in pregnancy.[9] In addition, relying heavily on healthcare professionals to promote the scheme means some women are left out of it, such as those who meet healthcare workers later in the pregnancy, after the therapeutic window for folic acid (i.e. after the first 12 weeks of gestation). When health professionals were asked how they chose to bring up the scheme with patients, many reported using the patient's geographical location as an indicator of whether the patient was potentially eligible, which could lead to a small number of patients with a low income who live in affluent areas not being informed of the scheme.[8] In other studies, eligible, but non-participating parents were asked why they refused help; many reported that they felt a healthy diet negated the need for supplementation. This misconception highlights the need for healthcare professionals to address and carefully discuss with pregnant patients the risks that they may face from non-supplementation.[11]

Participants and healthcare professionals reported, in numerous studies, that they disliked the essential countersignature by a healthcare professional on the application form for the Healthy Start scheme, as this made the application process more arduous.[8] This process is necessary to show a link between public health initiatives and government priorities, and to ensure that healthcare professionals talk to pregnant patients about supplements and diet. However, it may be perceived as yet another hurdle for patients who do not see a healthcare professional in the early days of pregnancy.

Figure 1 below provides a summary of suggestions for improvement of the current Healthy Start scheme.

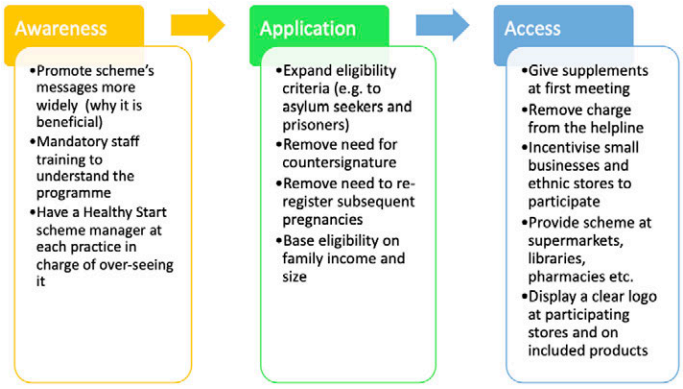

Figure 1. Suggestions for improvement of the Healthy Start scheme.

The American experience

In America, mandatory fortification of grain products with folic acid was introduced in 1998, adding 140 µg per every 100 g.[12] Despite this, the US Food and Drug Administration (FDA) Advisory Committee recommends increased folic acid intake, promoting this by using billboards to display shocking images of babies with NTDs, and featuring mothers of different ethnic backgrounds and ages that are usually left out of the Healthy Start programme because they tend not to consume these fortified goods.[10] It is hoped that this approach allows all population sub-groups to be given protection from NTDs. It also recommended that, for younger women, including those with teenage pregnancies, who tend to be less receptive to supplementation advice, the supplements should be a 'healthy lifestyle choice'.[10]

Mandatory fortification in the UK

Mandatory flour fortification with folic acid was recommended by the UK Scientific Advisory Committee on Nutrition (SACN) in 2006.[6] The main argument for this was that one in six pregnancies are unplanned.[13] Therefore, women who do not know that they are pregnant and do not intentionally take folic acid preconceptionally, will not leave their children susceptible to NTDs. In addition, a study in 2011 by Barbour et al investigated why some pregnant women did not take folic acid supplements; reasons included hectic schedules, nausea, peer influences and unplanned pregnancies.[14] Mandatory fortification may help to solve this problem. **Figure 2** illustrates barriers to universal coverage under the current Healthy Start scheme.

Conversely, there are reasons why mandatory fortification with folic acid has not been implemented by the UK government. For example, having a high folic acid intake along with a vitamin B12 deficiency could mask the symptoms of anaemia, which could be life-threatening.[15] It may also be possible that women from low-income backgrounds may not consume enough of the grains or fortified products to adequately benefit from this. In addition, there are concerns that excess consumption of folic acid could lead to an increased risk of certain cancers; however, this claim has been refuted by a meta-analysis.[16] It has also been claimed that the daily recommended intake of 400 µg of folic acid cannot be reached by fortification alone and that supplements are necessary,[17] indicating that fortification is unnecessary. These issues have been addressed by the SACN who recommend certain steps to ensure people are protected from the over-consumption of folic acid,[6] such as:

- Restriction of voluntary fortification
- Modification of supplement guidance for pregnant women
- Continued monitoring of the long-term impacts of folic acid fortification

Mandatory fortification in other countries

America, Costa Rica, South Africa, Chile, Canada and Argentina are some of many locations that have implemented a mandatory approach to folic acid fortification and have reported decreases in the number of NTDs, ranging from 19–55%.[18,19] In South Africa, it was found that, not only did the number of NTDs decrease after mandatory fortification, but the economic cost related to the prevention of these conditions outweighed the cost of implementing folic acid fortification.[20] In 2004, a meta-analysis found that increasing the current dose of folic acid from 0.4 mg to 5 mg could help to prevent 80% of all NTDs.[21] Such studies recommend that mandatory folic acid fortification is a strategy that all countries should implement. In contrast, in New Zealand, the main reason why folic acid fortification has not been introduced is because many see it as 'mass medication', which restricts consumer choice.[11,22] Overall, however, mandatory folic acid fortification has been beneficial, not just in decreasing the number of NTDs, but also according to cost-benefit analyses.[20]

Figure 2. Barriers to universal coverage of folic acid supplementation: the exclusion of potentially eligible families.

Conclusions

The current Healthy Start scheme to promote folic acid supplementation in pregnancy in the UK is not reaching pregnant women in an efficient manner.[23] The overwhelming conclusion is that mandatory fortification is the best method to achieve universal coverage of folic acid to prevent NTDs. However, the improvements suggested here should be adopted to enhance the Healthy Start programme until mandatory fortification is implemented.

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Review

The impact of social media on adolescent mental health: positive or negative?

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Background

Today's adolescents, 'Generation Z', have grown up with the internet and social media, with Ofcom figures indicating that 70% of 12–15 year olds have a social media profile.[1] In such an increasingly digitalised world, questions are starting to be asked about how social media affects the health of adolescents. Studies have looked at the dramatic changes social media has brought about in the way people communicate and the its impact on both behaviour and psychological wellbeing.[2] Data from the UK Millennium Cohort Study indicate that compared with the millennial generation, levels of depression are two-thirds higher and levels of self-harm are one-fifth higher in Generation Z and this is linked, in part, to the associated increase in social media use.[1] This article is a review of the current research findings on the impact of social media on adolescent mental health. The findings to date indicate that more research is needed as no conclusive results about the impact of social media have been reached as yet. However, emerging evidence does suggest that, with closer regulation and education on usage, social media can have a positive impact.

Introduction

Over the last few years, the increased use of social media has sparked controversy in the news. High-profile stories, such as the suicide of Molly Russell in 2017, which has been linked to social media use, led to a Government White Paper on online harms calling for stricter regulations to keep online users safe.[3] Actual research in this area seems limited and approaches used in older studies on internet use and its impact on adolescents need to evolve to encompass the wide range of social media in use today.[4] Comparing mental health in adolescents today with that in previous generations is not straight forward as definitions have changed and recent years have seen increases in people seeking help for mental health problems.[5] Between 2010 and 2015, there was a 31% increase in teenage suicides, and this occurred in parallel to steep increases in screen time and social media use; Twenge et al felt that this cannot be a coincidence.[6]

Literature search

A literature search was conducted in July 2019 using PubMed and Google Scholar, combining the terms "adolescent" "teenager", "social media" and "mental health". The search was limited to the past 5 years as this period is the most likely to capture information about social media rather than the internet as a whole. I tried to exclude papers focussing on screen time or general internet use rather than social media itself; however, this proved difficult as there was considerable overlap in many papers. The search found 400 papers, of which 14 were fully reviewed and seen as having the highest relevance for this article.

Summary of findings

Multiple studies identified clear potential for harm resulting from online activity and highlighted associations between social media use and depression.[1,6,7] They found social media use could contribute to sleep disturbances, low self-esteem and body image problems, all of which can contribute to mental health problems in their own right.[1,2,8] There also appears to be a greater detriment to the health of teenagers who are more "emotionally invested" in social media — a group defined as feeling distressed or "disconnected" when unable to access social media. Greater exposure to social media increased the likelihood of an impact on self-esteem, anxiety and depression, and often meant the teenagers would be on screens into the night, resulting in poor sleep quality, in turn, having a negative impact on mood and behaviours.[9]

In contrast, some papers acknowledge potential benefits of social media as a means of reducing social isolation and, for teenagers who find it difficult to express themselves, as a means of communicating distress and reaching out for help.[2,4,10] People with severe mental health problems may be more likely to share experiences via social media than the general population and a couple of studies have suggested this may contribute to their recovery.[7,8,11] Although some images found on social media negatively impact individuals who self-harm or have eating disorders, widespread education about safe internet use may allow use of digital media in therapy and recovery.[4]

Statistics show a decline in teenage pregnancy, smoking, alcohol abuse and violence over the past 20 years.[5] Therefore, it is questioned whether the dawn of the digital age can really be seen as the "downfall of a generation" as suggested by some papers.[6] A higher online presence may simply reflect current problems rather than directly cause them; this concept makes it difficult to separate online and offline behaviours.[5]

Cyber-bullying is not only identified as having a particularly negative impact on body image and self-esteem[12] but also shows an association with an elevated risk of suicidal thoughts.[8] A need for "likes" on Facebook or Instagram is causing individuals to change their appearance or behaviour. The constant scrolling through posts and pictures can also lead to teenagers making comparisons in terms of appearance or lifestyle, often contributing to low mood or feelings of failure if they perceive that somehow they do not measure up to their peers.[8]

It is argued that social media increases communication and connectedness;[10] however, it has limitations when compared with the support, empathy and compassion that face-to-face relationships can build. In a paper interviewing teenagers, they acknowledged these negative impacts, speaking of fear of missing out (FOMO), loneliness and anxiety, but also talked of a need to remain connected.[10] It is interesting to note that one paper reported that those with both high social media use and high in-person interactions had fewer depressive symptoms than those using social media with low in-person interactions,[6] whilst another suggested that those that used social media to connect with friends and family had a decline in depressive symptoms compared with those using it in isolation.[2] These observations suggest that the problem lies not with social media itself but in the reduction in face-to-face interactions. Several

studies suggest social media has no associated risks if used in moderation. Screen time of 5 hours or more per day has been shown to be detrimental for teenagers, but the same studies showed that shorter periods have a more positive effect on wellbeing than none at all.[5,6,13] These studies, therefore, suggest that social media should be seen as advantageous in that it allows a "connected world" but guidance should be given on safe usage and screen time.[14] As most of the studies were observational, even those that suggested a negative correlation cannot prove a causal link and are, therefore, unable to provide definite proof. **Figure 1** summarises the main themes mentioned in the studies included in this review, indicating how many reported specific positive or negative effects of social media.

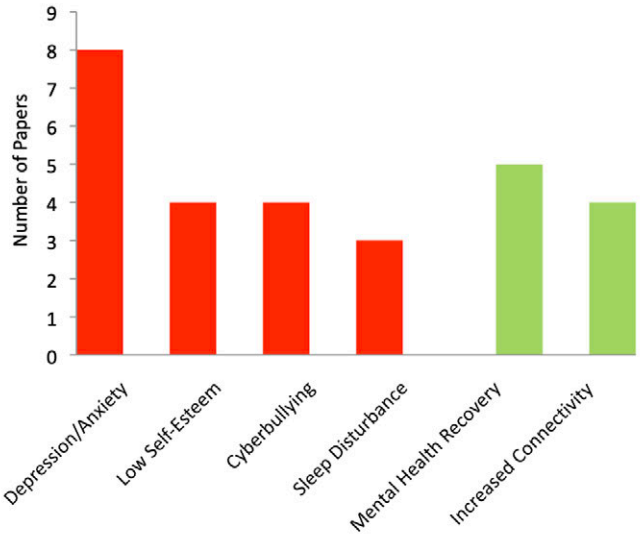

Figure 1: Number of papers included in this review that mention specific positive (green bars) or negative (red bars) effects of social media, by theme.

Discussion

A shift in attitude? Increases in social media use in adolescents today are likely to continue into their adulthood, reflecting the changes in habits and interactions of this generation. This, in turn, calls for adaptations and education on how to manage this.[12] The report leading to the Government White Paper called for a statutory code of practice for social media companies, stressing the importance of protecting children from harm when accessing social media sites but acknowledging the limited data available to assess the magnitude or nature of such harm.[15]

It seems that the focus should, therefore, be on adapting to social media use in everyday life by better understanding its risks and pitfalls and focusing on harnessing its positive aspects, namely, reducing social isolation, and incorporation into support and therapy. Encouraging education and reflection on social media use could be the first step in changing behaviours and introducing safer levels of use. Highlighting negative effects, the importance of a better night's sleep and not having screens in bedrooms could see teenagers start to regulate use.[1]

Conclusion Social media is a relatively recent development in the digital world, as is the constant access to it that smart phones allow. There are, therefore, limited empirical data and many papers only present anecdotal evidence in relation to the effects of social media on adolescent mental health. One difficulty in carrying out studies in this field is finding a control group, as it is difficult to identify a group of adolescents who do not use social media as a comparison. There is a clear need for more research in this area to gain a better understanding of the issues, especially as most studies thus far have been observational.

Evidence is emerging that seems to link increasing social media use to a negative impact on mental health, and reports like the UK Millennium Cohort Study are strong indicators that guidelines are needed on the safe use of social media. It is currently difficult to distinguish whether these effects are due to social media itself or the amount of screen time. However, it does highlight the need for social media companies to set out better regulations, not only on safety but also on hours of use.[1]

Acknowledgements Thank you to Dr Daniel Cooper (Oxford Health, Oxford, UK) for his hard work and enthusiasm towards this enjoyable and beneficial eSSC and also to all who helped him in delivering the teaching and guidance throughout this time.

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Review

Who cares for the caregivers? Application of vicarious trauma prevention research to prison healthcare professionals

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Vicarious trauma (VT), defined as disruption of an individual's important or fundamental beliefs about themselves, others or the world, is a complication of working with vulnerable patients. It affects the wellbeing of healthcare professionals, as well as their personal lives and ability to provide care. There is little literature on VT in prison healthcare professionals; however, vulnerable patient populations, empathy towards crime victims, the workplace environment and risk of assault place these individuals at risk. This study reviews the literature on preventing VT in high-risk healthcare professional groups, considering how findings could be applied to prison healthcare in the absence of group-specific research. Seven papers were included, covering VT prevention in social workers, rape crisis centre staff, obstetricians, intensive-care professionals and disaster workers. Successful interventions included both formal and informal workplace support, especially from senior staff, VT education and strategy teaching, and independent measures to build personal resilience. These interventions have potential application to prison healthcare. Group support appears especially appropriate, considering the complex environment and specific challenges. Future research looking into VT in prison healthcare is needed.

Introduction

Vicarious trauma (VT) is defined as disruption of an individual's important or fundamental beliefs about themselves, others, or the world, induced by prolonged exposure to patients' traumatic experiences.[1-3] This reduces the ability of healthcare workers to engage empathetically with patients and provide best care, having an impact on wellbeing. VT symptoms can mimic post-traumatic stress disorder and may include intrusive thoughts, depressed mood, tendency to withdraw, changes in world views, and negative impacts on self-esteem, feelings of safety and personal relationships.[1,3] If VT remains unidentified without intervention, it can develop into burnout, a state of emotional exhaustion and fatigue, to the detriment of professionals and institutions.[1,3]

Several factors within prison healthcare could promote VT. First, prisoners are vulnerable patients, with many having experienced difficult, traumatic lives, facing exclusion and social rejection. Prisoners are 13 times more likely to have been in care than the general population, up to half of female prisoners have experienced domestic abuse and one in three are thought to have experienced sexual abuse.[4] Furthermore, up to nine in ten have at least one mental health diagnosis, and risk of suicide is 3.7 times higher in the male prison population than the general male population.[4,5] As healthcare workers are trusted, patients may disclose past trauma. Consequently, over time, professionals accumulate secondary trauma from patients' experiences, creating a high-risk environment for VT.

Second, there is potential for empathy towards patients' victims, a unique prison healthcare factor derived from treating perpetrators rather than victims. Many professionals avoid details about patients' crimes; however, where details are known, there is potential for victim trauma to add to professionals' VT from dealing with prisoners, causing further secondary trauma.[3]

Third, prisons are noisy, overcrowded environments, often lacking facilities and resources to provide optimum healthcare. Noisier and harsher prison conditions correlate with poorer staff wellbeing, and increased smoking and drinking rates.[6] Reduced wellbeing could increase vulnerability to secondary trauma. Additionally, risk of inmate-on-staff assault is a potential stressor, especially if professionals have had previous incidents, increasing vulnerability to VT and burnout.[7]

There is limited literature describing VT risk in professionals with prolonged exposure to graphic descriptions of cruelty, abuse, assault and other traumatic events. However, there is little literature focused specifically on risk and prevalence of VT amongst prison healthcare professionals, and no interventions have been reported for the prevention of VT in prison staff. This study, therefore, reviews the evidence for VT prevention in other high-risk professionals, considering its application to prison healthcare professionals.

Methods

The online database Medline was searched (search date: 20 July 2018), identifying papers published between 2008 and 2018, using the search terms: "Vicarious Trauma" and "Prevention"; "Vicarious Trauma" and "Intervention". This provided 17 results. Inclusion criteria were English language, either 'prevention' or 'intervention' in the abstract, and discussing VT in healthcare professionals. Nine articles were excluded after abstract screening and, of the eight remaining articles, only four could be accessed. "Vicarious Trauma Prevention" was also searched on NICE Evidence (www.evidence.nhs.uk; accessed: 20 July 2018), giving 32 results, three of which met the inclusion criteria. Altogether, seven articles were included.

Results

The key findings from each of the articles included are summarised in **Table 1.** The main preventative measures were formal senior supervision, informal peer support (including support groups), education on VT and wellbeing techniques, improved working conditions, and individual measures to reinforce resilience.

Support was widely discussed, including both formal senior guidance and informal support from peers. Focus groups with oncology social workers highlighted the value of regular formal supervision sessions, tailored to seniority.[8] These groups gave opportunities for case discussions and reflection and supported professional development.[8] Several papers suggested younger professionals are at higher VT risk than more experienced colleagues, due to lack of experience or less-established coping mechanisms.[3,8,9] Therefore, senior supervision

should focus on younger professionals, tailing off as the professional becomes more experienced and senior. When surveying rape crisis centre staff, the protective role of supervision varied with seniority;[9] this is a factor to consider when designing support systems.[4]

The articles suggested that informal support from friends and family was useful,[10] but research focused on support from colleagues who understood workplace demands and trauma exposure. Informal support was valued, including discussions during breaks and within open-plan offices, and accessible open-door policies.[8] These gave social workers opportunities to discuss and debrief, helping minimise the emotional impact of work.[8] The National Society for the Prevention of Cruelty to Children's report on VT highlighted peer support in preventing isolation and promoting feelings of team working towards the same goal.[11] Case discussions and peer support was provided in monthly Balint groups for obstetrics and gynaecology doctors, which give clinicians space to discuss a patient that remains on their minds and recognise their emotional reactions to the case.[12] After 6 months, significantly lower levels of burnout and VT were reported and professionals found these groups so useful they were continued indefinitely.[12]

Institutions play a role in VT prevention through providing education and improving working environments. In one study in intensive care professionals, educational preventative measures were split into education about VT, awareness of symptoms and effects, and coping skills. Assessment of these preventative measures found that the most effective were person-directed interventions, such as relaxation, mindfulness, coping strategies and cognitive behavioural training.[13] Improvements in working environments, such as managerial awareness of caseload and ensuring even distribution of work between staff, also reduces the burden on individual professionals.[1,10] Provision of services, such as counselling, helps support employees by facilitating the processing of secondary trauma before it becomes problematic.[1,10] Using combined measures to support staff, institutions could reduce the risk of VT and subsequent burnout, benefiting both staff and patients.

Finally, independent measures to build up personal resilience were applied to disaster workers,[10] highlighting the importance of balancing professional, physical and emotional aspects of life by giving time to hobbies, relationships and emotional self-care.[10] Investing time into personal relationships was particularly important, creating a support network outside of work, further protecting against VT.[10]

Discussion

The VT risk from working with patients with traumatic backgrounds can be addressed by preventative measures. Staff support includes informal peer support, team building, socialising and case discussion. Combining formal and informal support, providing Balint and discussion groups for peer support, and one-on-one supervision may be options for incorporating support into prison healthcare. Barriers to the application of these interventions in prison healthcare include small teams and teams in which nurses, general practitioners and healthcare assistants are employed by different bodies. Alongside staff support, education on VT awareness, wellbeing, resilience and coping strategies can improve staff wellbeing and reduce the impact of secondary trauma. While training could be beneficial, time and resource pressures and dispersed teams make this more challenging within prison environments. Encouraging personal measures and hobbies may be more practical, encouraging work–life balance and self-care, alongside workplace support.

This review identified interventions to minimise VT risk in high-risk healthcare professionals. However, none of the studies included were conducted on prison healthcare professionals or in prison environments. Prison is a complex and unique workplace, so, although secondary trauma risk in prison staff is likely to be comparable with that in other healthcare professionals, key differences, such as potential empathy for patients' victims and chaotic, noisy workplaces, may limit intervention effectiveness. Furthermore, the studies included used small samples drawn from single institutions, and methodologies with limitations, such as cross-sectional studies or focus groups. Future research should focus specifically on prison healthcare professionals, using high quality study designs, such as randomised control trials, and large sample sizes, to increase confidence in intervention outcomes.

In conclusion, VT is a potentially serious complication of working within prison healthcare. A multifaceted preventative approach, strengthening an individual's coping mechanisms, alongside equal distribution of workload, informal and formal support provision and VT education, may help minimise VT risk.

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Table 1. Summary of results from articles included.

Authors, year [reference]	Cohort details	Type of article/study	Key relevant findings	Limitations
Joubert et al, 2013 [8]	Social workers based in an oncology department	'Exploratory study'. Quantitative data collected from four weekly focus groups assessing the impact of social work on their professional practice, personal lives and potential interventions. Quantitative data collected using scales (TSIBS and ProQOL), assessing positive and negative effects of helping clients who have suffered trauma	• The scales showed raised levels of intrusive thoughts, avoidance, numbing and heightened arousal in the group • The three main themes identified in the focus group were the 'professional role of social work', 'the uniqueness of oncology social work' and the 'role of supervision, professional development and wider organisational supports' • Regular supervision sessions were identified as an integral part of protection against VT, as these give opportunities for discussion, reflection and development • Significant importance was placed on informal support by peers, including meetings over tea breaks, open-door management policies and discussions within an open-plan office • Based on the focus group, a model was proposed for supervision of less experienced team members in oncology social work, with formal and informal aspects	• Small sample (n=16) • Results were collected in focus groups instead of individual interviews so risk of group opinion influencing individual's responses
Kanno and Giddings, 2017 [1]	Mental health professionals	Review	Defines the different types of secondary traumatic stress, including VT, and gives different preventative methods, including: • Regular supervisory meeting for processing traumatic cases • Peer support: informal or specific groups to form support networks • Equal distribution of case load • Education and training on self-care and coping mechanism • External supervision • Provision of formal counselling	• Acknowledges that few studies on preventing traumatic stress give strong empirical evidence • Does not look at the barriers to accessing preventative measures
Allen et al, 2017 [12]	Obstetric and gynaecology doctors	Assessment of effectiveness of an emotional wellbeing intervention (a monthly 'work-related emotional wellbeing intervention' [Balint group] for 6 months) using ProQOL score	• Scores significantly improved over the 6-month intervention (reduced burnout and secondary traumatic stress and increased compassion satisfaction) • The intervention was so successful that it has been continued indefinitely since termination of the study	• Small sample (n=22) • Lack of a control or comparison group
Dworkin et al, 2016 [9]	Rape crisis centre staff	Cross-sectional survey to assess secondary traumatic stress	• Found that younger staff are more prone to secondary traumatic stress • Lower caseloads and supervision were found to be protective against secondary traumatic stress, but the level of protection supervision offered may vary with seniority	• Unable to look at the impact of different interventions over time as results were gathered at one time using cross-sectional methodology
Palm et al, 2004 [10]	Disaster and trauma workers	Literature review looking at the effects of working in disaster environments on professionals, and potential measures to limit secondary trauma and VT	• Multiple professions are involved in disaster response; healthcare providers, emergency service workers and journalists are all exposed to slightly different risk factors, but are all placed at risk of VT through their work • Potential interventions to minimise VT risk can be categorised into individual factors (maintaining personal health, work–life balance, good social support and acceptance by colleagues) and organisational factors (provision of training, managing caseloads, improving work environment within limitations, supervision and support within the workplace)	• No comparison of interventions, or measures of effectiveness when put into practice
van Mol et al, 2015 [13]	ICU healthcare staff	Systematic review, measuring the prevalence of compassion fatigue and burnout in ICU healthcare professionals and investigating the preventative strategies that are successful in this group. Interventions in the studies included were differing work schedules, education on emotional distress, communication skills, coping and relaxation strategies and improving work environments	• The systematic review included 20 papers on interventions, testing the effectiveness or 11 interventions (grouped into organised-directed and person-directed interventions) • Communication strategy teaching, mindfulness sessions and discussion groups were all effective in reducing emotional distress amongst ICU professionals • Person-directed interventions (CBT, relaxation skills and counselling) were the most effective of the proposed interventions	• Lack of RCTs and vigorous studies on this topic, so a meta-analysis couldn't be performed
NSPCC, 2013 [11]	NSPCC staff	Literature review	• Managerial supervision and peer support are frequently identified as potential VT interventions in the literature, as they prevent isolation of staff, instead allowing them to share the burden of what they hear during their work • It is important to recognise VT within the workplace as a serious problem rather than 'just part of the job', and provide staff education around the risks of VT	• Conducted as part of an NSPCC report rather than a peer-reviewed paper. Lacks comparison or discussion of the suggested interventions

CBT, cognitive behavioural therapy; NSPCC, National Society for the Prevention of Cruelty to Children; ProQOL, Professional Quality of Life Scale; TSIBS, Traumatic Stress Institute Belief Scale.

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Review

The anatomical considerations in total aortic arch replacement surgery (island technique)

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Background

Thoracic aortic aneurysms (TAAs) present due to a weakened area of the aortic wall and individuals with TAAs have a poor survival rate without medical intervention. TAAs can either transect or dissect the aorta if ruptured and present as sudden chest pain, dyspnoea, hypotension, dysphagia and syncope. TAA can be diagnosed using imaging (MRI, computerised tomography [CT] scans, chest x-rays), with management available both medically and surgically.

Current surgical interventions include traditional median sternotomy, arterial cannulation and hypothermic circulatory arrest. Novel techniques, such as L-type incisions, circumvent risks involved in median sternotomy, allowing improved exploration and anatomical visuals to treat TAA successfully. In this article, the island technique (a surgical procedure) and its complications are discussed, and surgical procedures are demonstrated on a deer's heart ex vivo.

Introduction

Aortic arch surgery is one of the most technically demanding procedures in cardiac surgery, in which protection of the myocardium, brain and spinal cord are vital for patient safety.[1] The aorta can present with two main types of aneurysm: thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). The UK prevalence of TAAs is estimated to be 10.4 per 100,000 person-years and there is an estimation that there are 3000–8000 new cases of TAA each year. Therefore, further research in this field of cardiac surgery is highly important.[2-4]

TAAs mainly affect the aortic arch. They can pathologically present when the aorta increases in size and broadens due to weakness within the arterial wall lining. The healthy adult aortic diameter does not exceed 40 mm in size; TAA is diagnosed when the dilation of an aorta is at least 50% greater than 40 mm.[1] Aneurysms commonly develop in the ascending thoracic aorta (40% of cases), the descending thoracic aorta (35%), abdominal aorta (15%) and the thoracic arch (10%). Individuals with TAA present with symptoms, such as abrupt chest pain, dyspnoea, hypotension, dysphagia and syncope, and have a survival rate of 56% (without medical intervention).[5,6] Furthermore, due to the presence of a weakened aortic wall, TAAs can result in either transection or dissection of the aorta, leading to complications, such as chest pain, shock, heart failure and hypovolaemic death. Individuals may be genetically predisposed to aortic dissections (e.g. if they have Marfan's syndrome) or may be at higher risk if they are exposed to some infections, such as tertiary syphilis infection.[1,4,7]

TAAs are often diagnosed using imaging tests, such as x-ray, computerised tomography (CT) and MRI of the chest. Depending on the diagnostic test results, medical management may be provided before surgical intervention, including hypertensive medication and statins.[5] However, for aneurysms that are at risk of rupture or fatal complications, a procedure known as 'total aortic arch replacement' can be used. In this article, the complications that may arise from performing arch surgery are discussed.

Literature search and surgical procedures

Literature search

PubMed and Google Scholar were searched for relevant articles, using the search terms "Aortic Arch Surgery" AND "Island Technique". Articles were included if they were published between 2009 and 2019. The Boolean template terms, 'anatomy', 'complications' and 'pathologies' were used to rescreen the articles. In total, 20 relevant articles were found **(Figure 1)**.

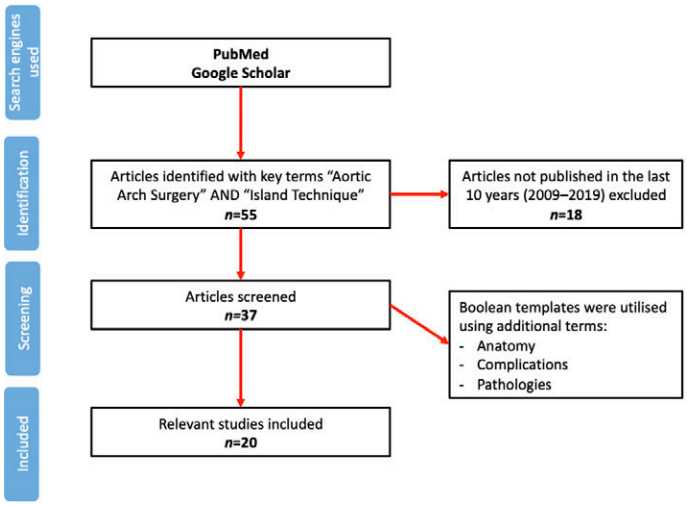

Figure 1. Article selection process. The Boolean template terms, 'anatomy', 'complications' and 'pathologies', were used to screen the articles.

Surgical procedures

Surgical procedures were carried out on a deer heart, with ethical considerations taken into account; the deer hearts were the by-product of the meat industry and acquired from an abattoir. Basic surgical equipment was used, as well as Dacron grafting material. Images were taken at the University Hospital Plymouth, NHS Trust (Plymouth, UK). The equipment used and the deer hearts were supplied by Medtronic (Watford, UK) and WetLabs (Warwick, UK).

Discussion of findings

Initial anatomical considerations prior to arch surgery

Healthy patient The aortic arch has three branches: the brachiocephalic artery, left common carotid and left subclavian artery.[8,9] The brachiocephalic artery forms the circle of Willis (CoW), which is a critical vascular region that supplies blood to important areas of the body, such as the upper spinal cord, brain stem, cerebellum and posterior region of the brain.[10] If the CoW

is pathologically compromised, cerebral infarction may result, potentially leading to death.[11]

Patients with branchial pattern variations Patients can present with several variations of the branching patterns at the aortic arch; in 70–80% of patients, the left common carotid arises directly from the right brachiocephalic artery, known as the 'bovine-type arch'.[12] Before surgical intervention is considered, the surgical team need to assess the anatomical variations of a patient's thoracic region, which may include positional deviations of the heart and apex in the thoracic region. The patient could present with the apex of the heart on the left side of the body (laevocardia), midline (mesocardia) or on the right side of the body (dextrocardia). Each of these presentations have been associated with congenital malformations, such as atrioventricular septal defect and transposition of great arteries, which should be investigated by the surgeon.[13] Some of the anatomical considerations (and associated complications) that should be assessed prior to arch surgery are shown in **Table 1**.[10]

Table 1. The different structural locations associated with the aortic arch and complications that could happen if they were damaged during surgery.

Anatomical consideration	Location	Complication
Aortic semilunar valve	Located between the left ventricle exit and the start of ascending aortic arch[10]	Damage to the aortic semilunar valve or tricuspid leaflet can cause paravalvular leak and result in heart failure, anaemia and infective endocarditis[14]
Phrenic nerve	Located laterally to the aortic arch and the initial parts of the left subclavian artery and left common carotid[10]	Damage during surgery can result in phrenic nerve injury or palsy. This can cause diaphragmatic paralysis, preventing the patient from breathing on their own[15]
Left recurrent laryngeal nerve	A branch from the vagus nerve, located posterior to the distal aortic arch, which is seen to loop around and travel superiorly anterior to the aortic arch[10]	Damage to the left recurrent laryngeal nerve can result in voice hoarseness or vocal cord paralysis[16]
Thoracic duct	Located between the descending thoracic aorta on the left side of the heart and the azygous vein on the right[10]	Damage to the thoracic duct can result in chyle leakage and chylothorax. This could cause shortness of breath and malnutrition[17]

This table includes regions that are most prone to common complications during aortic arch surgery.

Bovine heart surgery: Derriford Hospital training room

Total aortic arch replacement The goal of surgical repair of the aortic arch is to remove the diseased arch portions and replace them with synthetic graft material (Dacron) and, concomitantly, manage the blood flow to both cerebral and down-stream end organs.[16,18] The arch repair technique was introduced by DeBakey and Cooley in 1952 and was implemented in 1955.[18] There have been various techniques that have evolved since this time, which have been trialled over the past few decades, including the island, Spielvogel, trifurcated graft and frozen elephant trunk (gold standard) techniques.[16,18] The island or En-bloc technique is further discussed herein.

Preparative anatomical considerations and surgical schematic Before surgical intervention is commenced, the patient has to undergo specific procedural management. A schematic flowchart for successful aortic arch replacement surgery is shown in **Figure 2**. Due to the complexity of the surgery, the surgical field must be bloodless. This reduces the risk of post-operative complications, such as stroke, damage to the spinal cord, lung or kidney failure and general threat to life. The surgical procedure is completed by re-warming, reperfusion and weaning the patient off cardiopulmonary bypass (CPB).[19,20]

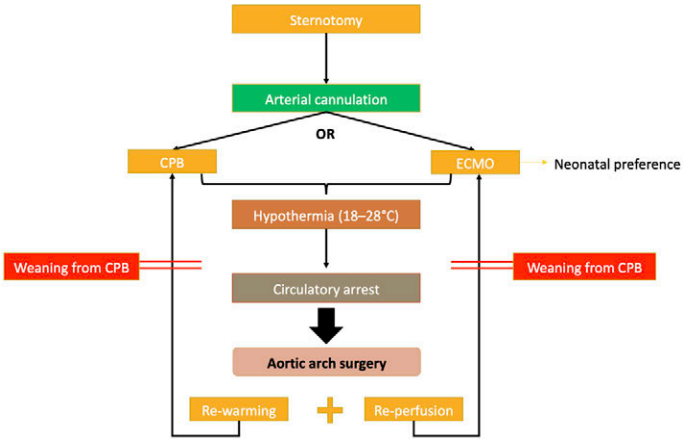

Figure 2. The pre- and post-operative procedural landmarks that are required to perform aortic arch surgery. Aortic arch surgery involves several procedures, with one of the first steps including arterial cannulation, which is vital for CPB. CPB is then carried out or, in rare cases of neonatal arch surgery, extracorporeal membrane oxygenation (ECMO) can be used. Hypothermic circulatory arrest is initiated to reduce the metabolic strain on vital organs, such as the brain, allowing general circulation around the body to be stopped. Subsequently, aortic arch surgery is conducted. Re-warming and re-perfusion are carried out after the surgery is completed. The figure was created using data from Bachet[19] and Peterss et al.[20]

Traditionally, median sternotomy is initially performed to gain access to the cardiothoracic cavity with a single incision. When conducting sternotomy, the proximity of the sternum to the heart and arteries within the thoracic cavity (bronchial, mediastinal, oesophageal, pericardial, phrenic and intercostal arteries) should be considered (see **Figure 3**). Additionally, it is fundamental to consider arterial presence (abundance of vasculature supply within the area) as there is a small risk of intercostal artery-related surgery-induced pseudoaneurysm.[1,19,21] Another complication of sternotomy includes sternal dehiscence (post-operative separation of the bony sternum), which leads to mediastinitis.[22]

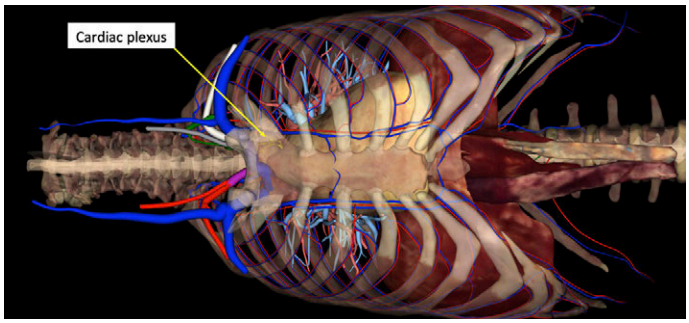

Figure 3. 3D dissection of the thoracic anatomy. This anterior view of the bony thorax (made translucent) includes the heart (within the pericardium), great vessels, diaphragm and intercostal arteries. The branches off the aortic arch are coloured as follows: brachiocephalic, pink; left common carotid, green; left subclavian, white. This image illustrates the close vicinity of the sternum to the heart, with the cardiac plexus (surrounding the arch) shown in yellow. Image acquired from Anatomage Inc. and copyright belongs to Anatomage.

Sternotomy has been shown to hinder the view of the distal aorta past the level of the lung hilum (vertebral level 5, 6 and 7) and commands a two-stage process (median and lateral anterior incisions), requiring two operations to access and replace diseased aortic regions, respectively, in patients with TAA.[23,24] Unfortunately, there is a risk of never completing the second stage of the procedure because the patient may perish either abruptly after the first-stage operation or from an aneurysm rupture while waiting for the second-stage repair. As an alternative, L-type incisions (as seen in **Figure 4**) may be used to overcome this issue. With L-type incisions, principally an

anterior incision is made from the fifth intercostal space, the lateral line is incised up to the axillary line and the conventional median sternotomy (incision along the sternum) is performed. Following the median retraction, the left anterior chest wall is lifted upwards using steel wires ('open door technique'). One limitation of L-type incisions is that they are associated with higher respiratory complications, leading to tracheostomy and ventilation.[24] Additionally, in certain instances, the patient can present with extensive aortic pathology that could involve the descending aorta and aortic arch.

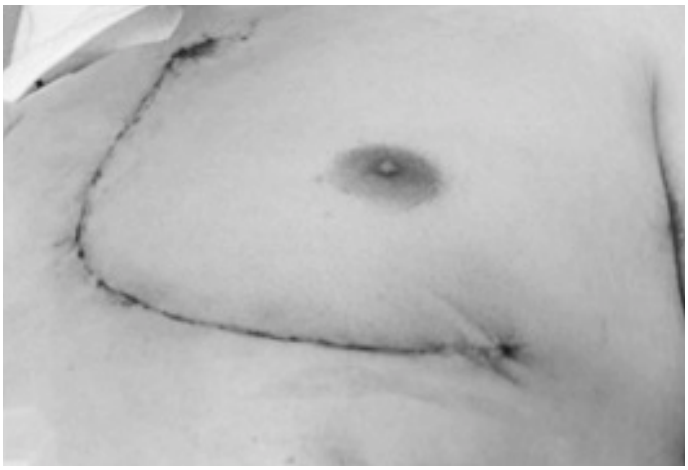

Figure 4. An L-type incision. Universally, the median sternotomy is preferred for arch surgery due to the rapid and secure procedural protocol. However, the L-type procedure provides an exceptional vision of the anterior aorta, which is required for TAA surgery. Image reprinted from Tokuda et al,[24] by permission of Oxford University Press.

For this article, the islet method was carried out on a deer heart to illustrate the complications that may arise and the final outcome of the procedure. It was noted that the deer heart had an extensive, thicker aortic arch than the human heart and a single brachiocephalic artery branch **(Figure 5)**.

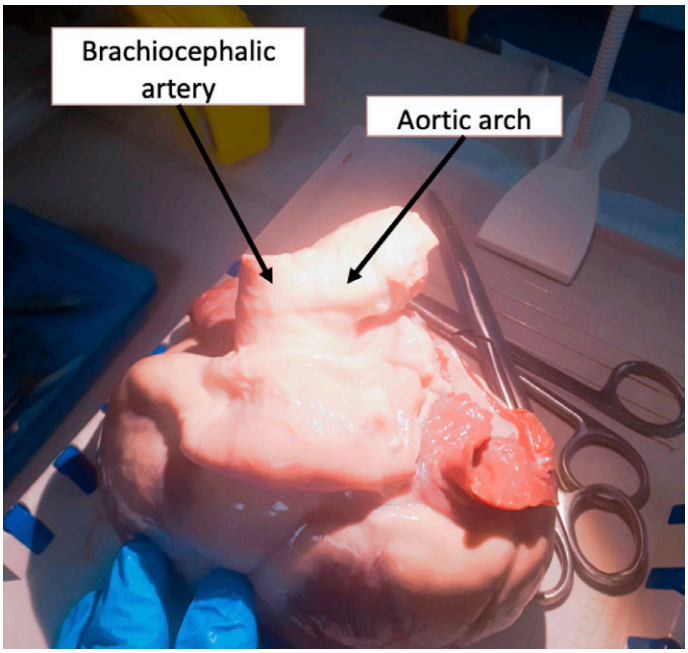

Figure 5. Deer heart. The deer heart has a thicker aortic arch compared with a human heart and a single brachiocephalic artery branching from the arch (instead of the three in the human heart).

Island technique The island technique is a surgical technique that re-implants the arch vessels from diseased aorta onto an artificial (Dacron) graft. The first step of the island technique involves the identification of the branched arteries (innominate [also known as brachiocephalic], left common carotid and left subclavian), which form the 'island', and the diseased aorta to be excised.[16] The next step includes excision of the aortic arch's branched arteries, which will form the 'island' or 'dome'. On the deer heart **(Figure 6)**, the single brachiocephalic artery forms the 'island', which is to be excised.[10]

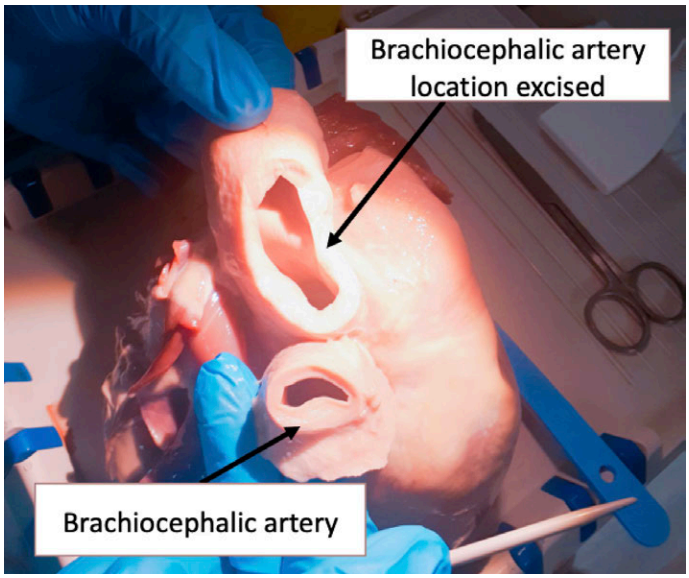

Figure 6. Removal of the brachiocephalic artery from the arch of the aorta in a deer's heart. The island would be anastomosed on a Dacron graft to replace the diseased aorta; the suturing process requires enough area on the brachiocephalic artery root to anastomose.

After excision of the brachiocephalic artery, the diseased aortic arch is removed, leaving the ascending aortic root. Subsequently, the Dacron graft is anastomosed, replacing the diseased arch (see **Figure 7**). At this stage, a potential complication of the island technique is that the aortic tissue that is left behind (island patch) can become aneurysmal and, thus, further operations may be required. This has been vastly reported in patients who present with connective tissue disorders, such as Marfan's.[1] In addition, there is a risk of anastomotic stenosis developing, depending on the suturing line employed during surgery.[9]

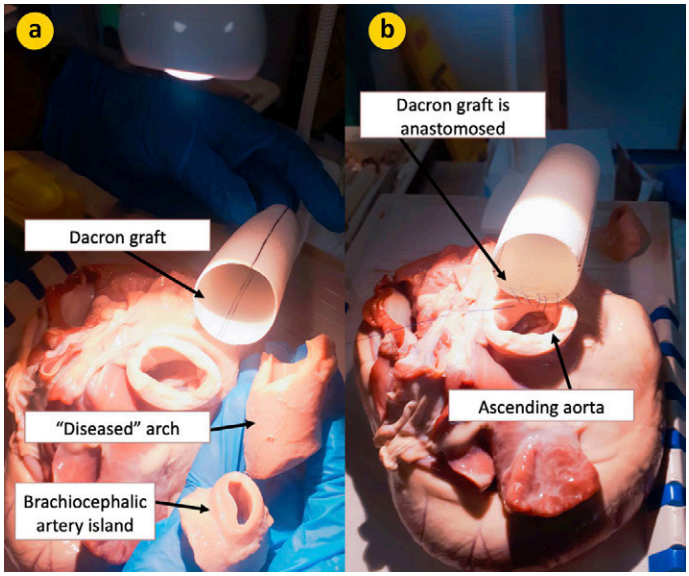

Figure 7. Dacron graft anastomosis in a deer's heart. (a) Image shows the diseased arch in comparison with the brachiocephalic artery 'island'. The Dacron graft can also be seen in contrast with the ascending aorta and the diseased aortic arch. **(b)** Image illustrates a single running suture implemented to anastomose the Dacron graft on the ascending aorta.

Post-anastomosis of the Dacron graft on the ascending root of the aorta, the brachiocephalic artery island is consequently anastomosed **(Figure 8)**. During the anastomosing of the island on the Dacron graft, it is fundamental that it is attached safely and securely without the suturing affecting the annulus. One of the complications associated with anastomosing the distal, proximal areas of the Dacron graft to the patient's healthy aorta is associated with suturing the island (branched arteries) on the graft while simultaneously keeping the patient under circulatory arrest; this has been shown to cause ischaemic strain on the body for an extended period of time, risking spinal cord damage and increasing the risk of permanent brain damage. Furthermore, complications, such as bleeding, have been shown to be harder to control after CPB has started.[25] The final outcome of the deer heart surgery using the island technique can be seen in **Figure 9.**

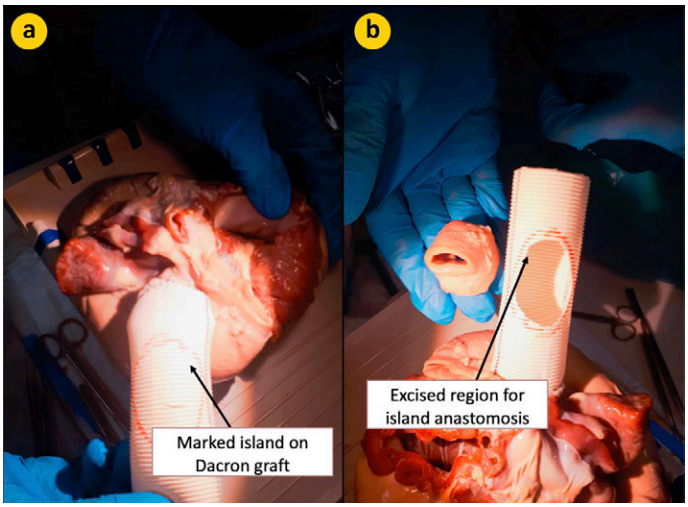

Figure 8. A Dacron graft, which is anastomosed on the ascending aortic root. (a, b) The anastomosed Dacron graft has been marked with a pen (red circle), displaying the location at which the brachiocephalic artery island is to be anastomosed. **(b)** Image shows a comparison of the excised region with the brachiocephalic artery.

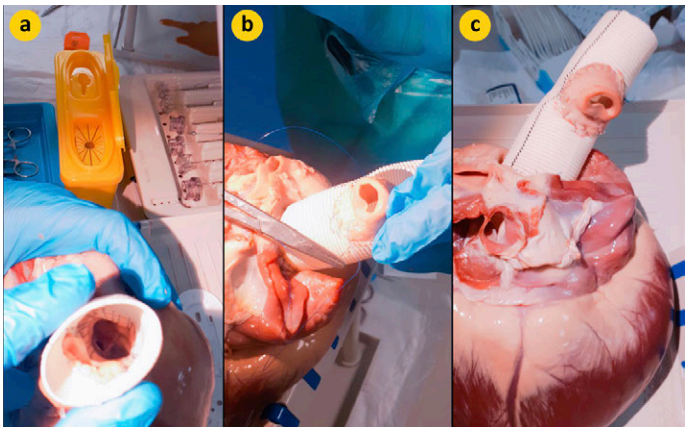

Figure 9. Outcome of the deer heart surgery using the island technique. (a) Bird's-eye perspective of the Dacron graft anastomosed on the root of the ascending aorta; the single running suturing can be seen. **(b)** Image illustrates the island anastomosing on the Dacron graft. **(c)** The outcome of the surgery, illustrating the replaced arch of the aorta and complete anastomosis of the island on the graft.

Conclusion

Cardiac surgery is a rapidly developing field and has seen immense growth over the past few decades. Diseases, such as Marfan's and tertiary syphilis, pre-dispose individuals to TAAs. Pathologies like TAA require fundamental surgical intervention. TAA management is best provided by evaluating and adapting to the patient's precise anatomical variations and the extent of the pathological damage that has been caused.

Acknowledgments I want to thank Mr Unsworth-White (Consultant Cardiothoracic Surgeon and Associate Professor; Peninsula Medical School, Plymouth, UK) and Dr Siobhan Moyes (Lead in Anatomy; Peninsula Medical School, Plymouth, UK) for their guidance. Furthermore, I want to thank WetLabs and Medtronic for the equipment and the deer heart provided for this project.

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Case Study

Metastatic spinal cord compression in a patient with multiple myeloma

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Introduction

Multiple myeloma (MM) is a B cell malignancy resulting in osteolytic lesions.[1] Pathological fracture of the vertebral body resulting in spinal cord compression is a common complication and accounts for approximately 5% of patients with MM.[2,3] To date, there are no definitive guidelines for the treatment of metastatic spinal cord compression (MSCC) as a consequence of MM. Radiotherapy has frequently been the preferred form of treatment. Some surgeons, however, feel that spinal lesions in multiple myeloma should be treated in the same manner as spinal metastases from solid organs.[4]

This is a case report of the management of a 46-year-old gentleman with multiple myeloma that had resulted in MSCC in the lumbar and thoracic areas. Treatment consisted of spinal decompression and stabilisation.

The spine is the third most common site of metastases after the lung and liver.[5] The incidence of metastatic spinal cord compression (MSCC) is up to 80 cases per million people each year.[6] This equates to 4000 cases per annum in England and Wales.[7] Treatment traditionally involves the use of corticosteroids and radiotherapy. However, evidence has suggested that only 50% of patients have a positive response.[8] This case report illustrates the successful use of surgery, particularly for patients who present with neurological deficit.

Case presentation

A 46-year-old gentleman presented with increasing back pain and pain in the left hip for 6 months. This pain was associated with numbness in the left leg. Over the previous 2 weeks, his symptoms had become intrusive, resulting in an ability to walk only with the aid of crutches. The patient reported no weight loss and no bowel or bladder dysfunction.

On examination, there was tenderness in the lower thoracic spine, lumbar spine and over the iliac crest on the left side. Neurological examination revealed reduced sensation over the left leg from the groin to the foot. Power was reduced upon left toe extension (MRC 3/5) and ankle dorsiflexion (MRC 3/5). On the right side, sensation was reduced over the little toe. Reflexes were bilaterally brisk in the lower limbs, but plantar reflex was normal.

Investigations

Full blood count (FBC), erythrocyte sedimentary rate (ESR) and calcium levels were normal. CT scanning revealed multiple areas of bony destruction in the vertebrae and left iliac bone **(Figure 1)**. MRI revealed destruction of T5, T10, L3 and L5 vertebrae with abnormal tissue causing severe compression of the spinal cord and nerves in these areas. Plasma electrophoresis was performed to check for multiple myeloma; this was positive for the presence of free light chains.

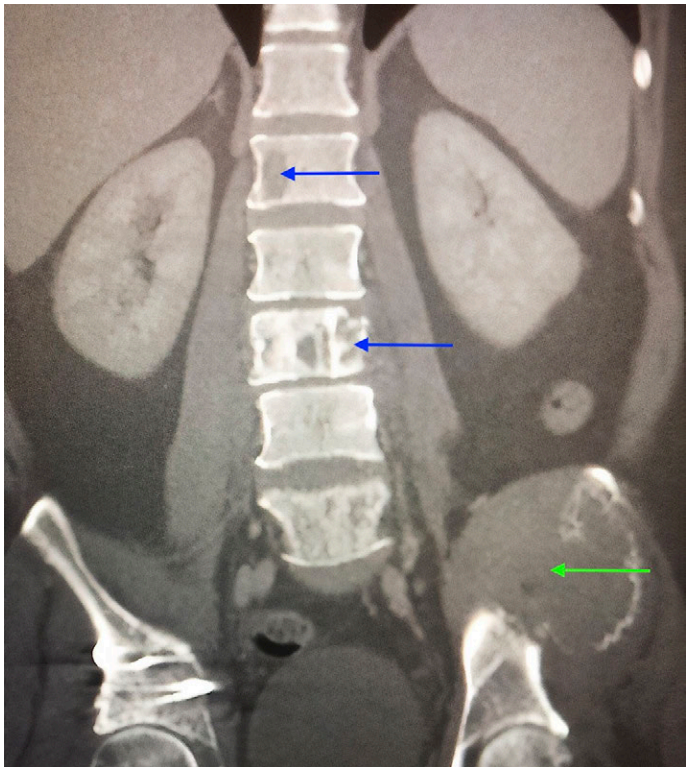

Figure 1. CT scan of the spine and pelvis. The CT scan highlights multiple areas of bony destruction in the thoracic and lumbar vertebrae (blue arrows). There is a large mass in the left iliac bone (green arrow).

Differential Diagnosis

Tuberculosis can present similarly to MSCC, in that spinal canal involvement can cause radiating pain and limb weakness.[9] However, tuberculosis was an unlikely diagnosis. The typical manifestations of spinal tuberculosis involve vertebral bone destruction, narrowing of intervertebral disc space and paraspinal abscess.[9] Despite MRI revealing vertebral bone destruction, there was no evidence of paraspinal abscess.

The possibility of osteomyelitis was also ruled out upon haematological testing. ESR in osteomyelitis tends to be raised to a level greater than 100 mm/hour.[10] However, the patient had a normal ESR and did not present with features of systemic infection.

Lastly, the probability of MSCC was increased by the presence of both motor and sensory symptoms. Radicular pain and sensory complaints tend to be initial symptoms in patients with lumbar metastases, whereas weakness in the limbs is more pronounced in patients with thoracic metastases.[11] As T5, T10, L3 and L5 were all affected, it was concluded that the patient would be treated for MSCC.

Treatment

The aim of treatment would not be curative, but rather aimed at improving quality of life.[12] Surgery was preferred and initially consisted of tumour tissue biopsy. Subsequently, the patient underwent spinal decompression and spinal stabilisation at the lumbar and thoracic areas **(Figure 2)**. Post-operative radiotherapy was initiated in line with The National Institute for Health and Care Excellence (NICE) guidelines.[13]

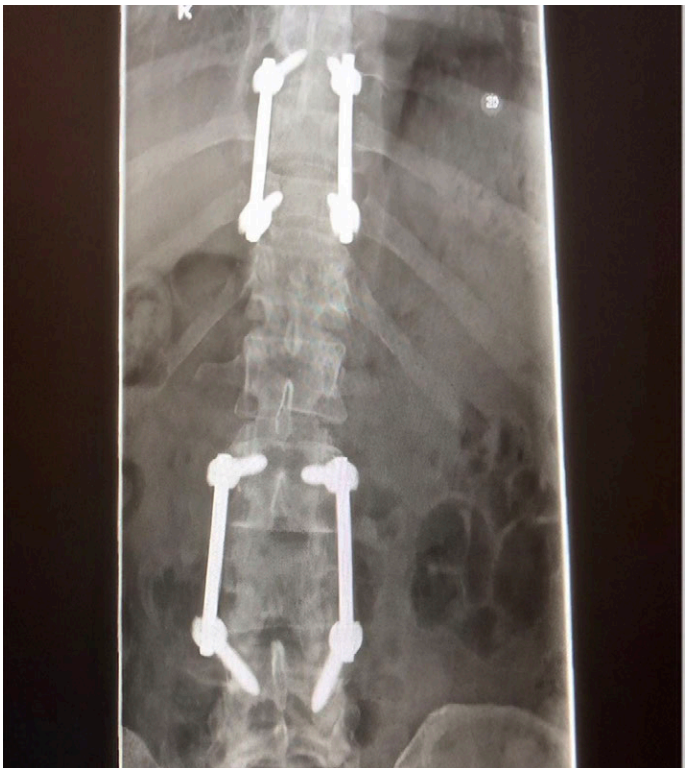

Figure 2. Post-operative x-ray. Post-operative x-ray demonstrating spinal stabilisation at the lumbar and thoracic areas using rods and screws.

Outcome and follow-up

The operation was successful, with numbness in the left leg improving within 4 days. The pain subsided within 1 month and the patient could walk short distances without the use of crutches. At 1-year follow-up, the patient regained full function of the spine and hip. Ambulation status was restored, and lower limb power returned to normal (MRC 5/5).

Discussion

MSCC may be the presenting symptom of cancer, as highlighted in this case. A retrospective cohort study reported that 21% of MSCC patients had no pre-existing cancer diagnosis.[14] Lower back pain may be the first sign of malignancy. Considering that lower back pain is prevalent in our population, it is unsurprising that the diagnosis of MSCC is often missed. In an observational study of 319 patients with MSCC, a median of 2 months passed from the onset of pain and the diagnosis of the condition.[6] Similarly, in this case, the patient's back pain was not investigated for 6 months. It required the onset of motor deficit and limb weakness for red flags to be raised. In view of this, clinicians should maintain a high index of suspicion of MSCC in a patient presenting with progressive lumbar and thoracic pain. Early detection is pivotal in preserving motor and sensory function.

This case outlines the efficacy of both MRI and CT scanning in the diagnosis of MSCC. MRI is the gold-standard investigation and concurs a sensitivity and specificity of 100% and 93%, respectively.[15] Furthermore, CT scanning, used in conjunction with MRI, can aid in preoperative planning and help detect the site of the primary tumour.[12]

Research has showed that surgery for MSCC can provide an improvement in pain, function and ambulation status. This is in comparison with patients receiving only radiotherapy as treatment for MSCC.[16] NICE, therefore, recommends spinal decompression and stabilisation for patients who are deemed fit.[17] Post-operative radiotherapy can be used in conjunction with surgery to treat further metastases. The success of this type of treatment was assessed in a prospective randomised control trial, which showed that patients with MSCC treated with direct decompressive surgery plus post-operative radiotherapy retained the ability to walk for longer than patients treated with radiotherapy alone.[8] Surgical treatment further reduced the need for corticosteroids and resulted in increased survival time.[8] However, survival time was dependent on metastatic spread.

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Research Article

Monitoring cardiac adaptation in elite, adolescent athletes using a novel, smartphone-based 22-lead ECG

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Abstract

Introduction The 12-lead electrocardiogram (ECG) is the primary cardiac screening and diagnostic tool for athletes; however, it lacks portability where it would be useful in making fast and accurate diagnoses at the pitch side. Recently, smartphone applications (apps) have become available that can record 12-/22-lead ECGs with only four electrodes, which could improve accessibility of ECGs in the athletic setting. In this study, a novel ECG app, CardioSecur, will be compared against the gold standard 12-lead ECG (herein referred to as normal ECG [nECG]) in 31 elite, adolescent footballers to establish if there are any clinically significant differences between the devices.

Methods A full range of amplitudes, durations, intervals and waveforms were manually measured in 93 ECGs (31 nECGs, 31 12-lead CardioSecur ECGs and 31 22-lead CardioSecur ECGs) and agreement was assessed using the Bland–Altman method.

Results Our data showed clinically acceptable agreement for heart rate, PR interval, QRS duration, Bazett's corrected QT (QTc) interval, T-wave axis, P-wave duration, Q-wave amplitude, Q-wave duration, rhythm, T-wave character and ST-segment position. Unsatisfactory agreement was observed in the QRS axis, P-wave axis, P-wave amplitude and QRS amplitude.

Conclusion CardioSecur sufficiently agrees with the gold standard for 'on-field' use in athletic training facilities but, at present, should not replace the gold standard for cardiac screening.

Introduction

To manage the increased cardiovascular demand of a high-level athlete, the heart undergoes an array of adaptations known as electrical and structural remodelling.[1,2] These changes can be identified using an electrocardiogram (ECG). It is now understood that, in some athletes, these changes, which include early repolarisation and left ventricular hypertrophy (LVH), may overlap with pathological findings.[3] Specialist guidelines exist for ECG interpretation in athletes.[4] However, data are lacking in adolescents. This is important, as competitive athletes are three times more at risk of sudden cardiac death (SCD) than the general population.[5,6]

The 12-lead ECG is an invaluable cardiac screening tool; however, it lacks portability and the attachment of ten electrodes is often subject to misplacement. CardioSecur (Personal Medsystems GmbH, Frankfurt, Germany) is a smartphone application (app) that can generate a 12- and 22-lead ECG from just four electrodes that are directly connected to a phone or tablet device. Based on the established EASI system (a vector-based, 5-electrode, 12-lead ECG),[7-11] CardioSecur has the potential to reduce electrode misplacement **(Figure 1)** and improve the accessibility of ECG recording in training or competition settings. Little, if any, data exists on 22-lead ECG interpretation in athletes. Therefore, in this study, CardioSecur ECG will be compared against the gold standard 12-lead ECG (herein referred to as normal ECG [nECG]) in adolescent athletes to assess its use in cardiac screening.

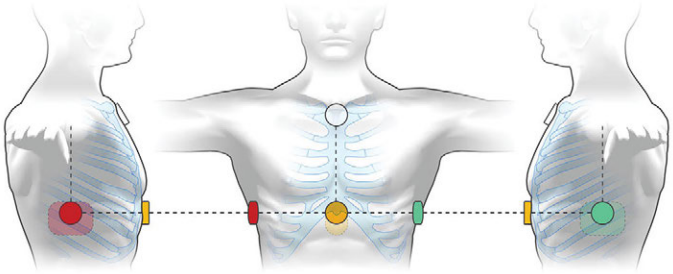

Figure 1. CardioSecur ECG electrode placement. Red, right mid axillary line (MAL) parallel with the xiphoid process; green, MAL parallel with xiphoid process; white, superior sternum (midline); yellow, xiphoid process (midline). Image provided by and used with permission from Personal Medsystems GmbH, Germany.

Methods

ECG recording

Written consent was obtained retrospectively from our study population of elite adolescent athletes and ethical approval was granted. Participants were between the ages of 13 and 16 years old and played for a premier league football academy (n=31). Data collection was conducted as part of a Football Association (FA)-approved cardiac screening programme and all nECGs were analysed by the team's cardiologist who was present at the time of data collection. Each participant received an nECG followed by a 12- and 22-lead CardioSecur ECG (see **Figure 1** for CardioSecur electrode placement). All ECGs were recorded at an amplitude of 10mm/mV and a paper speed of 25mm/s.

Data analysis

The parameters chosen for comparative analysis were heart rate, PR interval, QRS duration, Bazett's corrected QT (QTc) interval, QRS axis, P-wave axis, T-wave axis, QRS voltage, P-wave duration, P-wave amplitude, T-wave amplitude, Q-wave amplitude and Q-wave duration. Non-numerical parameters, including rhythm, ST-segment

and T-waves, were recorded as numerical codes. The 12- and 22-lead CardioSecur ECGs were compared with the nECGs in separate paired analyses. The additional leads (V7–V9, VR3–VR9) were omitted in the comparative analysis due to the lack of an equivalent comparator in the 12-lead nECG. Statistical agreement was assessed with a Bland–Altman[12] (mean-difference) plot performed with GraphPad Prism 8.0.2 (San Diego, CA, USA).

Statistical agreement To achieve statistical agreement, differences in parameter measurement must be minor enough to be of clinical insignificance and, thus, unlikely to result in misdiagnosis. Graphically, this corresponds with low bias (mean difference), narrow 95% limits of agreement (an estimated interval where 95% of differences will lie) and the absence of positive or negative trends that would indicate intrinsic bias.

Results

Comparison of the 12-lead CardioSecur ECG with nECG

Satisfactory agreement was observed in heart rate (bias= −2.00 bpm), PR interval (bias = −8.00 ms), QRS duration (bias=1.67 ms), QTc interval (bias=0.931 ms) **(Figure 2)**, P-wave duration (bias=2.67 ms), P-wave amplitude (bias=0.00167 mV), T-wave axis (bias=8.04°), T-wave amplitude (bias=0.0232 ms) and Q-wave duration (bias=5.36 ms). Unsatisfactory agreement was observed in QRS axis (bias=23.4°), QRS amplitude (bias=0.333 mV), P-wave axis (bias=6.33°) and Q-wave amplitude (bias=0.207 mV).

Comparison of the 22-lead CardioSecur with nECG

Satisfactory agreement was observed in heart rate (bias=0.613 bpm), PR interval (bias = −1.73 ms), QRS duration (bias=7.05 ms), QTc interval (bias=2.03 ms), T-wave axis (bias=6.55°), P-wave duration (bias = −0.941 ms), Q-wave amplitude (bias=0.0195 mV), Q-wave duration (bias=1.69 ms), rhythm (bias=0.0667), T-wave character (bias = −0.0460) and ST-segment position (bias = −0.0629). Unsatisfactory agreement was observed in QRS axis (bias = −19.4°), P-wave axis (bias = −0.670°), QRS amplitude (bias = −0.660 mV), P-wave amplitude (bias=0.0400 mV) and T-wave amplitude (bias = −0.0675 mV). Refer to **Table 1** for the 95% limits of agreement.

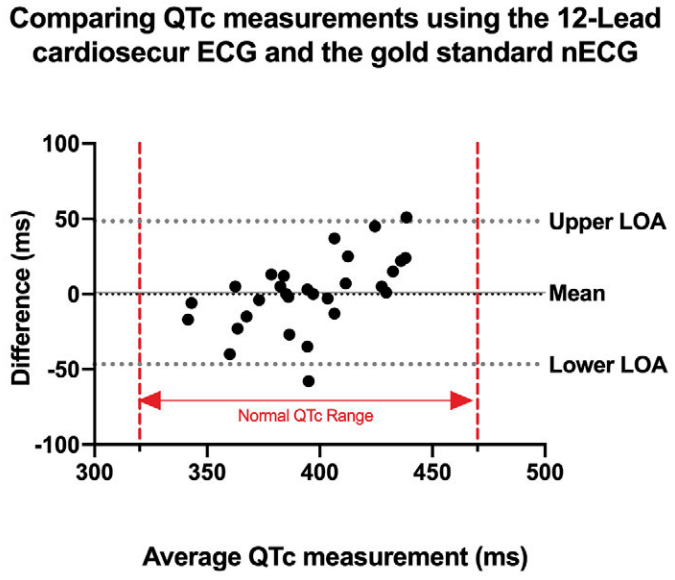

Figure 2. Bland–Altman plot comparing QTc intervals in the CardioSecur ECG (cEGG) and nECG (*n*=31). Variability is consistent and the mean difference (bias) is close to zero. One criticism would be that the 95% limits of agreement (LOAs) are marginally wide for QTc measurements.

Table 1. Assessing agreement: comparing the 22-lead CardioSecur ECG with the nECG.

Parameter	Bias	95% upper LOA	95% lower LOA	Interpretation of agreement
Heart rate (bpm)	0.6	11.2	-12.4	Low bias, narrow limits
PR interval (ms)	-1.7	30.4	-33.9	Low bias, narrow limits
QRS duration (ms)	7.1	29.2	-15.1	Low bias, narrow limits
QTc interval (ms)	2.0	53.2	-49.1	Low bias, moderate limits
QRS axis (°)	-19.4	28.4	-67.1	cECG underestimates and positive trend
QRS amplitude (mV)	-0.66	1.18	-2.50	cECG underestimates and wide limits
P-wave axis (°)	-0.7	83.4	-84.8	Low bias, wide limits
P-wave duration (ms)	-0.9	24.9	-26.8	Low bias, narrow limits
P-wave amplitude (mV)	0.040	0.158	-0.078	Low bias, wide limits
T-wave axis (°)	6.6	28.3	-15.2	Low bias, narrow limits
T-wave amplitude (mV)	-0.068	0.378	-0.513	Low bias, wide limits
Q-wave amplitude (mV)	0.020	0.155	-0.116	Low bias, narrow limits
Q-wave duration (ms)	1.7	19.3	-15.9	Low bias, narrow limits
Rhythm	0.067	0.782	-0.649	Low bias, narrow limits
ST-segment analysis	-0.06	1.62	-1.75	Low bias, narrow limits
T-wave morphology	-0.05	2.27	-2.36	Low bias, narrow limits

Satisfactory agreement, green; unsatisfactory agreement, red
cECG, CardioSecur ECG; LOA, limit of agreement

Discussion

Early studies on CardioSecur ECGs have shown excellent agreement with approved ECG devices in diagnostic accuracy; however, higher absolute wave peaks have been found[13,14] and our study confirmed these results. In this study, the Bland–Altman analysis, a statistical method for identifying bias and assessing agreement between devices,[12] was used to show that the CardioSecur device was reliable for T-wave, ST-segment and duration measurements, which are core parameters when distinguishing training-related physiological changes from cardiac pathology in athletes.[4] In our study, differences in parameter measurements were often negligible and clinically insignificant.

The QRS and P-wave axes recorded by CardioSecur ECG would potentially increase the misdiagnoses of axis deviation. Our data showed that, while CardioSecur ECG was accurate (low bias) in axis measurement, it lacked precision (statistically illustrated by wide 95% LOAs; **Table 1**). Similarly, the wide LOA for QRS amplitude could lead to false suspicion of an LVH, leading to unnecessary concerns.

Limitations of this study include the lack of adjustment for intra-observer variation, a transversal study design, the absence of comparative echocardiographic input (to correlate with ECG findings) and the low participant number. Adjustment for observer

variation and a larger study population would improve the strength of this study.

In conclusion, the statistical agreement between CardioSecur ECG and the gold standard nECG observed in this study means that CardioSecur ECG would be suitable for 'on-field' use by medical staff. However, cardiac screening programmes should, at present, still use the gold standard nECG. Importantly, the CardioSecur device was reliable for T-wave, ST-segment and duration measurements. With minor adjustments to axis and amplitude recording, this technology has great potential to streamline the ECG process.

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Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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Contribution statement All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data. All authors were involved in drafting the work or revising it critically for important intellectual content. All authors give final approval of the version to be included in Inspire. The guarantor of this article is Guido Pieles (project supervisor).

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Research Article

To what extent are guidelines adhered to in the management of chemotherapy-induced nausea and vomiting in paediatric oncology? A retrospective audit

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Abstract

Aims Chemotherapy-induced nausea and vomiting (CINV) continues to be a concern within paediatric oncology. Its management in children is important to prevent future physical and psychological complications. According to recently updated guidelines, the emetogenic potential of the chemotherapy being administered should be used to determine the most appropriate anti-emetic regime to manage CINV. This audit aims to assess whether guidelines are adhered to in the management of CINV in paediatric patients.

Methods A retrospective audit of 11 patients, each receiving three sequential cycles of chemotherapy, was carried out to assess prescribing adherence to the guidelines.

Results It was found that anti-emetic prescribing was not in line with recommendations, with 48% of recorded episodes having incorrect prescribing. Additionally, results suggested that the probability of subsequent anti-emetic treatment failure may be increased given that anti-emetics were not prescribed according to guidance.

Conclusions Prescribing habit may be a major factor in the discrepancies between guidance and prescribing. Following this audit, strategies to improve guideline adherence may be implemented with the potential for improved outcomes for paediatric patients undergoing chemotherapy.

Introduction

Despite common use of chemotherapy in treating paediatric cancer, chemotherapy-induced nausea and vomiting (CINV) remains a significant concern.[1,2] Managing CINV is particularly key in children because the effects of malnutrition can have significant implications on their future growth and development.[3] Therefore, it is important that emetogenicity of therapy (the chance that it will cause CINV) is understood and steps are implemented to reduce and prevent CINV. The Children's Cancer and Leukaemia Group (CCLG) published updated guidelines on the management of CINV. The recommendations focus on three over-riding principles: appropriate assessment of emetogenicity of chemotherapy, effective assessment of CINV and personalisation with adjustments when anti-emetic treatment failure occurs.[4] This audit assessed guideline adherence in the management of CINV within the paediatric oncology department at the Royal Devon and Exeter Hospital (Exeter, UK).

Methods

A retrospective audit assessed guideline adherence in the management of CINV in the paediatric oncology department of the Royal Devon and Exeter Hospital. Patients receiving chemotherapy in the department at the time of the audit were considered. Eleven patients with solid tumours who had received three sequential cycles of chemotherapy between January 2015 and March 2019 (33 episodes of care in total) were included. Parameters recorded were emetogenic potential of chemotherapy, anti-emetics administered, whether guidance was followed and any reasoning if it was not, anti-emetic treatment failure occurrence and whether there was any subsequent medication adjustment **(Figure 1)**.

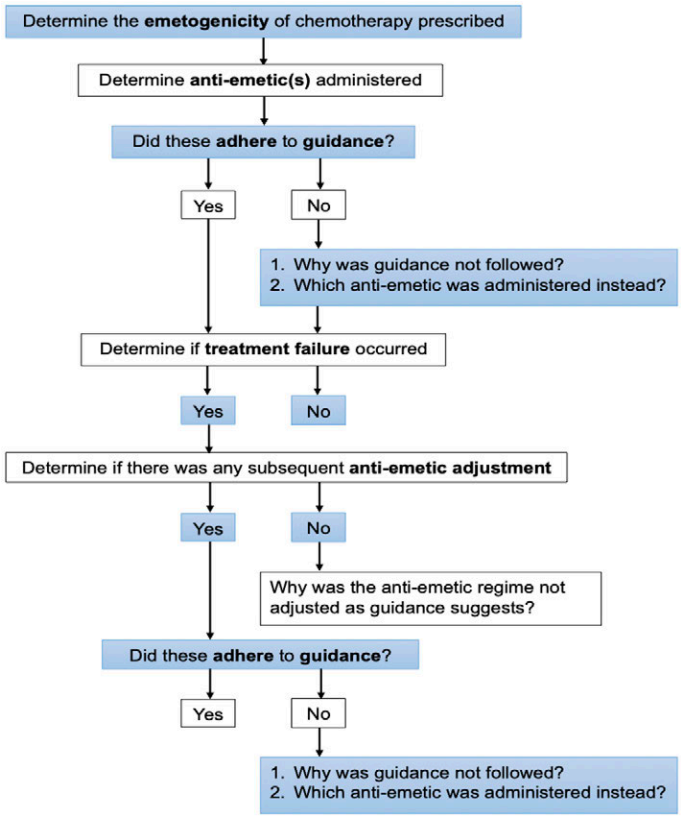

Figure 1. Parameters recorded to assess guideline adherence in the management of CINV in paediatric oncology.

Results

Fifty-two per cent of total chemotherapy episodes had anti-emetics prescribed in line with guidance. Of these episodes, treatment failure occurred in 14%. In comparison, 26% of episodes had treatment failure when anti-emetics were not prescribed in line with the guidance **(Figure 2)**.

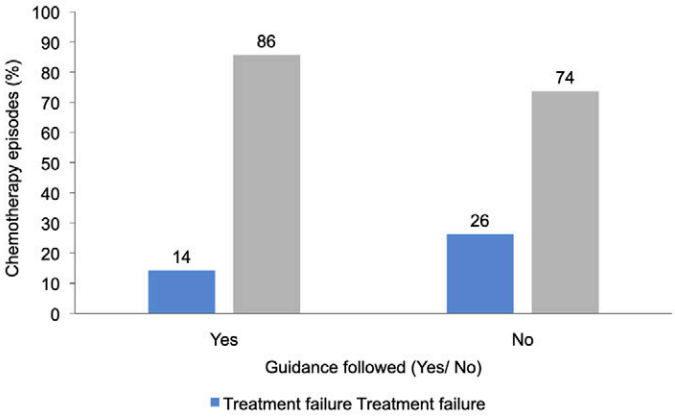

Figure 2. Anti-emetic prescription in chemotherapy episodes and associated treatment failure. The graph shows the percentage of chemotherapy episodes in which anti-emetics were prescribed according to guidelines or not and the associated percentage of treatment failure in each of these groups.

Additionally, six patients (55% of total patients) had incorrect anti-emetics prescribed. Of these, one patient had corrected anti-emetics prescribed in the subsequent two rounds of chemotherapy. Guidelines recommended that six of the patients should have received dexamethasone as part of their anti-emetic regime; however, only one of these patients (17% of recommended patients) received this.

Metoclopramide and hyoscine patches were the most common anti-emetics administered when not following guidance. Finally, most dosages were found to be prescribed in line with guidance but, in some cases, dosages were not correct for the patient's current weight.

Discussion

Overall, the results showed that the guidelines for anti-emetic prescribing are not always adhered to and almost half (48%) of anti-emetic prescribing is inaccurate according to guidance. Furthermore, results suggested that if anti-emetics are prescribed incorrectly, there is a higher incidence of treatment failure.

Additionally, metoclopramide and hyoscine patches, which were regularly prescribed, are not recommended first-line drugs. This may indicate that prescribing habit may contribute to prescribing discrepancies and further research may discover additional prescribing patterns. Results also implied a reluctance to prescribe dexamethasone; despite it being a key recommended anti-emetic, only 17% of the recommended patient group received it. Personal discussion with clinicians indicated this may be a result of hesitant steroid use in paediatrics. This should be explored further with prescribers, alongside the rationale for prescribing anti-emetics that are not recommended first-line drugs.

Despite a significant proportion of patients not experiencing treatment failure regardless of anti-emetic given, clinicians strive to provide patients with the best, evidenced-based medicine, as per guidelines. The effects of CINV can have serious psychological and physical effects;[3] therefore, every opportunity to reduce CINV in this patient group should be taken. In highlighting discrepancies between prescribing patterns and guideline recommendations, clinicians are given the opportunity to re-evaluate their prescribing habits. To increase prescribing adherence, some strategies suggested may include peer discussions or teaching and additional reminders in patient notes. In addition, adding an anti-emetic reminder into the chemotherapy-prescribing pathway may be an effective strategy. Clinicians can then prescribe appropriate, guidance-informed anti-emetics alongside chemotherapy.

The CCLG recognises guidance limitations. Potentially poor-quality evidence of anti-emetic outcomes within paediatrics and small studies are acknowledged. Furthermore, results can be confounded by the anticipation of CINV and the use of prophylactic anti-emetics.[4] The limitations of this audit include a small sample size, the use of patients from one department, and the restriction of using retrospective data as information was limited by documentation quality in hospital notes. Consequently, further prospective research with a larger sample size and varying demographics is warranted to increase reliability and generalisability.

Conclusion In conclusion, the results from this audit suggested that anti-emetic prescribing does not adhere to the current guidance, which leads to an increased probability of treatment failure. Managing CINV in children undergoing chemotherapy is imperative in reducing long-term complications. Therefore, it is essential that anti-emetic prescribing habits are reviewed. Strategies, including an anti-emetic reminder tool, could be implemented to improve adherence and potentially reduce CINV in this patient group. Further research on a larger scale should be conducted to increase validity of the findings and to assess if poor anti-emetic prescribing adherence to guidelines is a systemic problem that requires addressing.

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Contribution statement The author certifies that they have participated sufficiently in the work to take responsibility for the content, including participation in the concept, design, analysis, writing and revision of the manuscript. Abigail Wong is responsible for the work as a whole.

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Research Article

Infant feeding practices of HIV-positive mothers in a rural Ugandan hospital

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Abstract

Aims The aim of this audit was to evaluate the feeding practices of infants born to HIV-positive mothers in a rural Ugandan hospital. The audit compared these practices to the WHO Infant Feeding Guidelines, published in 2016.

Methods This single-centre retrospective observational study used data from the HIV-exposed infant register in Villa Maria Hospital, Uganda. Sixty-one HIV-exposed babies were included in the audit.

Results The WHO guidelines recommend exclusive breastfeeding for the first 6 months of life for HIV-exposed individuals. At 6 months, only 36% (*n*=22) of mothers in the study sample returned for follow-up. Of these, 77% (*n*=17) were exclusively breastfeeding.

Conclusions The results suggest that, in the mothers who returned for follow-up, most infants up to 12 months of age were being fed according to the recommendations set out by WHO. A limitation of this study was incomplete data and inconsistent follow-up. Future considerations for Villa Maria Hospital may be to consider the WHO recommendation of continued breastfeeding past 12 months and ensuring that data are complete for every infant registered.

Introduction

Uganda is a landlocked country located in East Africa with an estimated population of 34.6 million.[1] The prevalence of HIV in the total population is estimated to be 6.5%.[2] HIV can be transmitted from mother to child during pregnancy or labour, or through breastfeeding.[3] This audit focused on the mother to child transmission (MTCT) during breastfeeding, within the context of a rural Ugandan hospital, Villa Maria. Villa Maria is situated within the town of Masaka, south of Uganda's capital, Kampala.

This is an important topic because it is estimated that, of all the HIV-positive infants in Uganda, 95% acquired the infection through MTCT.[4] Furthermore, MTCT is preventable and there are evidence-based interventions to reduce the number of infants becoming infected.[5,6]

The WHO has published specific infant feeding guidelines for HIV-positive women living in resource-limited settings. The most recent guideline recommends exclusive breastfeeding (EBF) for the first 6 months of life and continued breastfeeding until 24 months.[5] The Integrated National Guidelines for Uganda, published in 2012, recommend EBF for 6 months, and complementary feeding from 6 to 12 months.[7]

Methods

This single-centre retrospective observational study used data from the HIV-exposed infant register in Villa Maria Hospital. It comprised all babies born between 1st March 2017 and 30th June 2017, which included 61 HIV-exposed babies. This allowed for data to be collected at the 12 month follow-up. Data was collected on maternal and infant antiretroviral treatment (ARV) status, infant HIV status at 6 weeks, and infant feeding status at each follow-up appointment. Data were anonymised and collected onto an Excel spreadsheet. Basic statistical methods were used to analyse the results.

Results

Between 1st March 2017 and 30th June 2017, 61 infants were born to HIV-positive mothers; 41% (*n*=25) were male and 59% (*n*=36) were female. Seventy-five per cent (*n*=46) of the mothers in the sample were on antenatal ARVs.

Infant feeding At the first PCR test, which usually takes place at 6 weeks of age, 72% (*n*=44) of the total sample returned for follow-up. In comparison, at 6 months, only 36% (*n*=22) of mothers in the study sample returned for follow-up. Across each time point shown in **Figure 1**, follow-up was inconsistent, with varying numbers of mothers returning with their infants for follow-up. Therefore, at each time point, the study population varied in the number of infants and thus may not be directly comparable. Of the total sample of infants, 82% (*n*=50) tested negative for HIV, 5% (*n*=3) tested positive and 13% (*n*=8) had an unknown test result.

The WHO guidelines recommend EBF for the first 6 months of life for HIV-exposed individuals.[5] Although only 36% of mothers returned for follow-up at 6 months, 77% of those who did return for follow-up were feeding by EBF at 6 months; the remaining were complementary feeding (*n*=4) or mixed feeding (*n*=1).

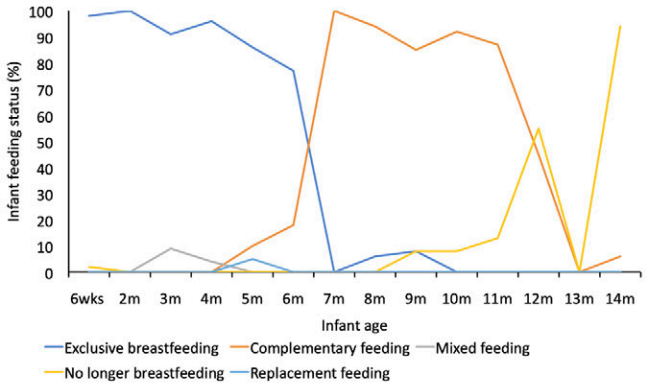

Figure 1: Infant feeding practices in HIV-positive mothers. This figure indicates that most mothers complementary feed from 6 months and continue until 12 months of age. This is aligned with the WHO and the Ugandan guidelines.[5,7] The rates of women no longer breastfeeding increased from 8 months to 14 months. At 14 months, 95% (*n*=17) of mothers were no longer breastfeeding. There were no data after 14 months and therefore the WHO recommendation to continue breastfeeding until 24 months could not be assessed. m, months; wks, weeks.

Discussion

The following discussion will compare the infant feeding practices of HIV-positive mothers to the standard set out by the WHO guidelines.[5] It will use the local data collected in Villa Maria Hospital and utilise data from other studies for comparison.

Exclusive breastfeeding for 6 months Both the WHO and the Ugandan guidelines recommend 6 months of EBF for women who are HIV-positive.[5,7] Breastfeeding in the context of HIV demonstrates a difficult balance of risks and benefits. However, it is suggested that in low-income countries, such as Uganda, the benefits of breastfeeding outweigh the risk associated with HIV transmission.[4,8] In a study of 118 HIV-exposed infants in rural Uganda, there was a 6-fold increase in risk of death in infants when they were breastfed for shorter than 6 months.[4] Breastfeeding is protective against gastroenteritis, one of the major causes of infant mortality in low-income settings.[4,8]

In this study, at 6 months, 77% (*n*=17) of mothers were still feeding by EBF. Other studies have found a wide variation in the percentage of mothers feeding by EBF at 6 months.[4,9,10] A study by Marquez et al reported that 84% of HIV-exposed uninfected infants in rural Uganda were fed by EBF up to 6 months.[10] However, other studies have found that only 25% of HIV-exposed infants in rural Uganda were fed by EBF at 6 months.[4]

This large variation in the studies between the percentage of infants being fed by EBF at 6 months may be explained by the differences in the populations, as urban populations may have more access to safe formula feeding. Furthermore, the definition of EBF may not be comparable between these studies, and the sample sizes are considerably different. However, it is encouraging to see that our study had one of the highest percentages of EBF at 6 months.

Barriers to EBF Although a large proportion of the infants in the study sample were fed by EBF at 6 months (77%), there may also be some significant barriers to EBF in this population of HIV-positive mothers in Uganda. It has been suggested by Muhumuza et al that in-adequate nutrition and access to healthy food is one reason why mothers may not be able to breastfeed exclusively.[11] Furthermore, these authors comment upon inadequate food as a cause of women not taking ARV, as the side effects are exacerbated when taken on an empty stomach.[11]

In recognition of this, the HIV support group in Villa Maria Hospital, which takes place every Wednesday morning, provides porridge for the mothers and their babies. The clinic provides health education talks, including nutritional advice and cooking workshops, an immunisation clinic, viral-load testing, drug dispensing, and basic monitoring of mothers and babies. This intervention may provide an explanation for the high percentage of mothers in this study sample feeding by EBF at 6 months.

Limitations A significant limitation of this study was incomplete data. Infants were followed up at inconsistent time periods depending on when mothers returned to the clinic. The mean number of follow-ups each infant received was 4 (range: 0–9). These follow-ups occurred between 6 weeks and 14 months. This inconsistent follow-up resulted in different study populations at each time point, which may not have been comparable. For health systems to improve, good quality robust data must be collected to measure the effect of any intervention.[12] Therefore, ensuring that each infant on the HIV-exposed register has a completed dataset will be an important future consideration for Villa Maria Hospital.

Conclusion This retrospective observational study of 61 HIV-exposed infants in Villa Maria Hospital aimed to audit the infant feeding practices against the WHO guidelines.[5] Data were limited by inconsistent follow-up and an incomplete dataset. However, the results suggest that, of those returning for follow-up, most infants up to 12 months of age are being fed according to the recommendations set out by WHO.

Reassuringly, a high percentage of mothers and infants were on ARV medication and the rates of transmission of HIV in this sample of infants was 5%. The observations made from this study reflect the success of the HIV centre in Villa Maria Hospital and its targeted programme to reduce MTCT of HIV.

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Contribution statement Hollie Garbett is responsible for the integrity of the work as a whole.

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Research Article

Hysterectomy as an outcome measure for women experiencing postpartum haemorrhage in Wales: the OBSCymru perspective

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Abstract

Aims Postpartum haemorrhage (PPH) is defined as blood loss greater than 500 ml within 24 hours of childbirth, representing one of the top five causes of maternal mortality in the UK. The Obstetric Bleeding Strategy for Wales (OBSCymru) project was introduced in Wales with the primary aim of reducing harm from PPH. The aim of this study was to review hysterectomy as a clinical outcome measure for women following PPH in Wales during the second and third years of the OBSCymru initiative. The uptake of the OBSCymru protocol in clinical practice was also reviewed.

Methods A comparison of process and outcome measures between two annual cohorts of women receiving hysterectomy following PPH was performed using data from the online national OBSCymru database.

Results Ten and 12 hysterectomies were performed for PPH in 2017 and 2018, respectively. Invasive placentation represented the most common cause of PPH, accounting for 41.2% of cases in 2017 and 46.6% in 2018. Improved adherence to all four principles of the OBSCymru protocol was observed; however, there was no significant decrease in measured blood loss (p=0.47; median 4600 ml vs 4300 ml) or overall number of hysterectomies performed (p=0.72).

Conclusions Improvement in all process measures assessed indicates an overall improvement in adherence to the OBSCymru protocol. However, significant improvements were not noted within clinical outcome measures. Early hysterectomy within the context of invasive placentation is recommended in recent guidance and may represent gold-standard clinical care within this group, therefore limiting the utility of hysterectomy as a clinical outcome measure within a national quality improvement programme.

Introduction

Postpartum haemorrhage (PPH) is the fourth leading cause of maternal death in the UK[1] and the most common cause of obstetric-related admissions to intensive care.[2] Early identification and management of bleeding is essential to reduce the need for interventions including hysterectomy. While sometimes necessary to preserve maternal life, this invasive procedure poses many consequences to a new mother including permanent loss of fertility, effects on mother–child bonding and psychological sequelae, such as post-traumatic stress disorder.[3] With this in mind, both the World Health Organisation (WHO)[4] and the Royal College of Gynaecologists and Obstetricians (RCOG)[5] recognise hysterectomy as an appropriate intervention in circumstances where medical and surgical interventions are unable to control bleeding. Therefore, hysterectomy has been identified as a core clinical outcome marker from an international perspective.[6] This highlights the relevance of hysterectomy as a marker for harm in PPH and indicates how it is appropriate to review its utility as an outcome marker.

The Obstetric Bleeding Strategy for Wales (OBSCymru) initiative was established in 2016 as a national quality improvement programme designed to prevent progression of moderate to severe PPH within Welsh hospitals. A standardised clinical proforma was developed for clinical practice based on a four-stage approach for PPH management underpinned by: (1) measurement of maternal blood loss rather than estimation; (2) risk assessment stratified by blood loss; (3) early mobilisation and action of the multidisciplinary team (MDT) at the bedside; and (4) early point-of-care (POC) testing to guide clotting factor replacement.

This study aimed to determine whether an improvement in clinical outcome markers for women receiving hysterectomy following PPH in Wales can be seen during the introduction of OBSCymru, alongside assessing adherence to the standardised OBSCymru protocol. This allowed the utility of hysterectomy as a clinical outcome marker to be assessed when reviewing the management of PPH in Wales.

Methods

The OBSCymru project was launched in 2016 across 12 obstetric units in Wales. Standardised paper management protocols were introduced from January to April 2017 and an all-Wales electronic database was created for women experiencing major PPH with blood loss greater than 1000 ml.

Table 1. Process measures and outcome measures compared between 2017 and 2018 for women receiving hysterectomy following PPH in Wales.

	Process measures	Outcome measures
1	No. of patients with **blood loss measured**	Median **additional blood product** use
2	No. of patients with **completed risk assessments** and **completed standardised four-stage protocols**	Escalation to **level 2** or **level 3 care**
3	Median hours between **delivery and first blood test** performed	Use of **interventional radiology**
4	No. of **laboratory blood tests** performed and **POC tests** performed	Use of **surgical interventions**

Process measures were assigned to the principle of the standardised four-stage OBSCymru protocol they best represented, denoted using numbers 1–4. Outcome measures did not correspond to an OBSCymru principle and instead represented a clinical procedure or process.

A retrospective analysis of data entered into the electronic all-Wales OBSCymru database between January 2017 and December 2018 was

performed. Data were analysed using Microsoft Excel to compare process and outcome measures between 2017 and 2018 **(Table 1)**. The lead research and development office (Cardiff & Vale University Health Board) deemed this project to be of quality improvement and not research, meaning that ethical approval and individual consent to collect and report data were not required.

Results

There were 31,532 deliveries recorded in Wales in 2017, and 30,214 in 2018. A total of 2791 and 3057 women experienced PPH in 2017 and 2018, respectively. Of these, 10 went on to receive hysterectomy in 2017 and 12 in 2018 (p=0.72). The hysterectomy rate was therefore 0.3 hysterectomies per 1000 pregnancies. Causes of PPH included uterine atony, surgical causes, placenta previa (a low-lying placenta) and placenta accreta (invasive growth of the placenta into the uterine wall) **(Figure 1)**. Invasive placentation was the most common cause of PPH for both years, representing 50% of cases in 2017 and 58.3% of cases in 2018.

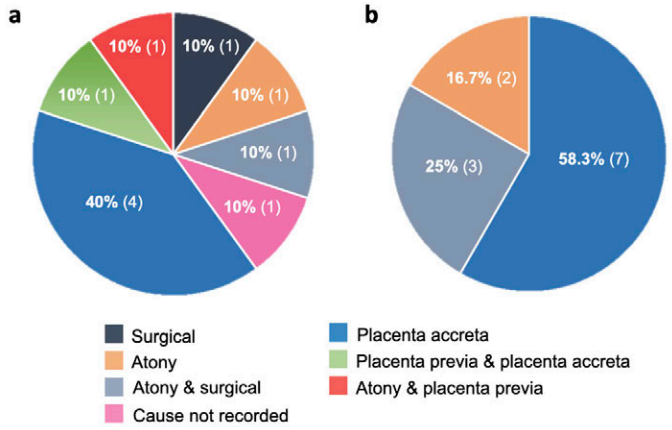

Figure 1. Underlying cause of PPH. (a) Underlying cause of PPH for women receiving hysterectomy following PPH in Wales in 2017. **(b)** Underlying cause of PPH for women receiving hysterectomy following PPH in Wales in 2018. Data are presented as % *(n)*. Placenta accreta can also be referred to as invasive placentation.

Process measures showed numerical improvement between 2017 and 2018 for all parameters assessed within the OBSCymru protocol **(Table 2)**.

Table 2. Process measures for women receiving hysterectomy following PPH in Wales between 2017 and 2018.

OBSCymru principle	Process measure	2017	2018
1. Measurement of blood loss	Blood loss measured	90.0% (9)	100.0% (12)
2. Risk assessment stratified to blood loss	Risk assessment completed	40.0% (4)	75.0% (9)
	Four-stage paperwork used	20.0% (2)	66.7% (8)
3. Early MDT mobilisation and action	Median hours between delivery and first blood test	01:08 [01:05–04:59]	00:48 [00:32–02:23]
4. Use of POC testing to guide fibrinogen replacement	Number of laboratory blood tests	5.0 [4.0–11.8]	5.0 [2.8–9.0]
	Number of POC tests	1.0 [0.0–2.0]	3.0 [1.0–4.3]

Results are reported as median [IQR] or % *(n)*. Time is reported as [hours:minutes]. Parameters are assigned to the principle of the standardised paper OBSCymru protocol they best represent.

A median [interquartile range (IQR)] of 4600 ml [1880.5–5875] and 4300 ml [3503.8–5542.5] measured blood loss was recorded from 2017 to 2018, respectively (p=0.47). Outcome measures revealed a modest numerical decrease in median red blood cell and fresh frozen plasma (FFP; a blood component containing clotting factors) use, number of patients receiving level 2 care outside the delivery suite, advice obtained for interventional radiotherapy and number of Bakri balloon interventions performed. All other parameters were observed to increase or remain constant from 2017 to 2018 **(Table 3)**.

Table 3. Clinical outcome measures for women receiving hysterectomy in Wales following PPH during 2017 and 2018.

Outcome measure		2018	2018
Median blood products	Red blood cells (units)	6.0 [3.0, 8.0]	5.5 [3.0, 7.3]
	Fibrinogen (g)	0.0 [0.0, 0.0]	0.0 [0.0, 4.0]
	Platelets (units)	0.0 [0.0, 0.8]	0.0 [0.0, 0.0]
	Cryoprecipitate (units)	0.0 [0.0, 1.5]	0.0 [0.0, 0.0]
	FFP (units)	3.0 [0.0, 4.0]	0.0 [0.0, 3.3]
	Recombinant factor VIIa (µg)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
Escalation of care	Patient received level 2 care on the delivery suite	90.0% (9)	91.7% (11)
	Patient received level 2 care outside the delivery suite	20.0% (2)	0.0% (0)
	Patient received level 3 care outside the delivery suite	40.0% (4)	41.7% (5)
Interventional radiology	Advice obtained	10.0% (1)	0.0% (0)
	Pre-planned procedure	0.0% (0)	25.0% (3)
	Emergency procedure	0.0% (0)	8.3% (1)
Surgical interventions	Homeostatic uterine suture	20.0% (2)	33.3% (4)
	Bakri balloon	20.0% (2)	8.3% (1)
	Internal iliac artery ligation	0.0% (0)	8.3% (1)

Results represented as median [IQR] or % *(n)*. Level 2 care can be provided on the delivery suite or on a high-dependency unit while level 3 care can only be delivered within an intensive care unit away from the delivery suite. Care separate from the delivery suite requires maternal–baby separation.

Discussion

Modest improvements were noted across all process measures between 2017 and 2018. This may reflect an improved adherence to the OBSCymru protocol within the clinical setting; however, a small sample size and limited study time makes this difficult to confirm. Further audit would be required to confirm improved adherence, but it is likely that annual teaching introduced as part of the PRactical Obstetric Multi-Professional Training programme (PROMPT)[7] during 2018 may have contributed towards these observed improvements. This is a promising outcome and it is possible that a positive uptake of the OBSCymru protocol could improve maternal outcomes over time.

No consistent improvement in clinical outcome markers was identified within the cohort, with no significant improvement in measured blood loss (p=0.47) or overall number of hysterectomies performed (p=0.72). This was likely to have been influenced by small sample size accountable to the rare incidence of hysterectomy within the setting of obstetrics. Furthermore, this low hysterectomy rate is comparable with those described in the USA[8] and Scotland[9] indicating that the small hysterectomy cohorts within this study in Wales can be expected.

Limited improvement in clinical outcomes may also be influenced by a high proportion of underlying invasive placentation in this population. Recent Green-top Guidance from the RCOG advises

early hysterectomy during PPH within the setting of invasive placentation,[5,10] indicating that hysterectomy may represent gold-standard care for these women and would have been unavoidable despite OBSCymru measures.

Future directions Hysterectomy is a complex, multi-factorial event and it may therefore be more appropriate to regard these events as individual case studies with independent learning points. This study focussed on data gathered following OBSCymru initiation, and it may be revealing to compare clinical outcomes with those before OBSCymru was implemented. However, this lies outside of the scope of this investigation and would be a topic of future research. Furthermore, exploration of different clinical outcome measures, such as admission to intensive care, may yield larger sample sizes and offer a more robust clinical outcome measure when assessing the effects of OBSCymru measures on PPH management in Wales.

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Contribution statement The author has made a significant contribution to the design, data collection and data analysis of the work. They have been responsible for the drafting and critical revisions of the piece, as well as the final approval of the version to be included within the *INSPIRE Journal*. Louise Brown is responsible for the integrity of the work as a whole.

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Research Article

How does the duration of treatment and post-treatment remission interval differ amongst patients with non-infectious uveitis who were treated across a 2–2.5-year period?

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Abstract

Introduction As patients with non-infectious ocular inflammation are weaned off treatment, the disease may relapse. The purpose of the study was to evaluate the association of treatment duration, type of therapy and uveitis aetiology with post-treatment inflammation remission interval.

Methods Inclusion criteria were patients with non-infectious ocular inflammatory disease with more than two visits spanning at least 90 days and a total treatment time of 2–2.5 years. A retrospective chart review was carried out with data collected for duration of treatment, post-treatment remission interval and treatments, and uveitis aetiologies of non-infectious ocular inflammation.

Results Fifty-eight per cent of those treated with corticosteroids achieved complete remission. Amongst patients treated with corticosteroids who relapsed, a duration of treatment of 4.6 months resulted in an inflammation-free period of 23.4 months. Amongst all treatment or aetiological groups, those with a duration of treatment that ranged between 2 to 2.5 months had a post-treatment remission interval of at least 21 months.

Conclusions Corticosteroids were an effective treatment. Following a treatment regimen with a shorter duration of treatment (yet a higher risk of relapsing) may result in a better quality of life for patients.

Definitions

Duration of treatment: The time of the first visit to the last visit where treatment was discontinued.

Post-treatment interval (in patients who achieved complete remission): The time between the last visit where treatment was discontinued and 3 July 2018.

Post-treatment interval (in patients who had a recurrence of inflammation): The time between discontinuation of treatment and when patients had a relapse in inflammation.

Introduction

In Europe, uveitis is the fifth or sixth leading cause of preventable blindness with an approximate prevalence of 5–15%.[1] Untreated, uveitis can cause glaucoma, retinal lesions, macular oedema, and eventual blindness.[2] Remission is possible with immunomodulatory treatments; however, ocular inflammation can relapse once therapy is discontinued, which puts the patient at risk of further vision loss. Although remission and relapse are known to occur, the factors that influence non-infectious ocular inflammation to either relapse or undergo remission are not understood.[2]

This study investigates the association between the types of uveitis therapy or aetiologies and the duration of treatment for non-infectious ocular inflammation and the post-treatment remission interval following treatment discontinuation. This study is the first to measure and compare the association of complete remission and relapse in inflammation and the associated durations across various treatments and aetiologies of ocular inflammation in a single study. Understanding which treatments or aetiologies are associated with better outcomes allows physicians to tailor and deliver efficient treatment and circumvent less effective and prolonged treatment.

Methods

A retrospective chart review was conducted using data from one uveitis specialist (author CG) at The University of Ottawa Eye Institute, Ottawa, ON, Canada. Ethical approval was not required for the use of this data. Inclusion criteria were patients with non-infectious ocular inflammatory disease (uveitis, scleritis, or episcleritis) and patients with more than two visits spanning at least 90 days and a combined duration of treatment and post-treatment remission interval of 2–2.5 years **(Figures 1 and 2)**.

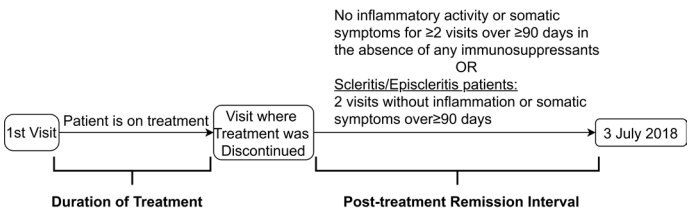

Figure 1. Timeline of patients who achieved remission.

Of 4798 available charts, 14 charts met inclusion criteria and were selected for review. The reason so few cases were selected was because few patients met the inclusion criteria, with a combined duration of treatment and post-treatment remission interval of 2–2.5 years. The duration of treatment is defined as the time of the first visit to the last visit where treatment was discontinued **(Figures 1 and 2)**. In patients who achieved complete remission, the post-treatment interval is the time between the last visit where treatment

was discontinued and 3 July 2018—the end of the review **(Figure 1)**; for patients who had a relapse, it is the time period between discontinuation of treatment and when they had a relapse in inflammation **(Figure 2)**.

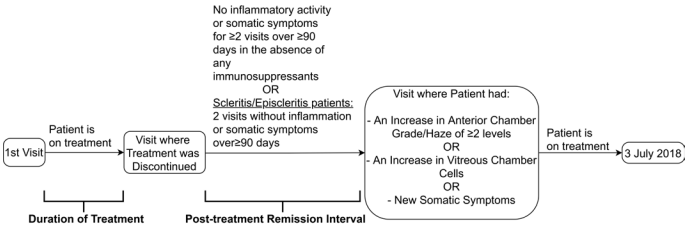

Figure 2. Timeline of patients who relapsed in inflammation.

Participants were separated based on the treatment they received and the aetiology of their ocular inflammation. These groups were further divided depending on whether a patient achieved remission or had a relapse in inflammation. The average (mean) treatment duration and the average post-treatment remission interval are reported.

Remission or relapse in inflammation The definition of "remission" was adapted from the Systemic Immunosuppressive Therapeutic Eye (SITE) study group and defined as a complete absence of any inflammatory activity at ≥2 visits spanning ≥90 days, in the absence of any immunosuppressant medications, without any somatic symptoms.[3] In patients with scleritis or episcleritis, remission was defined as two visits without inflammation or somatic symptoms over ≥90 days **(Figure 1)**. "Relapse in inflammation" was defined as an increase in anterior chamber cell grade of at least two levels in the Standardization of Uveitis Nomenclature (SUN) working group grading scheme of anterior chamber cells/flare or vitreous chamber haze or the development of new somatic symptoms following a period of complete remission **(Figure 2)**.[4]

Results

As shown in **Tables 1 and 2**, nine patients from our study group had achieved remission, while five patients had relapsed in inflammation. Corticosteroids were the most common treatments in patients who achieved remission (88.89%) and relapsed (100%). Anterior uveitis was the most common aetiological diagnosis in both patient groups, occurring in 66.67% of patients with remission and 40% of those who relapsed.

Table 1. Data for patients who had achieved remission.

Aetiology of ocular inflammation	Treatment	Treatment duration (months)	Post-treatment remission interval (months)	Total duration (months)
Anterior uveitis	Corticosteroids	11	16	27
Anterior uveitis	Corticosteroids	25	3	28
Anterior uveitis	Corticosteroids	19	5	24
Anterior uveitis	Corticosteroids	24	4	28
Anterior uveitis	Corticosteroids	19	7	26
Anterior uveitis (HLA B27*)	Corticosteroids	27	3	30
Birdshot retinocho-roidopathy	Corticosteroids	22	5	27
Scleritis	Methotrexate	25	3	28
Scleritis	Corticosteroids and NSAIDs	12	12	24

Table 2. Data for patients who relapsed.

Aetiology of ocular inflammation	Treatment	Treatment duration (months)	Post-treatment remission interval (months)	Total duration (months)
Anterior uveitis	Corticosteroids	12	18	30
Anterior uveitis	Corticosteroids	3	24	27
Autoimmune retinopathy	Corticosteroids	3	24	27
Fuchs uveitis	Corticosteroids	3	24	27
Scleritis	Corticosteroids	2	27	29

Treatments In patients who achieved remission **(Figure 3)**, combined treatment with corticosteroids and non-steroidal anti-inflammatories (NSAIDs) resulted in the shortest mean duration of treatment (12 months) and post-treatment remission interval (12 months). Methotrexate had an average treatment duration of 25 months and a post-treatment remission interval of 3 months, while for corticosteroids alone, treatment duration was 21 months and the post-treatment remission interval was 6.1 months.

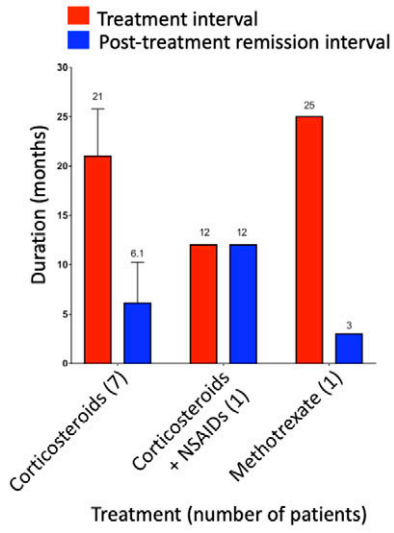

Figure 3. Average treatment interval and post-treatment remission interval for treatments amongst patients treated for 24–30 months who achieved remission.

The five patients who relapsed and were treated with corticosteroids **(Figure 4)** had an average treatment duration of 4.6 months and a post-treatment remission interval of 23.4 months.

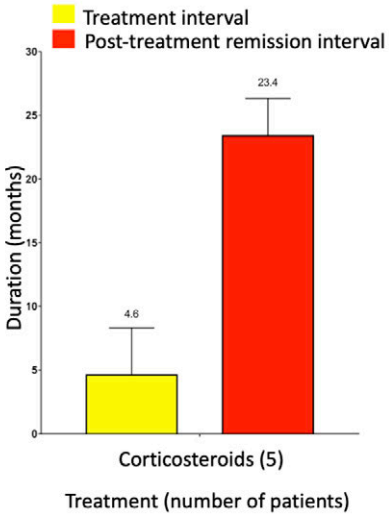

Figure 4. Average treatment interval and post-treatment remission interval for treatments amongst patients treated for 24–30 months who relapsed.

Aetiological diagnosis Patients with anterior uveitis who achieved remission **(Figure 5)** had an average treatment duration of 20.8 months and a post-treatment remission interval of 6.3 months. In the scleritis group, treatment duration and post-treatment remission interval were 25 months and 7.5 months, respectively, whilst for the patient with birdshot retinochoroidopathy, they were 22 months and 5 months, respectively.

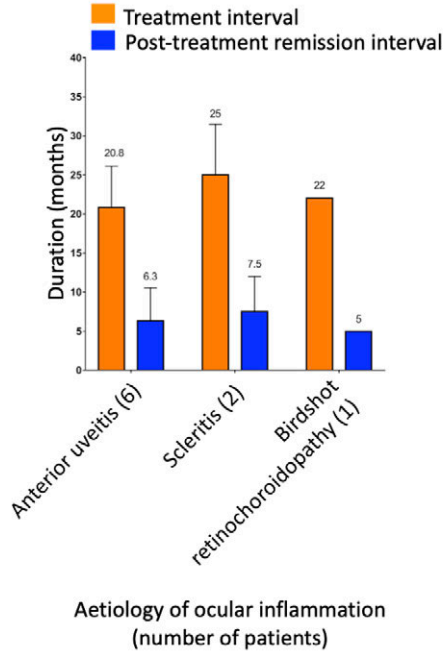

Figure 5. Average treatment interval and post-treatment remission interval for uveitis aetiologies amongst patients treated for 24–30 months achieving remission.

Amongst those who relapsed **(Figure 6)**, the patients with anterior uveitis had an average treatment duration of 7.5 months and a post-treatment remission interval of 21 months. For the scleritis patient, treatment duration and post-treatment remission interval were 2 months and 27 months, respectively, and for both the patient with Fuchs uveitis and the patient with autoimmune retinopathy, the values were 3 months and 24 months, respectively.

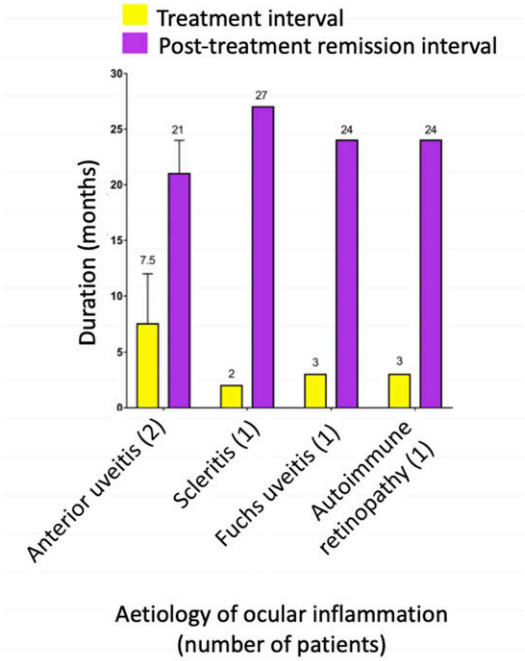

Figure 6. Average treatment interval and post-treatment remission interval for uveitis aetiologies amongst patients treated for 24–30 months who relapsed.

Discussion

This study found that a longer initial duration of treatment was associated with a higher success in achieving remission. As shown in **Figures 3–6**, those treated with an average treatment duration of at least 12 months achieved remission, while those with an average treatment duration of 2–7.5 months had a relapse in inflammation; however, these patients had a relatively long post-treatment remission interval of at least 21 months. Considering the many adverse effects of immunomodulators (such as corticosteroids and methotrexate), treating patients for a period of 2–7.5 months (with a post-treatment remission interval of at least 21 months) would most likely result in a better quality of life.[5]

Corticosteroids were the most common drug used to treat patients with ocular inflammation. Fifty-eight per cent of those treated with corticosteroids achieved complete remission. In patients who relapsed, a treatment duration of just 4.6 months resulted in an inflammation-free period of 23.4 months, suggesting that corticosteroids are effective for treating non-infectious inflammatory eye disease.

A limitation in this study was the small sample size; as a result, the power of our associations is quite low. Further research needs to be done to determine which treatments and aetiologies of non-infectious inflammatory eye disease are associated with a higher rate of relapse or remission of inflammation. Another limitation of our study is that, with such a small sample size, the findings cannot be truly representative of the population. Unfortunately, there is no current literature on such a topic to which we could compare our findings.

The study interval was short. Those that had a longer treatment duration and a shorter follow up period were, consequently, less likely to relapse in inflammation during the remaining period of the study. It is important to consider that, if the time period of the study was longer, these patients might also have relapsed. Further studies with a longer duration would give insight into which patients relapse or stay in remission.

Conclusion The longer the duration of treatment for non-infectious uveitis (at least 12 months), the more likely it is that a patient would achieve remission. Amongst those with a treatment duration of 2–7.5 months, there was a post-treatment remission interval of at least 21 months; following this treatment regimen might result in a better quality of life. Corticosteroids were the most common drug used and appeared to be effective treatments.

Contribution statement Saanwalshah Samir Saincher designed the project, analysed the data and wrote the manuscript. Chloe Gottlieb supervised this research, designed this project, aided in analysing the data and writing the manuscript, and approved the final version to be sent to the *INSPIRE Journal*. Saanwalshah Samir Saincher is responsible for the integrity of the work as a whole.

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Senior Editors, Summer 2020

Jonathan Bray

I undertook the role of Senior Editor for the *INSPIRE Health Sciences Research Journal* whilst working as an Academic Foundation Doctor in Wales, having just graduated from The University of Bristol. I have a passion for combining academic medicine with my clinical career, and have a particular interest in academic cardiology. The *INSPIRE journal* has been a fantastic opportunity to work with professionals and actively participate in the publication process.

Aarti Jalan

I am a third year medical student at Bristol University and came into medicine with a desire to learn both about clinical medicine and the research that underpins it. INSPIRE has allowed me to gain an insight into how research and publishing functions and an invaluable opportunity to develop skills and collaborate with students from different universities and disciplines. My main interests within medicine include paediatrics and neurology, amongst many others, and my biggest passion outside of medicine would have to be drama.

Viktorija Kaminskaite

I am a fourth year medical student at the University of Exeter and have been involved with the INSPIRE programme in various roles since my first year. Doing a year of medical sciences before transferring to medicine made me fall in love with research, and the central message of INSPIRE of widening student access to research was the reason why I got involved. I have thoroughly enjoyed my time as a senior editor for the journal. My current interests include ENT, obstetrics and gynaecology, and breast surgery. Next year I will be intercalating in MSc Genomic Medicine with a project on thyroid cancer. My interests include music, fitness, painting/drawing and travelling.

Izzy McNally

I am a third year vet student at the University of Bristol and have previously gained a BSc in Biological Science. I developed a keen interest in skeletal pathology research through my BSc and I hope to pursue a career as a specialist veterinary surgeon in this area. Being an editor for *INSPIRE* has given me a great opportunity to hear about research from the other health science professions. Outside of medicine, I enjoy running and cycling.

Weronika Nasterska

Originally from Warsaw, I am a third-year dentistry student at the University of Plymouth. My journey with academic research began with the INSPIRE studentship programme, which I completed in 2019. Since then I have been pursuing further research opportunities and engaging in other research-related activities. I am especially interested in the relationship between dentistry and systemic health and I enjoy exploring immunological perspectives in dentistry. I aspire to combine research with a clinical career.

King-David Nweze

Having completed a summer research project as part of the INSPIRE scheme at the Institute of Translational and Stratified Medicine (ITSMed) in Plymouth, I was convinced that taking the opportunity to be part of the editorial team for INSPIRE's student research journal would be a fantastic opportunity to further broaden my interest in research. I am a third year medical student at the Peninsula Medical School (Plymouth University) and my research interests mainly include clinical neuroscience research. From my experience of working alongside fellow students as a senior editor for the *INSPIRE Health Sciences Research Journal* I have been able to further enhance several personal skills, ranging from critically evaluating research work to teamworking.

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Temidayo Osunronbi

I graduated as a medical doctor from the University of Plymouth in 2020 after obtaining an MSc in Neuroscience from the University of Oxford in 2019. I have authored multiple peer-reviewed surgery-related articles in PubMed-indexed journals and presented at various (inter)national scientific meetings. My passion to encourage students' participation in research motivated my decision to join the *INSPIRE Journal's* editorial team. I aim for a career in academic neurosurgery and will commence an academic foundation programme (research) in August 2020. Outside of academic interests, my hobbies are football, cycling and basketball.

Christina Wainer

I am currently a fifth-year dental student at the University of Bristol. Having completed a BSc in Pharmacology at University College London prior to attending dental school, I have a passion for research and I hope to combine this with a clinical career in the future. I have thoroughly enjoyed being a senior editor for the *INSPIRE Health Sciences Research Journal*, and it has been a pleasure to see the growth of the journal during the past year. It has been a great opportunity to participate in the publication process and to contribute to the journal's aim of encouraging readers to have a wider appreciation for the many subfields of medicine, dentistry and veterinary science. In my spare time I enjoy scuba diving, skiing and baking.

Shannon Seet

I am currently a third year medical student studying at Cardiff University. Having not much experience in research studies, I thought joining INSPIRE will allow me to have a chance to explore and gain more understanding within this field. This opportunity has definitely allowed me to be more aware about research topics across the different disciplines and the effort that goes behind research. I am particularly interested in acute medicine, critical care and paediatrics. Aside from medicine, I enjoy binge-watching my favourite TV shows and spending time with my family and friends.

Emily Wales

I am a fourth year postgraduate medical student at Cardiff University. I have previously undertaken a degree in Biomedical Science and graduated with a first class honours. Coming from a research-based degree into medicine, INSPIRE has allowed me to continue my exposure to clinical research and meet like-minded people from other universities. I have a wide range of interests including neurology, surgery and anaesthetics. Outside of medicine, my interests include fitness, being outdoors, painting and cooking.

List of referees, Summer 2020

Natasha Alford, University of Bristol
Lauren Ashley, University of Bristol
Lelyn Osei Atiemo, University of Bristol
Aashna Bali, University of Bristol
Joel Braganza, University of Bristol
Rym Chafai El Alaoui, Cardiff University
Serena Dodhia, University of Bristol
Samantha Doyle, University of Bristol
Zach Du Toit, University of Bristol
Khadijah Ginwalla, University of Bristol
Grace Hosking, Cardiff University
Amina Kaloko, University of Bristol
Aurimas Kudzinskas, University of Exeter
Keng Siang Lee, University of Bristol
Courtney Lendon, University of Bristol
Hwai Yi Lim, University of Bristol
Qui Lim, University of Bristol
Sophie Lloyd, University of Bristol
Shruthi Mankal, University of Exeter
Rosie Mcdonald, Cardiff University
Ross Morgan, University of Bristol
Ellen Nelson-Rowe, Cardiff University
Ajijolaoluwa Oyedele, University of Cardiff
Sebastian Priest, University of Bristol
Samantha Raettig, University of Bristol
Paul Rival, University of Bristol
Brianna Robinson, University of Bristol
Georgia Rowley, University of Bristol
Shaneel Shah, University of Bristol
Sophie Stretch, University of Bristol
Jack Tremlett, University of Exeter

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University of Bristol

www.bristol.ac.uk/medical-school/study/undergraduate/inspire
www.bristol.ac.uk/vet-school/research/inspire

Leads: Elizabeth Coulthard, Associate Professor in Dementia Neurology;
Richard Coward, Professor of Renal Medicine and Consultant Paediatric Nephrologist;
Linda Wooldridge, Chair in Translational Immunology

University of Cardiff

http://cures.cardiff.ac.uk/inspire

Lead: Colin Dayan, Professor of Clinical Diabetes and Metabolism

University of Exeter

https://medicine.exeter.ac.uk/study/ug/medicine/researchopportunities

Lead: Joanna Tarr, Senior Lecturer, College of Medicine and Health

Plymouth University Peninsula School of Medicine and Dentistry

www.plymouth.ac.uk/about-us/university-structure/faculties/health/inspire

Leads: David Parkinson, Professor of Neuroscience;
Vehid Salih, Associate Professor in Oral & Dental Health Research

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