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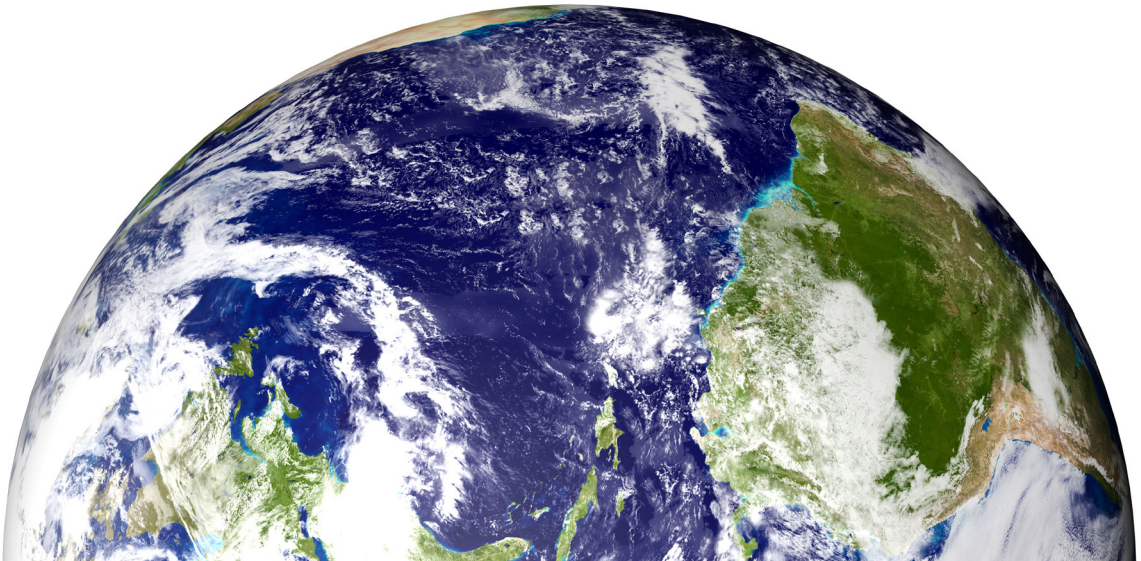

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Letter from UCDsmj Executive Commitee

The Executive Committee of the UCD Student Medical Journal is delighted to put forward the 4th Edition of this exciting publication. This edition is truly an excellent collaboration between different healthcare domains and experiences.

Ruky Agbahovbe *Aoife Nechowska* *Camilla English* *Lade Adeusi*

This past year marked the 10th anniversary of the UCD Summer Student Research Awards. This innovative undergraduate student initiative continues to highlight the importance of early exposure to the world of research to our medical students. This year's original research articles delved into the area of cardiovascular disease. Kengo Soghoyan explores radiological imaging of aortic valve replacements, and Anush Devadhasan looks at atrial fibrillation and its diagnostic techniques.

This issue also investigates how, with the continuous advancements in technology, conventional medical practices can be enhanced to yield improved outcomes for patients. Nauar Knightly and Naomi Fearon investigate and compare the surgical treatment of respiratory tract and upper digestive tract cancers. Barry Singleton discusses anaesthetics and how a person's genome affects their response to different drugs. Kevin O'Malley summarises the many factors contributing to the development of antimicrobial resistance and Aleksandra Szycman looks at the huge danger that infection is to pregnant women and the means by which the risk can be minimized.

This fourth edition of the Student Medical Journal unravelled many aspects encompassing the topic of global health and medicine overseas. Niamh Corcoran looks at the history and current events surrounding the infamous Zika virus. Eimear Byrne interviews Dr. Trish Scanlon about her great work in childhood cancers in Ireland and in Tanzania. Additionally, we highlight the endeavours taken by our fellow students with a segment from Tiarnán Byrne in which he discusses his experience completing a clinical elective in Emergency Medicine in Sydney, Australia. Ning Xuan Ho, a representative of the Association of Medical Students Ireland, reveals the many international opportunities that UCD medical students can avail of during their degree programme. We believe that exposing medical students to healthcare systems outside of Ireland is crucial to strengthening the future of our own medical system.

Closer to home, Niamh Conlon examines Cystic Fibrosis, a condition in which Ireland has the highest incidence in the world. She uncovers the history and challenges surrounding the understanding of this common genetic disease. Michael Germansky, discusses his experience with Crohn's disease from the perspective of a medical student. This past year saw the creation of the UCD Social Medicine Society, a student run group dedicated to promoting social and community health. The society hosted an inaugural inter-faculty Ideas for Change event. The winning team, Stéphane Blouin, Daniel Gourlay and Riya Varman, share with us their proposal to provide storage spaces for the homeless in order to improve the health and wellbeing of this marginalized population of Ireland.

It is with great pleasure that we present to you this edition of the Student Medical Journal. The content that we have received this year is of an excellent standard and we hope that the topics covered in these pages will inspire all of us as we progress in our careers as healthcare professionals. We would like to thank the authors, collaborators and the School of Medicine for their involvement in the production of this edition, and we the Executive Committee, hope you enjoy this wonderful piece of student work.

Atrial fibrillation

Written by Anush Devadhasan

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ABSTRACT

Atrial fibrillation (AF) is a cardiac disorder characterised by a rapid, irregular heartbeat. Onset often comprises no symptoms, making AF difficult to diagnose.[1] If left untreated, AF poses potential risks of blood clot formation, leading to ischemic stroke.[1] However, two atrial fibrillation conditions exist: terminating and non-terminating. The terminating condition spontaneously ceases whereas the non-terminating condition requires medical intervention. Furthermore, rural/impoverished regions are at heightened risks due to lack of healthcare facilities and clinicians. High AF prevalence rates put millions at risk of this cardiac disorder globally.[1]

This study proposes a Support Vector Machine-enabled Electrocardiogram device for algorithmic diagnosis of healthy, terminating AF, and non-terminating AF conditions. The signal was acquired from a differential amplifier; integrating low-pass, high-pass, and bandstop filters for electrical interference reduction.[2] The class determination algorithm, through autonomous extraction of instantaneous amplitude, zero crossing rate, and power spectral density for application to SVM classification in dimensionally reduced feature space, detected cardiac arrhythmias in ECG signals.[3] The SVM learning model detected unknown signal classes though training with data comprising extracted, labelled ECG signal features. Corresponding diagnoses were displayed via LED indicators. The objective was to develop a feasible system for AF diagnoses through interfacing of the amplifier with the SVM algorithm.

ECG signal QRS-complex features were adequately captured through the amplification system. Algorithmic SVM classification yielded sensitivities of 80.00-83.33% to signal class. Therefore, significant progress has been achieved and, with further development, may be ready for deployment to appropriate regions.

I. INTRODUCTION

Atrial fibrillation

Atrial fibrillation is a rapid and irregular heartbeat induced by electrical disturbances in the sinoatrial node. It is categorised into three classes: paroxysmal, persistent, and permanent. Paroxysmal AF is characterised by self-terminating episodes whereas persistent and permanent conditions are non-terminating and require medical intervention to prevent complications. Atrial fibrillation occurs with minimal symptomatology and high prevalence rates, thereby presenting risks of complications, arising from non-terminating AF, to many people. Furthermore, rural regions lack the necessary medical instruments, which can be costly, and skilled cardiologists, trained to identify minute variations in ECG tracings, for AF diagnoses. This presents the need for an affordable device, integrating an ECG device with the diagnostic abilities of a cardiologist through signal processing and algorithmic classification, for AF detection/classification.

AF Diagnostic Device

This study proposes a Support Vector Machine-enabled Electrocardiogram device for algorithmic determination of ECG signal class: healthy, terminating AF, or non-terminating AF. The signal will be acquired from a differential amplifier; integrating low-pass, high-pass, and bandstop filters for reduction of various electrical interferences[2]. The class determination algorithm will, through autonomous extraction of instantaneous amplitude, zero crossing rate, and power spectral density for application to SVM classification in dimensionally reduced feature space, detect cardiac arrhythmias in ECG signals.[3] The SVM learning model will detect unknown signal classes though training with data comprising extracted ECG signal features labelled with one class, projected onto a 3,840 dimensional feature space, then dimensionally reduced by principal component analysis. A 70%-80% sensitivity to classes is hypothesised.

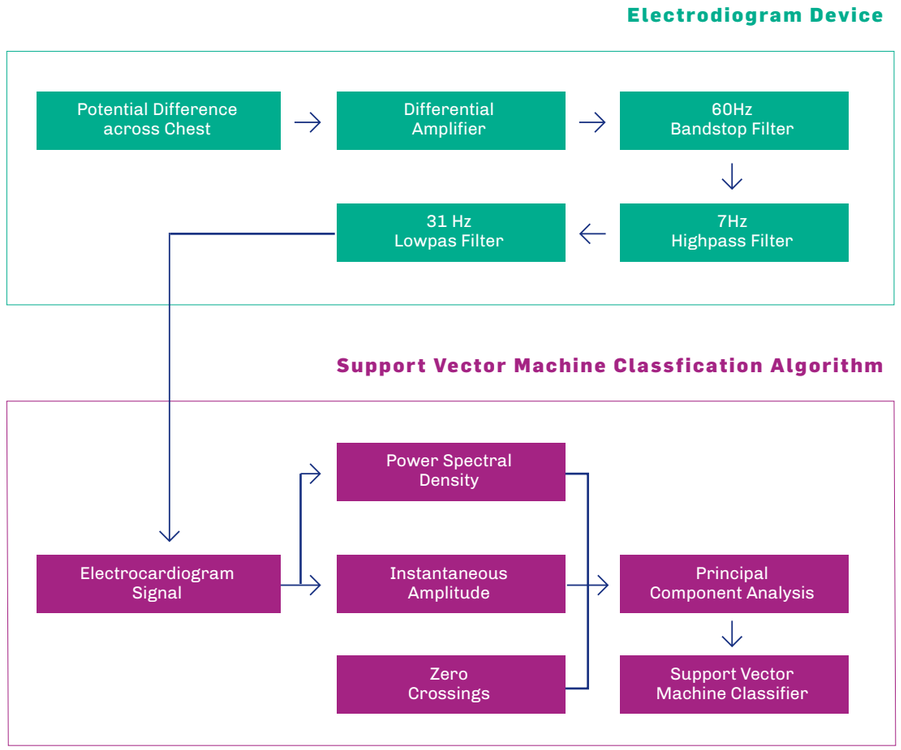

Figure 1:
Flowchart for Proposed Device Desig

Rationale

Chugh et al., in 2010, estimated that 33.5 million individuals suffered from atrial fibrillation worldwide. This study found a general increase in AF-associated mortality over time and concluded "systematic, global surveillance of AF is required to better direct prevention and treatment strategies". The proposed device would assist in achieving such systematic and global surveillance of AF, particularly in rural and poverty-stricken areas.

ECG Device

Prior studies have attempted to develop low-cost electrocardiogram devices for deployment in resource-limited areas. The Biosignal Pi, developed by Abtahi et al. (2015), is an affordable biosignal measurement platform capable of obtaining various readings, including ECG tracings. However, this device is rendered ineffective without medical specialists for the analysis of biodata and resulting diagnosis. The proposed device integrates a classifier algorithm with an affordable ECG device to overcome absence of medical specialists.

SVM Classifier

The classifier algorithm utilises Support Vector Machine for ECG signal class detection. The SVM algorithm initially determines "support vectors" for two separate classes of training data, then calculates a maximum-margin separating hyperplane in the n-dimensional feature space.[4] When provided a data set of an unlabelled class (in this case the ECG signal obtained from the patient), SVM determines its position with respect to the hyperplane; the side of the hyperplane to which the data set lies.[4] This determines the predicted class (diagnoses) of the ECG signal by SVM[4]. The proposed device detects three different classes, and thereby, training data belonging to each of these classes are required. Healthy, terminating AF, and non-terminating AF ECG tracing files were obtained from the Physionet database and extracted features were used to train the SVM learning model.[5]

Feature Extraction

The extracted features for training were instantaneous amplitude, zero crossing rate of instantaneous phase, and power spectral density[3]. For R-peak analysis, an analytic signal was derived from each ECG tracing through Hilbert transform; from which instantaneous amplitude was obtained.[6] Derived instantaneous phase from the Hilbert transform of the signal allowed determination of the zero crossing rate. Mohebbi et al. (2014) demonstrated that power spectral density is an effective feature descriptor for training of AF termination prediction learning models. This algorithm extracts power spectral density from raw ECG signals. PCA is carried out for dimensionality reduction. The developed algorithm was implemented in python using the Numpy, Scipy, Sci-Kit Learn, and Matplotlib modules.

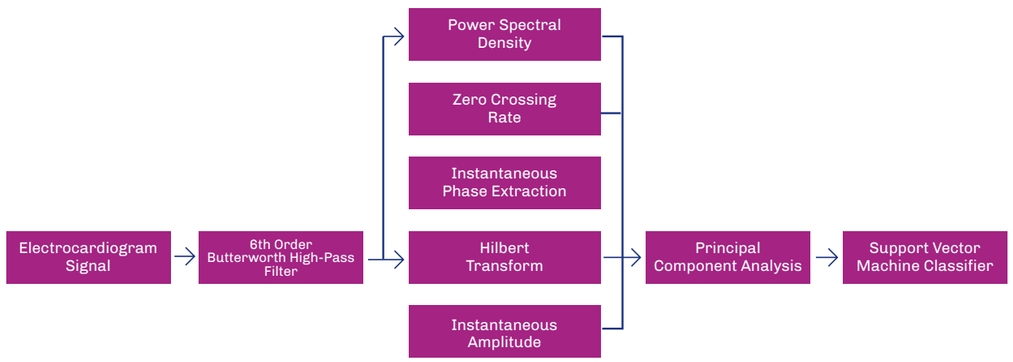

Figure 2:
Flowchart of Classification Algorithm

Signal Processing

ECG recordings must be processed for electrical noise reduction and baseline wandering elimination. Noises arising from power line interference will be filtered out by a bandstop filter attenuating frequencies around 60Hz and myogenic activity by a 7Hz high pass filter.[6] Baseline wandering elimination will be done through a 6th order high pass Butterworth filter.[6] implemented in the SVM algorithm.

II. MATERIALS AND METHODS

A. ECG Device Construction

Differential Amplifier

For ECG signal measurement, an AD620AN instrumentation amplifier was used to measure potential difference across the chest. Amp gain is given by Equation 1, where R is resistance and G is gain. A 560ohm resistor was set, equating to a 89.21 gain.

$$G = \frac{1+49{,}400}{R}$$

Equation 1

Two 9v batteries are used to set +9v, 0v, and -9v. Pins 2 and 3 connect to copper penny electrodes. The signal is output by pin 6.

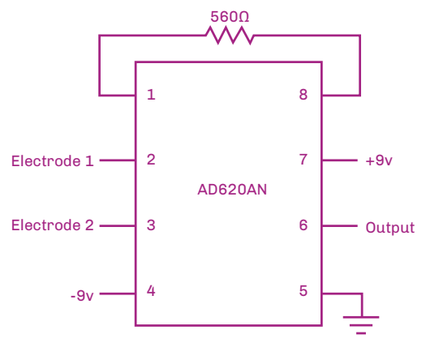

Figure 3:
Schematic of Differential Amplifier

60Hz Band-Stop Filter

Frequencies at 60Hz were attenuated by a notch filter, a type of band-stop filter, due to power line interference. Low and high pass components connected in parallel collectively filter frequencies at 60Hz. The filter is constructed using an operational amplifier for introduction of a gain. Resistance and capacitance values are determined by equation 2, where the filtered frequency band is given by the variable fr, C is the capacitance of capacitors 1 and 2, and R is the resistance of resistors 0 and 1.[7]

$$f_r = \frac{1}{2CR\pi}$$

Equation 2

At a notch frequency of 60Hz, C1 and C2 equate to 270pF and R0 and R1 equate to 10MΩ. C0 is twice C1 and C2, 540pF. R2 is half R0 and R1, 5MΩ. R3 and R4 are 10MΩ.

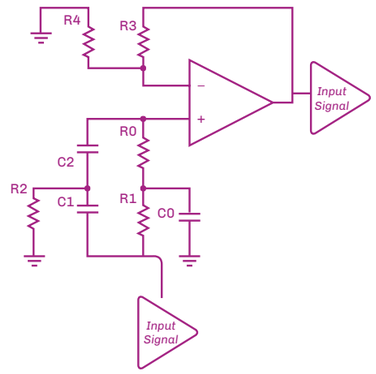

Figure 4:
Schematic of Notch Filter

7 Hz High Pass Filter

The gain of frequencies below 7Hz was dampened by a High Pass Filter for elimination of interference from Galvanic Skin Response. This circuit has a second order design, consisting of two connected high pass filters. The cutoff frequency, fc, is given by equation 3.[8]

$$f_c = \frac{1}{2\pi\sqrt{R_1C_1R_2C_2}}$$

Equation 3

Setting R1 to 47kΩ, R2 to 220kΩ, and C1 and C2 to 220nF yields a cutoff frequency of 7.11Hz.

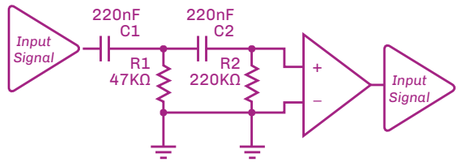

Figure 5:
Schematic of 7 Hz High Pass Filter

31 Hz Low Pass Filter

The gain of frequencies greater than 31Hz were dampened by a Low Pass Filter due to the insignificance of data above this frequency cutoff; the acquired ECG signal will not exceed a frequency 31Hz. The cutoff frequency, fc, as for the High Pass Filter, is given by equation 3.[8] Setting C1 to 100nF, C2 to 25nF, and R1 and R2 to 100kΩ yields a cutoff frequency of 31.83Hz.

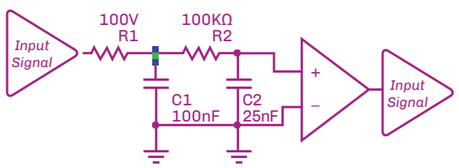

Figure 6:
Schematic of 31 Hz Low Pass Filter

Reading the Analog Signal

The processed analog signal is subsequently input to an Arduino though the A0 (analog) port. A burnt analog read program on the Arduino, through a serial connection, sends the signal data to a Raspberry Pi running the classifier algorithm (using the Serial module) for backend processing.

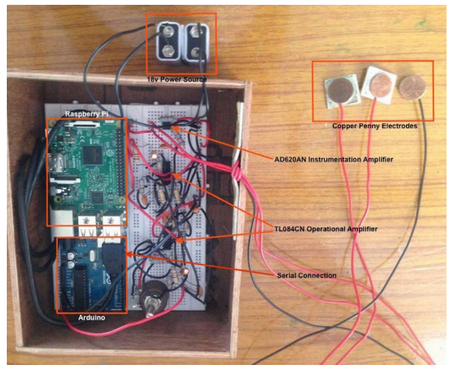

Figure 7:
Hardware of Developed Device

Front End

A pushbutton initiates patient ECG signal recording/ storage in the Arduino. Following class detection, the determined class is relayed to the Arduino via serial communication. Subsequently, one of three indicator LEDs (for each class) are lit for display of diagnosis.

B. SVM Classifier Development

Two classification algorithms are required for this device: 1) for differentiation between healthy and AF conditions and, 2) between terminating AF and non-terminating AF. Regardless, both are constructed similarly. The algorithm is executed in accordance with Fig.2.

Baseline Wandering Elimination

The Scipy Python module is used for construction and implementation of a 6th order high-pass butterworth filter for BW elimination.

Feature Extraction

Hilbert transform allows analytic signal derivation, a complex-valued function comprising no negative frequency components, for R-peaks analysis. The analytic signal is obtained using the Scipy module. Signal features used by the algorithm include instantaneous amplitude and zero crossing rate, both computed using the Scipy module. Scipy is also used for extraction of the signal power spectral density.

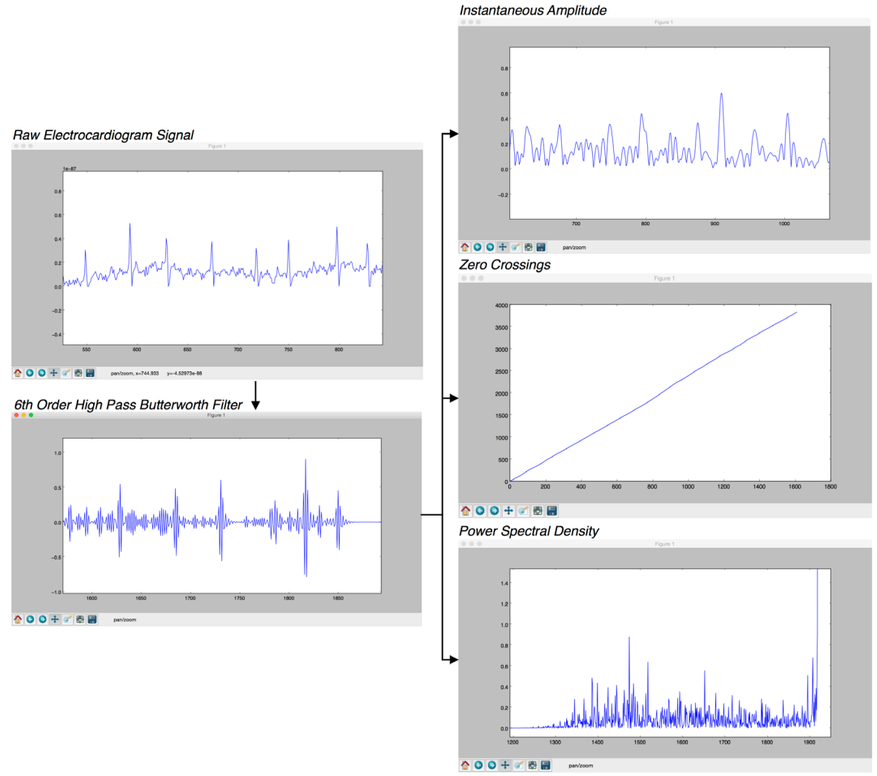

Figure 8:
Signal Processing of Sample Signal

SVM Training/Implementation

The Sci-Kit Learn module was used for SVM implementation. ECG signals with labelled diagnoses were obtained from Physionet's AF Termination Database for training.[5] Then an SVM Learning Model with a Radial Basis Function kernel is generated. The training data is fit to the Learning Model for prediction of a label (diagnosis) for an unlabelled signal represented in dimensionally reduced feature space.

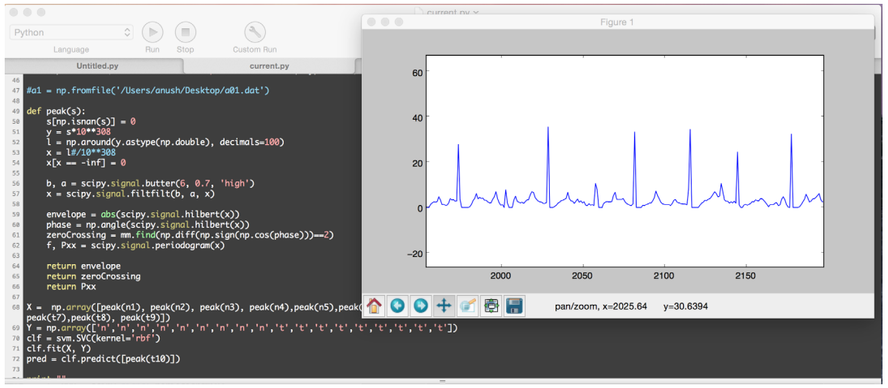

Figure 9:
Sample Code from the Classifier Algorithm

III. RESULTS

Testing of the developed device consisted of two stages: determining quality of the captured ECG signal through identification of the QRS complex of a normal sinus rhythm and cross-validation of the ECG signal class determination algorithm against pre-diagnosed tracings. Due to inaccessibility to atrial fibrillation patients, the device could not be tested on humans for a measure of conjoined functionality of the ECG device with the classification algorithm.

A. ECG Device Capture Quality Evaluation

A normal sinus rhythm was recorded by the developed ECG device for identification of the QRS complex and evaluation of capture quality.

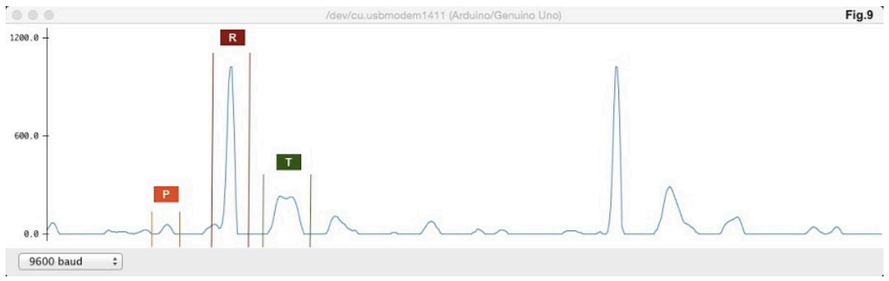

Figure 10:
Acquired ECG Tracing from the Developed Device

The acquired ECG tracing from the ECG device exhibited prominent features of a QRS complex. Right and left atrial depolarisation is represented by the P peak. Right and left ventricular depolarisation is represented by the R peak, which is preceded by the Atrioventricular node conduction delay. The final T peak is representative of ventricular re-polarisation. Therefore, characteristic features of a normal sinus rhythm have been sufficiently captured.

B. SVM Classification Algorithm Cross-Validation

For determination of the SVM classifier's accuracy, algorithmic atrial fibrillation diagnoses of ECG tracings were cross-validated against predetermined signal classes using data obtained from the Physionet online database.[5] This procedure was executed for two different classification algorithms: 1) general AF versus healthy tracing detection (Classifier A) and, 2) terminating AF versus non-termination AF tracing detection (Classifier B).

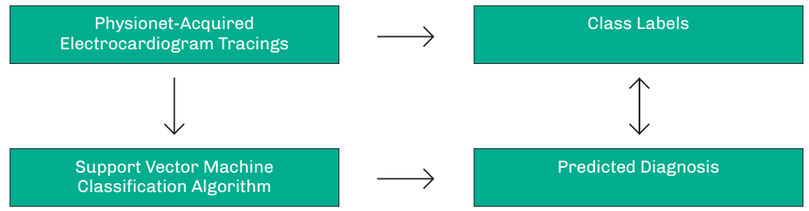

Figure 11:
Cross-Validation Procedure

A set of 60, labelled .dat ECG tracings (evenly distributed among the Terminating AF, Non-Terminating AF, and healthy classes) were acquired from the Physionet database.[5] Half the tracings were used for SVM training and the other half were set aside for cross-validation testing, with tracings equally distributed among classes for both sets. ECG signal sets were algorithmically classified by both SVM programs for acquirement of diagnoses. Evaluation of classification accuracy (percent sensitivity) involved matching predicted diagnoses with corresponding, database-determined labels and subsequent verification of a match. Only the Terminating AF and Non-Terminating AF classes of ECG tracings were used for cross-validation of Classifier B whereas all 30 ECG tracings were used for Classifier A cross-validation.

SUPPORT VECTOR MACHINE CLASSIFIER A ACCURACY

Healthy Electro-cardiogram Traing Quantity	Atrial Fibrillation Positive Electrocar-diogram Tracings Quantity	False Positive for Healthy (%)	False Negative for Healthy (%)	General Sensitivity to Signal Class (%)
10	20	6.67	10.00	83.33

SUPPORT VECTOR MACHINE CLASSIFIER B ACCURACY

Healthy Electro-cardiogram Traing Quantity	Atrial Fibrillation Positive Electrocar-diogram Tracings Quantity	False Positive for Healthy (%)	False Negative for Healthy (%)	General Sensitivity to Signal Class (%)
10	10	10.00	10.00	80.00

Table 1:
Classifier Accuracy Data

A percent sensitivity of 80% or greater was achieved by both classifiers. Therefore, the SVM classifiers exhibited diagnosing abilities to a considerable degree of accuracy. Furthermore, when trained with smaller sub-sets of the training data, a decrease in percent sensitivity was observed. This suggests, through data extrapolation, potential increase in percent sensitivity with a larger training data set.

IV. DISCUSSION

Limitations

A radial basis function kernel for support vector machine was assumed to yield optimum performance in this study. However, trial and error methods for evaluation of classification accuracy with other kernel functions may reveal a new optimum. Application of alternate classification algorithms, such as block-based neural networks, have also performed with considerable accuracy.[9] Therefore, an investigation into an optimum kernel function may yield greater precent sensitivity to signal class. Furthermore, minor redundant electrical noise was evident in signal recordings by the ECG device. This suggests the need for further signal processing for adequate signal extraction. Previous research has successfully demonstrated effective signal processing methods rooted in wavelet optimisation.[10]

Recommendations

As a result of discrepancies in recording quality between commercial ECGs and the developed ECG device, the SVM classifier may exhibit greater accuracy if trained with tracings derived from the developed device itself. Therefore, a database-acquired training data set would be rendered insufficient for accurate diagnoses. Future work requires procurement of ECG tracings by use of the developed ECG device and corresponding labels (diagnoses) through analysis by a certified cardiologist. ECG tracing collection must be distributed equally among the three classes for adequate training data. Future work also includes evaluation of alternate supervised machine learning techniques for increased performance of AF classification and diagnosis. Potential candidates for AF diagnostic abilities testing include Artificial Neural Networks (ANNs) and K-Nearest Neighbours (k-NN) implementations. Furthermore, an unsupervised learning model may be utilised if no trained cardiologist is accessible for labelling of the developed device-acquired training data. Unsupervised learning extracts hidden structures from unlabelled data sets for class allocation.

V. CONCLUSION

The developed diagnostic device has successfully interfaced an affordable ECG device with a clinician-emulating classification algorithm for portable, accessible and affordable atrial fibrillation detection and classification. Prominent features of associated QRS complexes were evident. Support Vector Machine Classification, executed by the diagnosis algorithm, exhibited percent sensitivities to ECG signal class of 80% - 83.33%. Acquired results have proven the hypothesis partially correct: percentage sensitivity of Classifier B was 80% whereas that of Classifier A exceeded the predicted range (83.33%). Coupled functionality of the aforementioned components could yield a feasible technique for automatic AF diagnoses through algorithmic analysis of patient ECG signals in rural, impoverished regions; particularly those lacking medial specialists.

The lack of symptoms associated with atrial fibrillation onset poses risks including blood clot formation, potentially resulting in ischemic stroke. Residents of rural and impoverished areas experience heightened threats brought about by lack of medical care and specialists for AF diagnosis. The developed device in this study would be a potential contender for rapid and automatic AF diagnosis for undertaking of the clinician's role. Furthermore, affordability and portability ensure the device's potential to be deployed to the lacking regions. Algorithmic signal processing and analysis have replaced the traditional visual-based approach of clinicians. Predicted diagnosis would subsequently be indicative of necessary action for AF treatment. Total costs incurred for development of the device accounted to about $60. However, commercialisation may further reduce costs.

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Role of Radiographic Imaging *in Transcatheter Aortic Valve Implantation*

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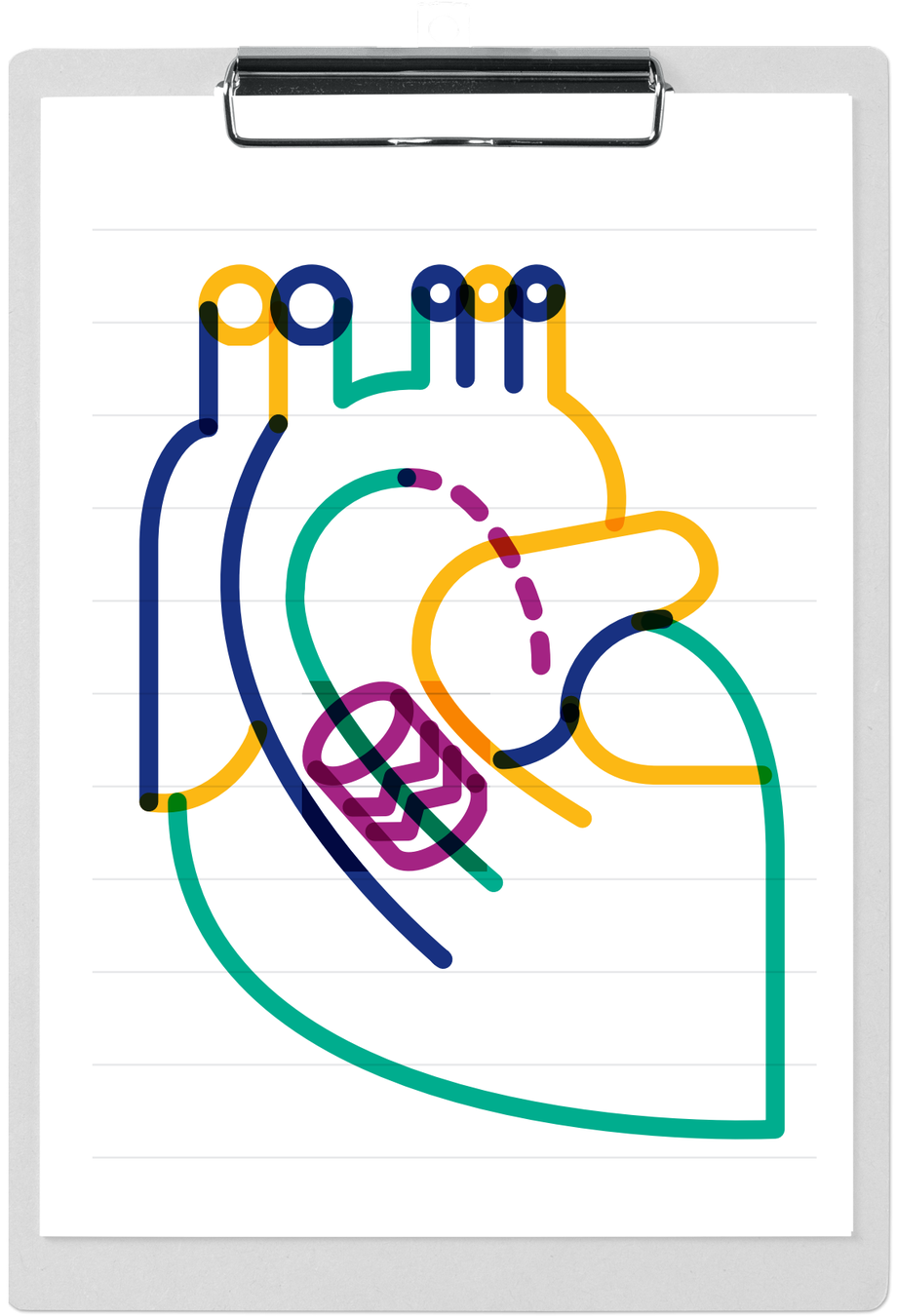

ABSTRACT

With increasing rates of cardiovascular disease worldwide, it is imperative to provide a means of definitive treatment for stenotic and regurgitant valves. Transcatheter aortic valve implantation (TAVI) has become a definite treatment for end-stage valvular disease. The role of radiological imaging in the transcatheter aortic valve implantation allows for vital pre-procedural planning, guidance during the procedure, and postoperative evaluation. Transthoracic echocardiogram is the first-line imaging modality for pre-procedural planning. Although multidetector computed tomography is reserved as the optimal modality, there are some drawbacks associated with its use. Fluoroscopic angiography is the primary method used during the procedure. Postoperative evaluation imaging is not standardised but transthoracic echocardiogram is often the modality of choice. In addition to imaging, it is crucial to understand the natural history of aortic valve disease and the details regarding the transcatheter aortic valve implantation procedure itself.

INTRODUCTION

Cardiovascular disease is the leading cause of death in Europe and around the world.[1] Amongst the various types of cardiovascular disease, valvular diseases comprise a particular niche. With advancing technologies and diagnostic techniques, valvular diseases such as aortic stenosis are being diagnosed more rapidly and are being treated with increased precision. Aortic valve stenosis, or stiffening of the tissue, is the most common form of valvular disease in the Western world.[2] Aortic valvular stenosis is now a more manageable disease with the advent of procedures such as transcatheter aortic valve implantation (TAVI). This has become the standard procedure for patients with severe disease, and has outstanding short and long term results.[3] TAVI is at the forefront of multidisciplinary treatment with the coordinated effort of radiologists, anaesthetists, interventional cardiologists, and support staff. By accessing a patient's faulty aortic valve through a distal vascular location (ilio-femoral, brachial, subclavian, or even directly via the aorta) the team guides a frame and a bioprosthetic valve to replace the native.[4] This procedure is not possible without help from radiological imaging. Various imaging modalities—from multidetector computed tomography (MDCT) to transthoracic echocardiography (TTE)—are used for diagnosis, pre-procedural planning, the procedure itself, and for postoperative follow up. Imaging allows the physicians to assess the extent of the disease, quantify the patient's heart function and guide the treating physicians during the procedure itself. This paper will discuss how radiological imaging makes TAVI possible.

PATHOLOGY AND NATURAL HISTORY OF AORTIC STENOSIS

Cardiac valves act as vital alternating barriers and Cardiac valves act as vital alternating barriers and conduits for the circulation of blood through the heart and systemic circulation. The aortic valve allows for the outflow of oxygenated blood from the left ventricle of the heart into the systemic circulation. The morphology of the valve contributes to its function: it has three leaflets that normally close and meet at a central point; they open inwards into the left ventricle with each leaflet attached to tendinous cords and muscles that help prevent prolapse. Of the four valves in the heart, the aortic valve is exposed to the highest pressure. This increases the likelihood of sustaining damage over time, which may require treatment and possibly replacement. Various factors can lead to stenosis of the leaflets and of the valve as a whole. These include congenital abnormalities, chronic hyperlipidaemia, hypertension, rheumatic autoimmune disease, increased age, infection, and calcification.[2,5]

The most common natural history of aortic valve stenosis is increased calcifications and/or scarring due to damage or inflammation with age. These processes narrow the valve and lumen of the aorta.[5,6] They reduce the valve and aortic distensibility and ability to conduct blood, causing increased pressure inside the left ventricle. The myocardium of the left ventricle begins to hypertrophy with the addition of concentric layers of muscle throughout the ventricle. This allows the heart to eject the blood at elevated pressures. Chronically elevated and sustained pressures cause the heart to continue remodeling. However, the thickened left ventricular wall is not viable as blood vessels in the wall fail to provide it with nourishment, causing the muscle to begin to atrophy. In turn, the left ventricle can no longer eject the cardiac output at elevated pressures. This leads to the symptoms commonly seen in aortic valve stenosis, including: murmur, exertional dyspnoea, angina pectoris, syncope, valvular regurgitation, and palpitations.[5,6] If left untreated, this can lead to congestive heart failure, stroke or death.[6] By replacing the valve, many of these symptoms can be eliminated and the disease process halted.

PRE-PROCEDURAL PLANNING

TAVI is reserved for high risk patients with symptomatic aortic valvular stenosis and can be indicated for those with asymptomatic aortic valvular stenosis (AVS) with rapid disease progression.[7] The patient's eligibility for TAVI is assessed through guidelines outlined by European and American Cardiology Associations (ESC/EACTS and AHA/ACC, respectively).[7,8] The degree of severity of a patient's AVS must also be determined. The patient is then classified based on their valve anatomy, hemodynamics and symptoms.[7,8] These values are obtained by a series of examinations that are reviewed by the multidisciplinary team. Imaging plays a vital role in the pre-procedural planning phase. It is vital for assessment of AVS disease state, estimation of the survival score, measurement the aortic root, and for the evaluation of sites for peripheral access.

There are several different imaging modalities used during pre-procedural planning. These include transthoracic echocardiogram (TTE), multidetector computed tomography (MDCT), and magnetic resonance imaging (MRI).[7] Imaging studies demonstrate the morphology, severity of aortic valve disease, absence of other valvular diseases and other contraindications. Given the modalities speed, lack of ionising radiation and availability, TTE is considered first-line for imaging. It is used to identify any mitral regurgitation and to assess left and right ventricular function. Doppler is used to measure both the systolic and diastolic peak velocity in both ventricles and the peak velocity across the aortic valve.[7] The tendency for Doppler to underestimate flow rates must also be considered.[8] Additionally, transoesophageal echocardiogram (TOE) can be used to better visualise the aortic root; it is usually reserved for cases in which TTE is inadequate.[9] Two separate studies conducted by Altiok et al and Jilaihawi et al compared 2D and 3D imaging studies for pre-procedural planning, and both found that 3D imaging is superior to 2D for measuring the aortic root.[10,11]

Once AVS is confirmed and evaluated, the patient's risk and survival are estimated using the European System for Cardiac Operative Risk Evaluation in Europe (EuroSCORE) and the Society of Thoracic Surgeons Predicted Risk of Mortality in the U.S.[12,13]. A EuroSCORE of ≥20% and an STS PRM score of ≥4 is considered the minimum for eligibility by the respective associations.[7,8] With a satisfactory survival prediction, the patient's aortic anatomy and surgical access site are evaluated to determine whether the proposed device can be safely and sustainably implanted.[13]

Multiple Detector Computed Tomography (MDCT) allows the cardiac team to obtain precise measurements of the aortic root, including the aortic annulus and aortic sinuses. Measurements are obtained using coronal and oblique sagittal slices in mid-systole.[11] The obtained images can be reconstructed using various software packages (e.g. INSIGHT) in order to generate a 3D image of the aortic valve, aortic annulus and ascending aorta.[11] Precise measurements with the use of MDCT allows the cardiac team to estimate the implantable size, as an effort to prevent paravalvular regurgitation, which is the passage of blood along the sides of the implanted valve.[14] MDCT generally overestimates the annular size by 1-1.5mm.[15] Willson et al found that overestimation of the size of the implantable TAVI significantly reduced the major postoperative complication of atrial regurgitation.[14] Thus, the precision provided by MDCT allows the cardiac team to recommend and utilise the correct valve for the best fit. Afterwards, the peripheral access sites are evaluated.

MDCT is also used to determine the eligibility of a peripheral access site.[11] The main approaches are anterograde, which is either transapical via the subclavian artery or retrograde via ilio-femoral artery4. This route varies based on the cardiac team's evaluation of the patient's condition. For example, in a patient with severe calcifications throughout his peripheral vasculature, transaxillary via the brachial artery or direct aortic routes may be considered. Van der Boon et al evaluated the morbidity and mortality rates related to transfemoral versus transapical TAVI. They found a significant increase in mortality related to transapical procedures when compared to transfemoral.[16] Such findings are considered by the team when designing the procedure plan for each patient. With a single MDCT scan, all of the potential locations can be evaluated4. Previously, conventional angiography was used to evaluate peripheral access sites and vascular flow, however, this is now reserved as an adjunct imaging study.[4]

If TTE and MDCT do not provide sufficient information, MRI is indicated to assess the severity of aortic valve stenosis and allow the team to plan the optimal strategy for the sizing and placement of the valve. Friedrich et al demonstrated that MRI is equally as effective as TTE and cardiac catheterisation.[17] However, due to cost and other limitations, it is reserved as a later stage imaging modality.[7,8]

The procedural plan involves selecting the proper bioprosthetic valve by considering the patient's valve size, peripheral access site and hemodynamic state. Once the valve and peripheral access site and route are selected, potential contraindications and complications are considered. A medication regimen is designed and then the procedure is scheduled.[7,8]

PROCEDURE

The goals of imaging during the procedure is to ensure correct heart valve selection, assessing TAV placement and function and identifying any complications. Fluoroscopic angiography is the recommended method for all TAVI procedures and the native valve is viewed in the coplanar or perpendicular view.[18] This modality allows for real time observation of the catheter and valve route and accurate assessment of flow. In addition, images from pre-procedural MDCT or angiography can be superimposed onto the fluoroscopy screen for more precise visualisation.[18]

The standard procedure involves a balloon angioplasty while the patient is under general anaesthetic. If the retrograde path is chosen, an 18-French (Fr) catheter is most commonly inserted transilio femorally, or if the anterograde path is chosen, a 25-Fr catheter is placed transapically.[4] Once again, the path is determined by the size of the valve and the patient's condition. The bioprosthetic valve is then advanced across the native valve in a series of concurrent steps. As the right ventricle pace is increased, the balloon at the end of the catheter is inflated to crimp the heart valve and overlay the frame while simultaneously deploying the prosthetic valve. This expands the frame and secures the new valve to the underlying annulus and leaflets. With the valve securely in place, angiography and TOE are used to evaluate the placement and blood flow through the valve.[4]

There are two major balloon expandable bioprosthetic valves that are commercially available. They are the Edwards' SAPIEN and Medtronic's CoreValve. Both have seen significant commercial success and are very similar. However, the CoreValve can only be deployed retrograde in a transiliofemoral approach.[4]

Another class of prosthetic valves are the self-expandable valves (Medtronic CoreValve R, Edwards' CENTERA). They do not require a balloon for expansion and use a self-expanding nitinol frame.[13] In a multicenter randomised control study, Adams et al proved the self-expandable valves to be equally as effective as the standard balloon TAVIs.[13]

In the near future, 3D printed heart valves will be designed and created per specifications for each patient. Duan et al have created a proof-of-concept, anatomically correct human heart valve using human cells and hydrogels19. This new technology will likely be refined and utilised in the future.

OUTCOMES AND COMPLICATIONS

TAVI is considered a last resort treatment. However, the procedure significantly improves the quality of life and the life expectancy, with long term survival rates close to those of the age-matched general population8. Following the procedure, the patient must be placed on antithrombotic dual antiplatelet therapy for six months and must remain on a lifelong daily aspirin regimen.[20] The patient will receive a short course of prophylactic antibiotics to prevent endocarditis. The gold standard antibiotic is a penicillin, but in cases of allergy or insensitivity, a cephalosporin is used.[21]

The complexity of the procedure and morbidities associated with the patient population can lead to significant complications. Many factors including older age, female gender, advanced disease state, emergency operation, left ventricular dysfunction, pulmonary hypertension, co-existing coronary artery disease, and previous bypass or valve surgery have been shown to increase the risk of postoperative mortality.[8] Additionally, the need for postoperative transfusion, major vascular surgery, pacemaker insertion, stroke, renal failure, and pneumonia are common.[9] Valve embolisation and the need for a second replacement valve are uncommon.[22]

Imaging is essential to evaluate the device's efficacy and to assess for annular rupture, atrial regurgitation, valvular migration, and heart block4. TTE is the modality of choice for these studies.[9,22] However, MDCT can also be used to further examine any detected valvular problems.[14]

Thus far, there are no guidelines for acceptable postprocedural assessment values from neither the European nor the American associations9. Jayasuriya et al use changes in the aortic valve area and pressure gradient across the aortic valve as their markers for efficacy.[9] Both of these parameters are measured using TTE, and can be obtained using MDCT.[9]

CONCLUSION

The critical role of imaging cannot be understated in the TAVI procedure. From diagnosis to the postoperative follow up, imaging is a vital tool for the cardiac team during the entire process. With the advancement of technology, conventional imaging modalities have given way to more precise visualisation of the aortic root with MDCT and the ability to 3D render the structure for accurate planning. Once the patient's aorta is evaluated and the procedural plan constructed, fluoroscopic angiography is utilised to properly visualise the route of the tools, the placement of the device, and its function. After the new valve is in place, TTE is used to assess the valve's activity. It is clear that imaging is vital to every step of the TAVI process. Just as technology has improved the implantable devices, the future will most likely bring new imaging modalities that reduces the patient and staff radiation exposure.

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The Greatest Threat to Modern Medicine : *Antimicrobial Resistance*

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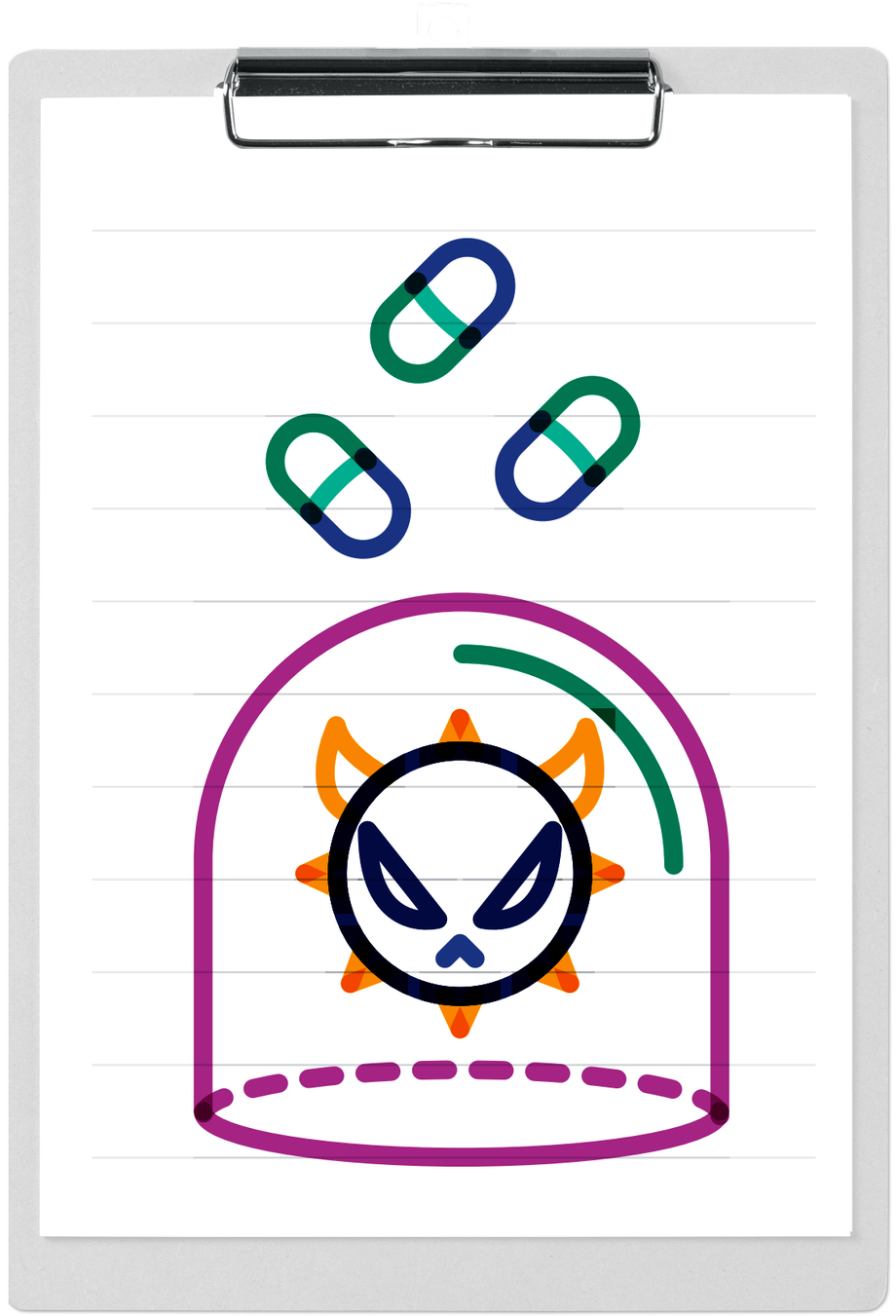

ABSTRACT

Antimicrobial resistance (AMR) poses an unprecedented and growing threat to modern medical practice. The implications of resistance are profound given that our ability to prevent, manage, and treat infection underscores most advances across the spectrum of healthcare disciplines in recent years. It has been suggested that AMR may surpass cancer as the leading cause of death worldwide within the first half of this century. Economist Jim O'Neill (Chairman of the UK Review on Antimicrobial Resistance) estimates that by 2050, unless radical action is taken, AMR may be responsible for up to 10 million deaths per year[1]. This paper seeks to provide a brief overview of antimicrobial resistance. Mechanisms of resistance are outlined alongside a number of factors identified as contributing to growing rates of AMR. Recent efforts to promote research and development of new antimicrobials are described; alternative and complementary therapies are examined; and recommendations are proposed.

ANTIMICROBIAL RESISTANCE (AMR)

Mechanisms underlying resistance

Bacterial resistance to antimicrobials can occur via numerous mechanisms, either intrinsic or acquired. The most common example of an intrinsic resistance mechanism is the relatively impermeable outer membrane of Gram-negative bacteria, which reduces their susceptibility to many classes of antimicrobials. Chromosomally-encoded efflux pumps which transport and expel toxic antimicrobial molecules are another example.[2]

Bacterial resistance can also be 'acquired' via the transfer of plasmids or other mobile genetic elements. Resistance genes can be transferred in a number of ways, the most common of which are conjugation, transduction, and transformation.[3] Conjugation requires cell-to-cell contact and involves the transfer of plasmids to a recipient cell via pilli. Transduction involves the transfer of bacterial DNA from one cell to another of the same species via plasmids enclosed in bacteriophages. Transformation involves the uptake and integration of naked DNA from the environment by bacteria.[3]

Finally, microorganisms may become resistant due to spontaneous chromosomal mutation.

Contributing factors

In the context of the healthcare setting, many factors contribute to the development of antimicrobial resistance, including empiric treatment with broad-spectrum agents, inappropriate use of antimicrobials (e.g. in cases of viral illness), inappropriate duration of treatment, and patient non-adherence or failure to complete full course of treatment.[1] In countries with fewer regulations, the availability of antimicrobials without prescription exacerbates these issues, particularly in terms of overuse. In addition, the non-therapeutic use of antimicrobials in animals poses significant risks.[4]

WHO ANTIMICROBIAL RESISTANCE, GLOBAL REPORT ON SURVEILLANCE (2014)

Following a rise in the incidence of infections caused by multidrug resistant organisms, global surveillance of resistant bacteria has come to the forefront in the last decade. In their 2014 report on AMR surveillance, the World Health Organisation highlighted seven "bacteria of international concern". These included *Escherichia coli* (resistant to third-generation cephalosporins and fluoroquinolones), *Klebsiella pneumoniae* (resistant to third-generation cephalosporins and carbapenems) and *Staphylococcus aureus* (resistant to methicillin).[5] Of particular concern are findings that the proportion of these resistant strains exceeded 50% in certain WHO regions.

Reports from the Irish Health Protection Surveillance Centre (HPSC) show a promising decline in rates of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection in Ireland over the past decade following a concerted effort on the part of healthcare authorities. Of 1,412 cases of *S. aureus* bloodstream infections reported in 2006, 592 (41.9%) were found to be resistant to methicillin. In 2015, just 199 (18.4%) of 1,082 reported cases of *S. aureus* bloodstream infection were resistant to methicillin. In terms of proportion of MRSA versus MSSA (methicillin-susceptible *S. aureus*), this was a decrease of over 66% during this period.[6]

In contrast, 16.7% of *E. coli* bloodstream isolates reported in Ireland in the first quarter of 2016 were classified as multi-drug resistant (MDR).[7] The proportion found to be producers of Extended Spectrum Beta Lactamase (ESBL) has risen steadily from 5.8% in 2009 to 11.7% in 2016. ESBL-producing bacteria are resistant to the majority of the beta-lactam antimicrobial agents, including penicillins and cephalosporins. Similarly, rates of MDR *Klebsiella pneumoniae* rose from 11.9% of bloodstream isolates in 2009 to 19.8% in 2015.

ANTIMICROBIAL USE IN AGRICULTURE

Antimicrobial resistance is emerging in domains beyond hospitals and healthcare facilities, particularly in agricultural settings.

Colistin use in pig-farming

The non-therapeutic use, or overuse, of antimicrobials in livestock poses another cause for concern. Perhaps the most serious example is the use of the antimicrobial colistin (a polymyxin) in pig-farming, which perfectly illustrates the risks associated with such casual practice. In humans, colistin is considered to be a last line agent for the treatment of multi-drug resistant gram negative bacteria, particularly carbapenemase-producing enterobacteriaceae. The toxic effects observed in humans are not seen in pigs, as colistin is not absorbed in the gastrointestinal tract of pigs. As such, colistin is seen as an ideal agent to treat gastrointestinal infection in swine and is widely used in pig-farming across the globe, including many European countries such as the United Kingdom, Germany, and Belgium.[4,9] However problems have arisen as a result of metaphylactic use of colistin, that is, the treatment of clinically healthy pigs alongside those with symptoms. Antimicrobials are not being used in cases of infection, but rather are given (often in excessive quantities) for purposes of growth promotion and weight gain. Alarmingly, scientists recently discovered a plasmid-mediated colistin-resistance gene (mcr-1) in pigs in China.[10] Another study in China, the world's largest producer of pigs, has reported evidence of colistin resistance in patients without a history of colistin exposure but a history of contact with swine.[11]

ENVIRONMENTAL CONSIDERATIONS

In the environment, transmissible plasmids may transfer between species and spread via various means including wind, surface water, and soil.[12] Levels of antimicrobials found in pig manure have been found to positively correlate with the quantity of the agent used in pig farms.[4]

Waste water treatment

A number of studies have documented the presence of antimicrobials and AMR genes in urban wastewater, including effluent discharges from hospitals and wastewater treatment facilities.[13] Studies of treatment facilities in China found that the removal of pollutants such as antimicrobials (including parent compounds and transformation products) was incomplete, leaving residual levels in the environment.[14] Another study has described the presence of various sulphonamide resistance genes in seawater and sediment from the North Yellow Sea.[12]

A study conducted in the west of Ireland found that ESBL-producing *E. coli* can survive the modern wastewater treatment processes and recorded high levels of ampicillin resistance in *E.coli* discharged from the treatment facility.[15] This study noted the potential risk to food produce irrigated with contaminated water.[15] Other studies have also highlighted similar concerns of risk to public health. A 2014 Dutch study of supermarket vegetables (celery, carrots, lettuce, mushrooms) reported high levels of bacteria containing ESBL genes on the produce examined.[16] The authors acknowledge that the bacteria found is relatively harmless. However, if these vegetables were consumed raw, there is a risk that the ESBL-genes may be transferred to opportunistic bacteria in the gut.[16]

ANTIMICROBIAL RESEARCH AND DEVELOPMENT

Since the 1980's, few new antimicrobials have been developed. The small number that have entered clinical use include two new classes: oxazolidinones such as linezolid, and lipopeptides such as daptomycin.[3] These are the exception however, and not the rule.

Antimicrobial development does not represent an appealing investment for most companies. Estimates suggest the cost of bringing an antimicrobial agent to market stage is as high as £1 billion, or €1.2 billion. In addition, the risk of failure associated with research and development is considerable, and notably higher than other fields.[3,17] Moreover, when prescribed, antimicrobials are used in limited doses for short durations, which ultimately translates into low returns. It is unsurprising that pharmaceutical organisations are instead focusing their energies on the significantly more profitable market of chronic disease management and the development of "lifestyle drugs" such as statins, antidepressants, and antihypertensive medications.[18]

Incentivising drug companies

In response to the dearth of activity in this sphere, and in light of growing resistance, governments are now prioritising antimicrobial research and development. In 2012, the United States introduced the Generating Antibiotic Incentives Now (GAIN) Act, an initiative to incentivise pharmaceutical companies.[19] Under this legislation, companies that develop novel antimicrobial agents that are effective against specific pathogens will benefit from priority FDA review and expedited approval of qualifying agents, as well as an additional five years of patent exclusivity in the marketplace.[3] Similar efforts can be seen with the EU Innovative Medicines Initiative which represents the largest public-private partnership in Europe. Its "New drugs 4 bad bugs" programme aims to foster collaboration between academic researchers and pharmaceutical companies.[20]

iChip technology

The vast majority of antimicrobials used in practice today originated from bacteria cultured from soil. Until recently, soil was cultured directly onto culture medium. This method embodied significant limitations such that a mere 1% of bacteria present in soil were actually cultivable. Novel technology has revolutionised this practice. Isolation chips (iChips) facilitate the culture of bacteria which previously could not be grown in laboratory conditions, allowing the growth of 40-60% of bacteria present in soil.[21,22] Using dilutions of soil, iChip achieves this by placing a single bacterium in each of a vast number of agar-filled microchambers. The device is then placed back in the original soil environment where a semi-permeable membrane allows the diffusion of nutrients to the bacteria within the chambers. In this natural environment the bacteria colonise and are then further cultivated on growth media.[21] This development has already led to the identification of new antimicrobials such as teixobactin (effective against S. aureus, M. tuberculosis, and C. difficile), and is thought to hold significant potential for similar discoveries in the future.[20]

ALTERNATIVE THERAPEUTIC OPTIONS

In spite of the above efforts, it is likely to be a number of years before any new antimicrobials enter the market. Other avenues that are being explored with renewed interest are therapeutic options which complement or enhance current agents. Phage therapy and nanoparticle optimisation are two such examples.

Phage therapy

The use of bacteriophages to target and kill bacteria is not a new concept. Bacteriophages (also referred to as "phages") are viral entities which target only bacterial cells, penetrating the cell wall and inserting genetic material into the cytoplasm. In the case of lytic phages (also referred to as virulent phages), this material replicates exponentially once inside the bacterial cell, synthesising more phage particles before lysing the bacterium. This process facilitates very high concentrations at the infective site.[23] Chief amongst the advantages conferred by phage therapy is that it is highly specific to particular pathogens with no harmful effects on commensal flora, and exhibits significant bactericidal effects against MDR strains of bacteria.[24] In addition, phage therapy exhibits strong action on bacterial biofilm, particularly those of P. aeruginosa, which can be found in hospital water networks.[25] Used in combination with antimicrobials, phage therapy is extremely effective and may prove a key player in antimicrobial treatment in the future. Few trials involving humans have been conducted to date, however early indications suggest the therapy is safe. The scope to treat numerous infections with the same agent is limited by the specificity of phage therapy for individual strains of bacteria, which prevents empiric or presumptive use. Concerns have been raised, however, that phage therapy may induce antibody production in patients, thus rendering its potential obsolete.[26]

Nanoparticles

Another option described in recent literature involves the use of metallic nanoparticles to enhance the bactericidal effects of antimicrobials.[24] Penetration of the bacterial membrane is facilitated by the small scale of the particles. One study outlined the biosynthesis of amoxicillin and gold nanoparticles. The conjugate agents were found to not only exhibit broad-spectrum activity against both Gram-positive and Gram-negative species, but successfully cleared MRSA infection in experimental animals.[27]

RECOMMENDATIONS

In terms of what lessons can be drawn from the literature, a number of recommendations are outlined:

- Antimicrobial stewardship should be integrated into medical education and training, to shift away from the current tendency of empiric treatment.[28]
- A concerted effort must be made to reduce demand for antimicrobials via increased public awareness, improved sanitation and hygiene, promotion of vaccination, and employment of rapid diagnostic facilities in the acute setting.[1]
- Curbing agricultural antimicrobial use via the introduction of additional antimicrobial fees (based on usage) to prevent overconsumption, revenue from which could be directed toward the cost of researching and developing newer drugs.[29]
- Restrictions should be placed on hospital effluent discharges and requirements made that wastewater must be treated appropriately before being discharged into urban wastewater systems.[25]

CONCLUSION

There is no question that antimicrobial resistance poses a unique threat and formidable challenge for the medical profession. In light of the substantial negative effects exerted by resistance in terms of mortality, morbidity and consumption of healthcare resources, it is in society's best interest to prioritise this issue.[1]

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From A to Zika: A Review of Zika Virus

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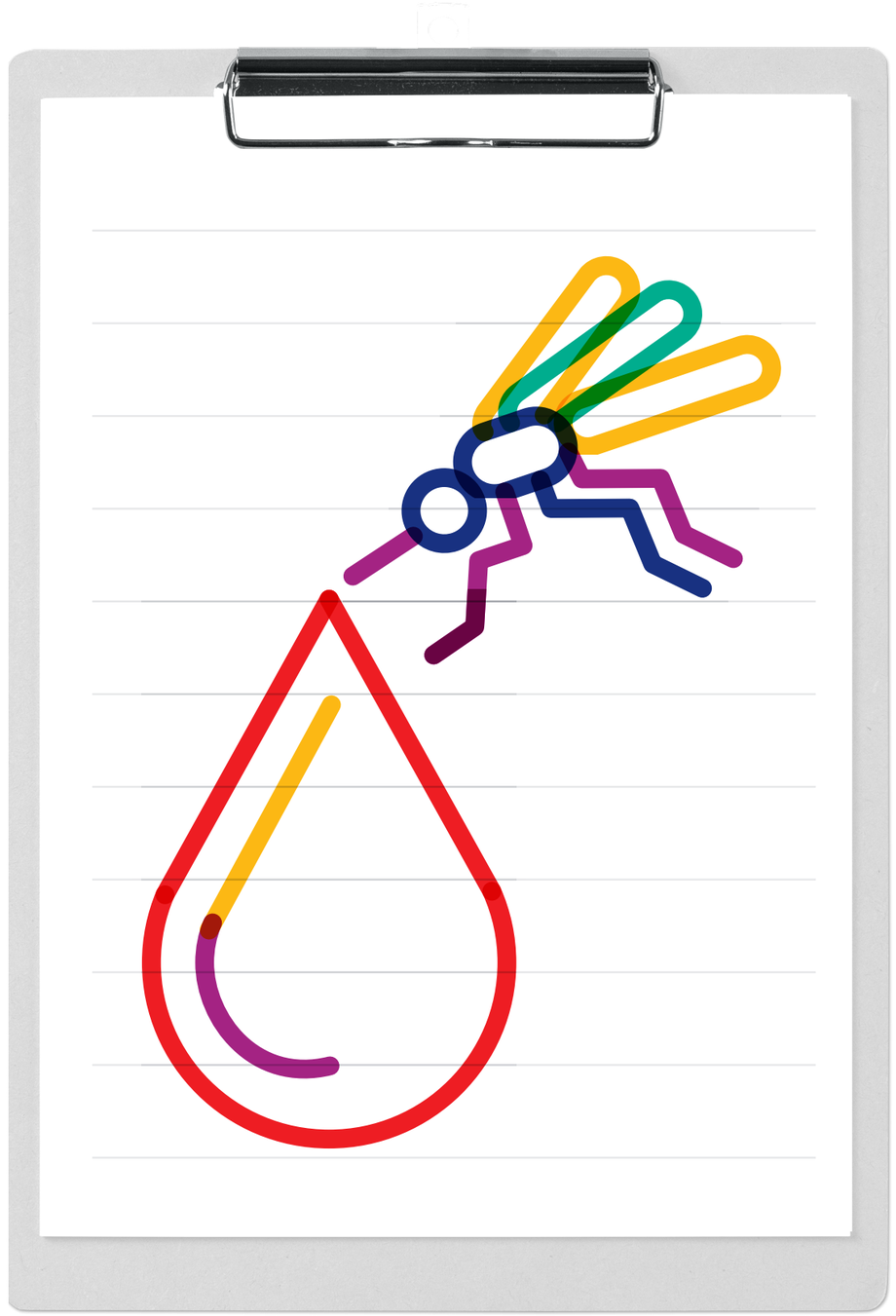

ABSTRACT

Zika virus poses a significant risk to the worldwide population. The mosquito-borne flavivirus has long fascinated the medical community, particularly in the year 2016 as it came to the fore, spreading rapidly and causing symptoms previously not recognised. Since its discovery in 1947, Zika virus has progressed from causing relatively mild illness in regions of Africa to becoming a worldwide epidemic with severe consequences for many infected individuals. Zika virus is now known to cause congenital abnormalities such as microcephaly as well as neurological disease in adults. The mechanisms by which Zika virus elicits its effects are not yet fully understood, though congenital abnormalities indicate the possibility of vertical transmission from mother to child, and evidence shows that the virus may be sexually transmitted. In many ways, Zika virus has defied expectations and confounded researchers, breaking many of the so-called "rules" and pre-conceived notions that we have regarding viruses. This article further explores the history, pathophysiology, and mechanisms of transmission of Zika virus, as well as summarises the ongoing research and current recommendations regarding prevention.

INTRODUCTION

Zika virus is an arbovirus primarily transmitted by mosquitoes between human or animal hosts. It is classified as a flavivirus, a genus comprised of over 70 viruses, many of which are common and potentially deadly human pathogens causing infections such as Dengue fever, Japanese encephalitis, and yellow fever.[1]

A BRIEF HISTORY

Zika virus was first identified in 1947 in the Zika forest of Uganda. Researchers placed rhesus monkeys in cages suspended in the canopy of the forest for the express purpose of being bitten by mosquitoes. In April 1947, one monkey came down with a fever which, according to a blood test, could not be attributed to any of the previously identified arboviruses such as yellow fever virus or dengue virus.[2] Thus, a new virus was discovered, and named after the forest from which it came.

Zika virus was not identified in a human subject until 1952.[3] In 1954, a ten-year-old Nigerian girl experienced headache and fever, but no more serious symptoms. Results of blood tests from members of the girl's village showed that 60% of the population had antibodies to Zika virus, and therefore must have previously been infected.[4]

Despite only 14 reported cases of human Zika virus between 1947 and 2007, it is theorised that Zika virus has been endemic in African populations for thousands of years, existing as a relatively mild illness.[5]

The first indication that Zika virus was spreading was in 2007 when the Pacific Island of Yap, part of the Federated States of Micronesia, experienced a large outbreak. 73% of the population became infected over the course of six months, but again experienced only mild influenza-like symptoms.[6]

This outbreak is likely explained by a lack of immunity on the island of Yap, allowing a huge proportion of the population to become ill quickly upon exposure to the pathogen. African populations were consistently exposed, leading to sporadic rather than epidemic patterns of disease. Furthermore, it is possible that the clinical similarity between Zika virus and a variety of other arboviruses such as yellow fever virus and dengue virus led to a lack of reporting of previous outbreaks.

French Polynesia was the next area to be hit by a major outbreak in 2013. Ten percent of the population, approximately 30,000 people, were infected with Zika virus. This time, however, doctors noticed an unusual increase in the incidence of Guillain-Barré Syndrome (GBS), an autoimmune disorder attacking the peripheral nervous system and resulting in acute peripheral neuropathy, paralysis, and paresis.[7] The incidence rate was 20 times greater than expected,[8] and the temporal and spatial association with the Zika virus outbreak could not be ignored.

The first locally acquired cases of Zika virus occurring in the Americas were reported in Brazil in May of 2015, but it was not until later in the year that more serious side effects began to be noticed. There was an increase in the number of patients with GBS post-infection, as could be expected following evidence from the French Polynesian outbreak, but an even more unusual pattern of complications also arose.

Approximately eight to nine months after the first cases of Zika virus, paediatricians and obstetricians working with newborns were seeing far more babies with microcephaly than they ever had before. In an example of the importance of open communication between physicians, doctors throughout Brazil consulted one another and made the connection between Zika virus and microcephaly.[9] Subtler birth defects were also seen, such as cerebral calcifications, ventricular enlargement, spasticity, eye defects, and growth restriction, all of which are indicative of abnormal CNS development.[10]

One main question for researchers remained: why is what was thought to be a mild virus suddenly spreading and causing severe complications not previously seen? Several factors contribute to this unusual epidemiological pattern. In the areas in Africa where Zika virus is endemic, most girls are infected as children, prior to puberty and before they become pregnant. Thus, they are immune by the time they are having children. Foetuses are therefore not exposed to the pathogen and the congenital complications seen elsewhere are not present. Furthermore, because of the spread to non-immune populations, there are simply more cases now than have ever been reported before, allowing for clearer correlation between cause and effect.

PATHOPHYSIOLOGY AND TRANSMISSION

Flaviviruses such as Zika virus are single stranded, non-segmented, positive-sense RNA viruses. The envelope protein surrounding the virion can bind to receptors on host cells and allow internalisation of the virus. Once within the cell, the viral RNA is released and endogenous mechanisms are utilised to replicate and produce further virions. These virions are then exocytosed to further the infection.[11] Unlike many DNA viruses such as HIV or herpes viruses, Zika virus does not integrate into the host genetic material or form viral reservoirs. This means the virus can be completely eradicated by the immune system or by antiviral treatment.

Transmission of Zika virus is typically vector-borne following a bite from an infected mosquito. On infection, 80% of healthy adults are asymptomatic, while the remaining 20% experience fever, rash, joint pain, myalgia, and headaches which subside after a few days.[12]

As mentioned previously, a rare but serious side effect of Zika virus infection is Guillain-Barré Syndrome. Scientists do not yet fully understand the mechanisms underlying the development of GBS in patients with Zika virus, but it is possible that the virus contains peptides which bear significant resemblance to those in the host, leading to cross-reactivity and autoimmune destruction of host tissue.[12] In this case, the host tissue affected is the myelin sheath of the peripheral nervous system.

Zika virus may also cross the placental barrier and gain access to the intra-uterine environment, resulting in maternal-foetal transmission. In fact, due to the placental tropism of Zika virus, concentrations of Zika virus RNA were found to be 1000 times greater in the placenta of mice than in maternal serum. Zika virus induces apoptosis of trophoblast cells, causing a smaller placenta and compromising the placental barrier, thus permitting foetal infection. Placental insufficiency and malformed placental vasculature can result in decreased foetal growth, commonly seen in Zika virus infected pregnancies.[13]

Infected pregnant women may experience the same symptoms as their non-pregnant counterparts, but the consequences of infection are much more serious for the developing foetus. As described previously, Zika virus outbreaks have been closely associated with an increase in the incidence of microcephaly and a number of other congenital abnormalities. Zika virus is neurotropic, meaning it preferentially targets the nervous system. In particular, the virus has been shown to inhibit the proliferation of human cortical neural progenitor cells.[14]

Mouse models have shown that Zika virus upregulates genes involved in immunity and apoptosis, while pathways involved in cell proliferation, differentiation, and organ development were downregulated, many of which involve specific genes associated with microcephaly.[15]

The neurotropic effects of Zika virus within the foetal brain could explain the consequential congenital syndrome post-infection, though microcephaly is thought to be multifactorial in causation, and may also be related to cross-reactivity and autoimmunity. The severity of the congenital syndrome varies according to the gestational age at which Zika virus is contracted, with the more serious cases occurring earlier in pregnancy.[13]

The Zika virion can interact with AXL, a receptor tyrosine kinase found on the surface of human radial glial cells, cortical astrocytes, and microglia. AXL has been shown to increase in the brain tissue of foetal mice infected with Zika virus, indicating that it may provide a means of entry for the virions into the host cell. Similarly, toll-like receptor 3 (TLR3) is upregulated in the brain tissue of infected mice.[15] Zika virus may activate TLR3 in the CNS, leading to inhibition of Sonic Hedgehog and Ras-ERK signalling pathways which will cause an increase in apoptosis.[16] AXL expression is also increased in the developing retina, which may account for the optic defects seen in congenital Zika virus.[17]

Zika virus may also be transmitted sexually. Two male American scientists conducting research in Senegal contracted Zika virus in 2008 and were symptomatic on returning home, with one of the scientists having haematospermia. Subsequently, his wife became ill, with classic symptoms of Zika virus infection. The wife had not been present in Senegal, nor had she travelled anywhere else where Zika virus might have been present. At the time, the climate at the patients' home was not permissive to vector-borne transmission dynamics. Direct contact or exchange of non-sexual body fluids could be ruled out, as the children of the scientists did not become infected. Further, the couple reported having vaginal intercourse one day after the male's return home.[18] Thus, sexual transmission was ruled the most likely method. Prior to this, there had never been a report of sexual transmission of an arbovirus.

Since 2008, many more cases of sexual transmission of Zika virus have been reported. In the 2013 outbreak in French Polynesia, a man experienced hematospermia approximately two weeks post-infection with Zika virus. Despite his blood containing no detectable Zika virus, there was a high load of Zika virus RNA found in semen samples.[19] In fact, one study found that Zika virus persisted in the semen for at least 62 days after the patient was symptomatic.[20] This indicates that sexual transmission may occur for a prolonged period post-infection. The current recommendation is that men who may have contracted Zika virus should wait six months before having unprotected sex.[21]

Thus far, all reported cases of sexual transmission have been either male-to-female or male-to-male. One study analysed cervical mucus samples of a woman with Zika virus infection, and found that Zika virus was present in her genital tract at least 11 days after the onset of symptoms, again despite negative results on urine and blood samples.[22] This suggests the possibility of female-to-male sexual transmission.

RECOMMENDATIONS AND RESEARCH

Since the Brazilian epidemic in 2015, Zika virus has continued to spread rapidly across the world. To date, 69 countries have reported evidence of mosquito borne Zika virus transmission. 13 countries have reported person-to-person transmission, 29 reported microcephaly and congenital neural malformations, and 21 countries reported an increase in the incidence of GBS.[23] Research continues, and there are still many unanswered questions. At present, the Centres for Disease Control and Prevention have made a number of recommendations based on the currently available evidence.

There is currently no vaccine available against the Zika virus, so prevention relies upon safe practice by the population. Persons should avoid mosquito bites by using insect repellent, wearing long-sleeved shirts and long trousers, and using mosquito netting.[24] In order to prevent sexual transmission, men who have travelled to areas with Zika virus should use condoms or not have sex for six months after travel, and women for eight weeks after travel. If living in an area with Zika virus, persons should use condoms or not have sex for the entire time that Zika virus is present.[21] Pregnant women or couples planning on becoming pregnant should avoid travelling to areas with Zika virus transmission if possible, and women should wait eight weeks after infection before attempting pregnancy.[25]

Research is currently focused on risk assessment, management, and prevention of Zika virus. Many longitudinal cohort studies are being conducted to assess the long term effects of Zika virus infection,[26] and 31 vaccines are in development.[27]

CONCLUSION

There is no denying the significant risk that Zika virus poses to the worldwide population. It is a virus with a fascinating history of scientific discovery and is a prime example of the importance of the pursuit of information and openness to new findings. The speed with which Zika virus spread in the past few years has been matched by the huge gains of knowledge made by researchers and physicians across the globe. It is hoped that in the coming years, as we conduct further investigations and new information comes to light, we will be able to control and manage Zika virus.

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Can You Beat Bionic? *A Review of Transoral Robotic Surgery*

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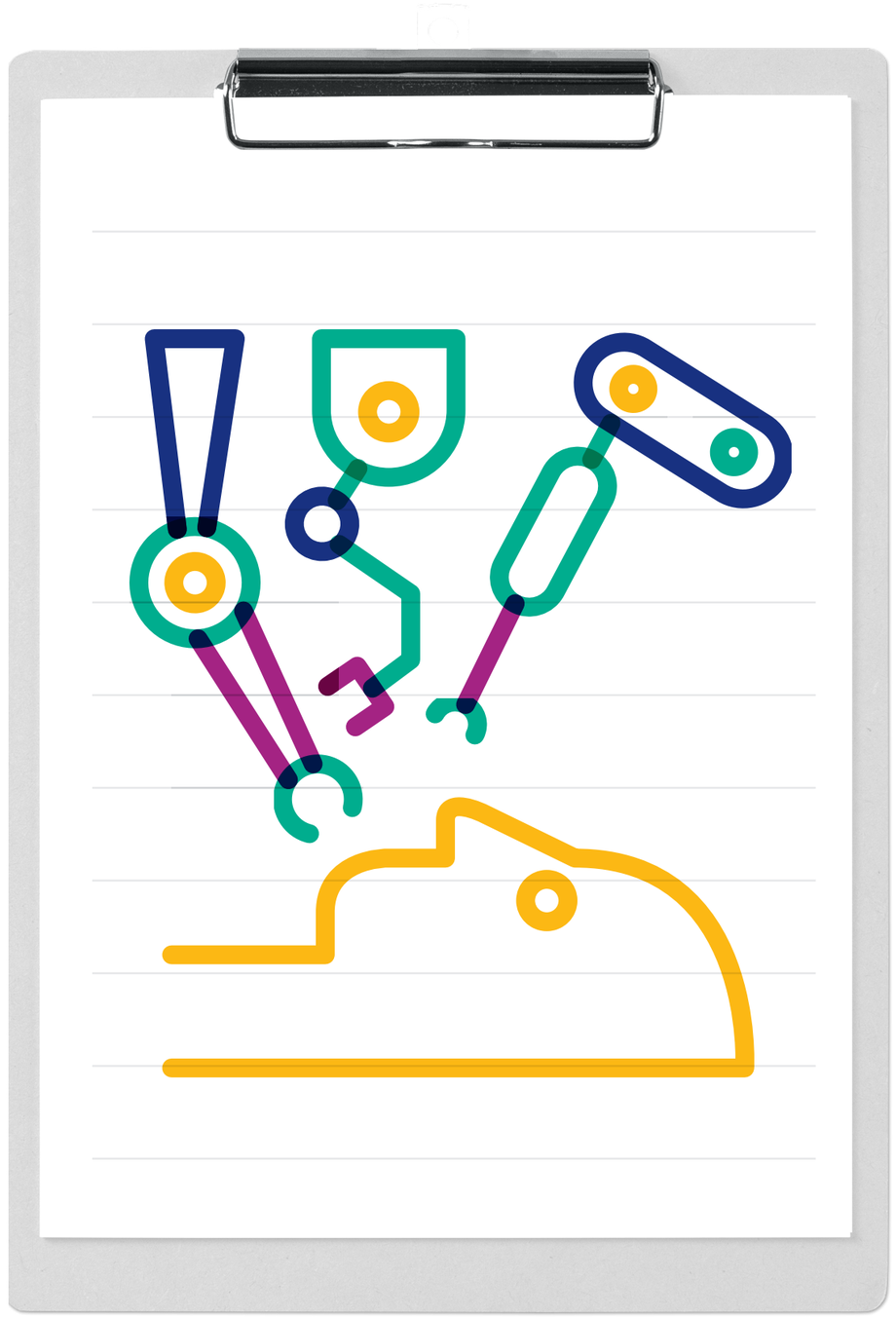

ABSTRACT

Transoral robotic surgery (TORS) is being employed more frequently to perform tissue sparing surgery for the management of cancers of the aerodigestive tract. The uptake of TORS can be attributed to encouraging results of functional and aesthetic outcomes when compared to open surgery and the widely practiced transoral laser microsurgery (TLM). There is also a trend towards performing more technically challenging surgeries using advancements in technology and robotics in order to preserve quality of life (QOL), whilst maintaining favourable outcomes and overall survival. The aim of this review was to assess the functional and oncologic outcomes of the evolving TORS. A *ScienceDirect* search was used out to find studies reporting the functional and survival outcomes using TORS for the treatment of laryngeal and hypopharyngeal cancers. QOL postoperatively was also considered. 166 results were displayed by *ScienceDirect*. In total, 11 papers were identified providing information regarding outcomes associated with TORS.

TORS offers no improvement in survival for the management of laryngeal and hypopharyngeal cancers when compared to laser microsurgery or open surgery. However, TORS offers improved functional and aesthetic outcomes with faster recovery times and reduced postoperative pain when compared to open surgery. Although the functional outcomes are similar to TLM, it does not have the technical drawbacks of TLM and has greater future potential, utilising its sophisticated high definition 3D visualisation, tremor free handling and malleable controls.

INTRODUCTION

Cancers of the oropharynx, hypopharynx and larynx are intimately related to smoking, alcohol and HPV infection. The incidence of these cancers is rising in the developing world due to the recent surge in HPV infection.[1,2] Head and neck surgery was historically aggressive with large amounts of tissue excision and dissection, resulting in collateral damage to the surrounding structures. The focus is on improved QOL, functional preservation and use of minimally invasive techniques, with emphasis on minimal tissue dissection to achieve these goals.[3-7] Current challenges are adequate illumination and visualisation, especially in locations such as the piriform sinus.[8-10] The benefits offered by robotics are improved visualisation, elimination of physiological tremor and untiring actions in difficult positions facilitated by EndoWrist.[7-9] The robotic assistance allows for multi-planar dissection. The system consists of the surgeon console, patient side robotic cart and a high definition 3D vision system.[8-11]

TORS has surpassed what is offered by radical open approaches in terms of operation times, reduction in overall morbidity and faster recovery times.[4,8-9] When compared to TLM the results are more modest. The limitations of TLM include the distance between the surgeon and operating field as well as restriction to single handed use for tissue manipulation, while using the other to operate the laser.[1,3] Thus far, studies reporting the functional outcome and benefits of TORS consist of small cohorts and carefully selected patients who undergo comprehensive assessment prior to being considered for the surgery. Today TORS has been adopted widely across North America and is making progress establishing itself across European centres.

METHODS

A literature search of *ScienceDirect* was performed on all original articles describing transoral robotic surgery. This database was chosen because it provided results for numerous studies on the subject and unrestricted access to all the relevant literature. Only articles written in English were considered. Review articles were read for background knowledge but were not included in the results of this review. Search terms used were, “transoral robotic surgery on pharynx”, “transoral surgery for laryngeal cancer”, “robotic surgery for neck cancers”, “TORS for hypopharyngeal cancer”, “robotic surgery for laryngeal cancers” and “robotic surgery for hypopharyngeal cancer”.

Inclusion criteria:

1. Studies that examined the outcomes of TORS for hypopharyngeal cancers,
2. Literature comparing the outcomes of TORS to TLM or open surgery,
3. Subjects 18 years or older,
4. Malignant lesions,
5. Original research.

RESULTS

There were a total of 166 results. Irrelevant results were studies which focused on non-surgical treatments of head and neck cancers. They were excluded based upon their abstract description. Review papers were also filtered out alongside correspondence articles. The eight papers which published results on the transoral robotic approach and compared them to results from more conventional methods of surgery (open surgery and TLM) are outlined in (Table 1).

Patient Demographics

The gender, mean age and follow up time were extrapolated from the research papers. The mean age of patients across the studies listed in Table 1 was 63.1 years. The patient cohorts consisted predominantly of male patients, who made up 80% of the patients across the studies. The follow-up times reported varied significantly, ranging between 3-36 months with some studies not reporting any follow-up.

Treatment

Patients who underwent TORS were assessed prior to surgery with full physical examination, CT, PET-CT and panendoscopy with biopsy to confirm the diagnosis. Patients were excluded if the disease was deemed to be too advanced for surgical intervention or too invasive to vital surrounding structures. When the tumours were resected, peripheries of the tissue were checked for clear margins via frozen section in the pathology department. Positive margins were re-excised until clear borders were achieved. Following this neck dissection was performed in most circumstances.

Technical and Oncologic Outcomes

Concerning operating times, the robotic system is twice as efficient overall as the open approach, even when the robot set-up time is considered[4] which is a statistically significant difference ($p < 0.001$). TORS for the management of laryngeal and hypopharyngeal cancer is safe, versatile and oncologically impressive, with studies reporting their entire cohort disease free at 6 and 12 months[8,14] and other literature data describing an 83-89% overall survival at 3-years.[4,15] Research papers with long term follow-ups (18-22 months) have shown a mortality ranging from 9-14%.[4,15] There are some impressive results from Olsen et al,[11] which showed complete disease control in 77% of the patients (at 24 months), most of whom had stage II-IVa disease. When compared to radical surgery, TORS has a slightly superior outcome (5-8%)4 in terms of 3-year disease free survival and overall survival but the difference is not statistically significant. It should be noted that the majority of these patients who underwent TORS also had some form of adjuvant therapy whether chemotherapy, radiotherapy or both depending on the stage of the disease. Lastly, in-spite of the fact that overall survival between open surgery and TORS is not statistically significant, what must also be considered is recovery, long term functional outcomes and QOL.

Functional Outcomes

Tracheotomy was performed in a few studies. This was to prevent airway compromise secondary to laryngeal oedema or haematoma.[4,7,14-15] Laryngeal oedema was a documented postoperative complication in a few cases where tracheotomy was not routinely performed as a preventative measure. In such cases, emergency intervention was necessary to maintain a patent airway.[3,5,6,8] Intraoperative corticosteroids injections were also employed as a different technique used to minimise the risk of laryngeal oedema.[8]

A basic outline of the swallowing and feeding outcomes can be seen in Table 1. Patients who underwent open surgery reported postoperative dysphagia and odynophagia.[4,14] Bordeux et al noted that 30% of their patients were nasogastric tube (NGT) dependent postoperatively due to severe dysphagia.[6] Olsen et al reported NGT placement in patients who had significant dysphagia and lacked a safe swallow.[11] The average time patients spent on NGT feeding post TORS was approximately 8 days.[4-6,7] In comparison, radical open surgery required NGT feeding for at least 11 days, with an average time of 20.6 days.[4] The same study 4 showed that three times as many patients who had undergone open surgery ended up on long term PEG feeding in contrast to the TORS group. Therefore, swallowing function outcome is superior in the TORS group compared to the open surgery cohort ($p < 0.001$).

Problems with phonation are frequently overlooked and under-reported in the literature with particular studies failing to mention it in their results.[5,6,8] Olsen et al measured speech outcome using three parameters: phonation, resonance and articulation. Speech was possible without long term issues in particular cases.[7,14] Park et al documented detailed reports of the voice outcome in his 3-year follow up study.[15] The assessment of speech was evaluated through acoustic waveform analysis which showed that frequency variation and jitter occurred in patients after piriform sinus resection because the ipsilateral vocal cord dexterity was affected from the resection.

Quality of Life

This was assessed using the University of Washington Quality of Life Scale, after a minimum of 6 months following surgery.[4] When TORS was compared to open surgery, it surpassed in terms of chronic pain ($p = 0.013$), cosmesis ($p = 0.005$), physical activity ($p = 0.009$), speech ($p < 0.001$), swallow ($p = 0.003$) and anxiety ($p = 0.004$). In addition, a better overall health related outcome was achieved in the TORS cohort.[4]

QOL does decline postoperatively from baseline in terms of speech, swallowing and cosmesis. This is most notably seen in patients who received adjuvant radiotherapy. Fortunately, QOL continuously improves with time and at 12 months follow up there was no statistically significant difference in the QOL from baseline.[3]

COMPLICATIONS

Threats to the airway are the main postoperative concern. Laryngeal oedema is the most commonly reported complication in many of the studies; it necessitates emergency intervention and is a cause of morbidity. There was only one reported case of laryngeal haematoma compromising the patency of the airway and necessitating emergency surgical drainage. Park et al routinely perform tracheotomies to avoid these complications involving the airway, which have an incidence of <10% based on the literature data reviewed (Table 1). Haemorrhage is the second most common issue encountered postoperatively. Bleeding can occur acutely postoperatively or chronically months after the initial procedure.

Authors	Patients (N)	Cancer Site (N)	Airway Status	Swallow /feeding	Mean Hospital Stay	Complications (%)
Park et al.[4]	(30); All had successful resection	Hypopharynx (30)	Temporary tracheotomy in all patients to prevent airway compromise	Swallow function returned within an average of 8.4 days	26.1 days	Bleeding (3%)
Iseli et al.[5]	(62); 54 patients had successful resection	Oral cavity (6) Oropharynx (33) Larynx (12) Hypopharynx (3)	ET intubation retained for 48hrs in 22% of patients. Tracheotomy rate 9%	Within 14 days 83% were on oral intake. 69% PO prior to discharge	4.6 days	Laryngeal Oedema (9%) Bleeding (6%) Aspiration (6%) Fistula (2%)
Boudreaux et al.[6]	(36); 29 had successful resection	Oral cavity (3) Oropharynx (22) Hypopharynx (1) Larynx (10)	72% were extubated post-op. The rest within 48hrs	55% were PO prior to discharge. 89% started oral intake within 14 days	2.9 days	Laryngeal Oedema (7%) Bleeding (7%) Aspiration (3%) Dehydration (14%) Hemoptysis (3%)
Park et al.[7]	(5); All had successful resection	Larynx (4) Hypopharynx (1)	Temporary tracheotomy in all patients to prevent airway compromise	Oral diet was commenced within 1 week of surgery	NR	No reported peri-operative complications
Aubry et al.[8]	(17); 15 underwent TORS and 2 open surger	Oropharynx (5) Hypopharynx (12)	Tracheotomy rate 12%	Swallow function returned within an average of 5.6 days. 2 required gastrostomy tube while undergoing rehabilitation	10 days	Pharyngocervical fistula (6%) Haematoma (6%) Laryngeal Oedema (12%)
Olsen et al.[11]	(9); All had successful resections	Larynx (9)	7 Planned preoperative tracheostomies.	55% had safe swallow post-op and 45% had dysphagia and underwent gastrostomy tube placement	NR	No reported peri-operative complications
Park et al.[14]	(10); All had successful resection	Hypopharynx (10)	Temporary tracheotomy in all patients to prevent airway compromis	Normal swallow returned within an average of 8.3 days	NR	No reported complications
Park et al.[15]	(23); All had successful resections	Hypopharynx (23)	7 Planned preoperative tracheostomies.	Swallow function returned within an average of 8.1 days and oral feeding was commenced	NR	Bleeding (4%)

DISCUSSION

TORS has impressive oncologic outcomes with overall survival of up to 89% at 3-years.[15] Hypopharyngeal cancer has the worst prognosis of the aerodigestive cancers.[4,7,15] The survival benefit of TORS is equal to open surgery and primary radiotherapy but it is superior in terms of functional outcome, reduced postoperative pain and better quality of life.[3-4,6-8]

Patients who underwent TORS in the studies reviewed were meticulously selected, received physical examinations, CT imaging, PET-CT, and panendoscopy to assess the full extent of the disease prior to selection for TORS. Resectable tumors were selected for these studies and some authors reported up to 100% success rate.[10] Inherent selection bias for lower stage cancers was noted due to the experimental design of the studies and the cautious patient selection.[4] Accessibility is still an issue concerning certain anatomical sites, but site exposure can be maximised with specific setups, tools and patient positioning. This facilitates access to more challenging anatomical locations such as the piriform sinus.[10]

Many of the research articles are based on small patient cohorts, making it difficult to draw confident conclusions from the small sample size.

Long-term NGT dependence was examined by Bordeux and Dziegielewski.[3,6] Dependence was associated with more advanced disease (pT3/ pT4), advanced age and a lower MDADI score.[6] Patients with pT3/ pT4 neoplasms are 27 times more likely to remain on long term NGT.[3] TLM became the new standard of treatment after demonstrating better functional outcomes compared to open surgery especially in speech and swallowing.[16A-C] However TLM has technical limitations, mainly the issue of limited mobility and line of sight limitations. This means that resection is only possible in one direction. TORS has the capacity to overcome the technical limitations of TLM, facilitating superior visualisation, with the use of a movable camera with three-dimensional views, magnification and high-definition video output.[14]

LIMITATIONS OF ROBOTIC SURGERY

The potential technical capabilities of robotic surgery are alluring, often obscuring the limitations of this new technology. The cost of the DaVinci robot is €1.7 million with annual maintenance costs of up to €140,000. Despite the costs, this investment does not improve survival when compared to the accepted standard of transoral laser microsurgery (TLM), making it a luxury for many clinical centres in Europe.

A notable limitation of the technology is the requirement of acute angles of approach when using the multiple robotic arms through the oral opening. This limitation is worsened by interference between the multiple robotic arms, which require manual repositioning for conflict resolution. This is especially problematic when operating on deeper structures of the aerodigestive tract such as the deep recesses of the piriform sinus.

CONCLUSION

TORS has achieved competitive outcomes when compared to TLM and radical open surgery and is quickly evolving in its use for neoplasms of the head and neck. It has potential to become the new standard of care following encouraging results in terms of functional outcome and QOL. Indication for its use is growing as surgeons build experience and new techniques are applied. In conclusion, the evidence suggests that TORS is a valid, safe and minimally invasive procedure which should be considered when managing laryngeal and hypopharyngeal cancers.

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65 roses: *Oversimplify Cystic Fibrosis?* Watch out for the thorns!

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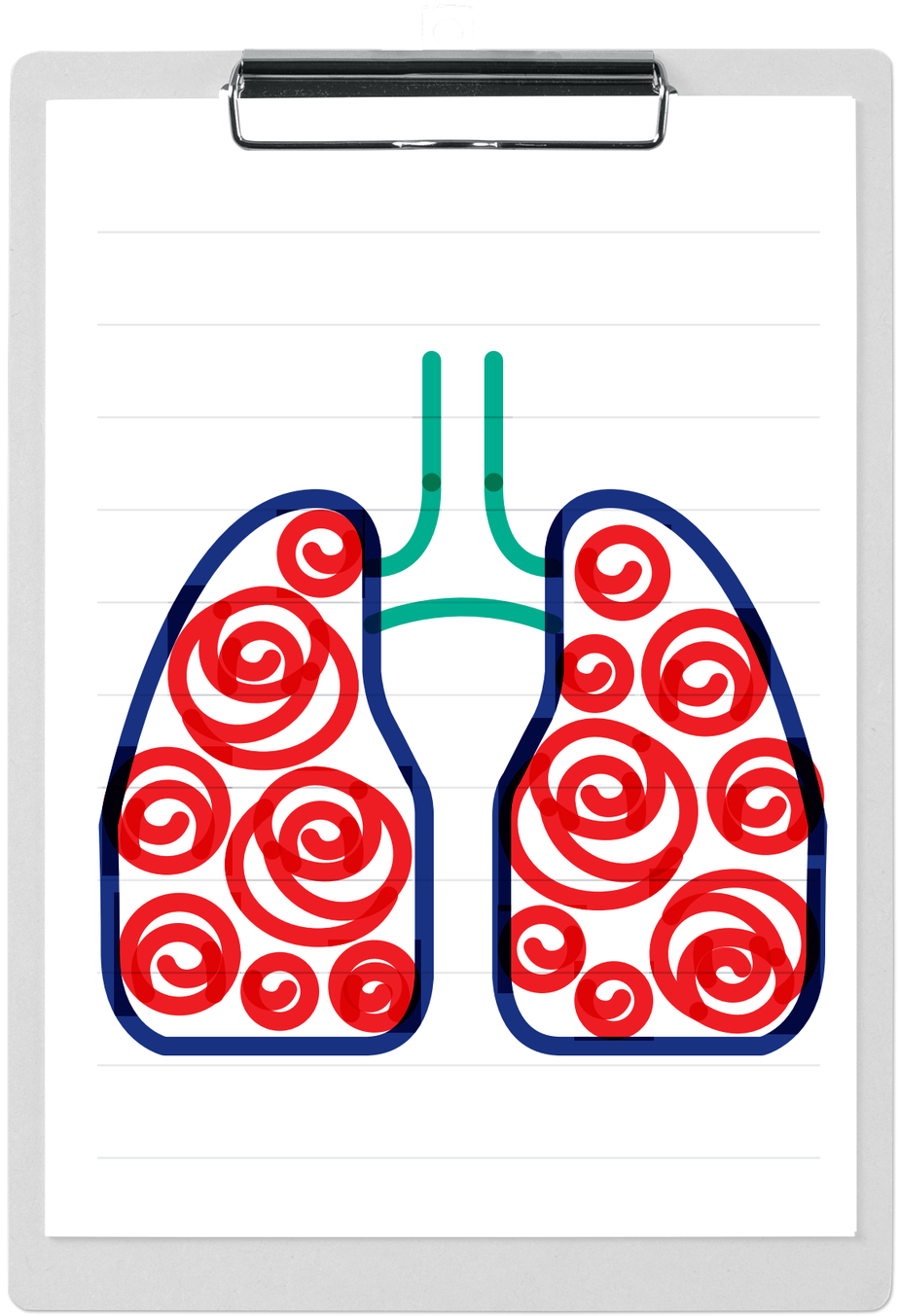

ABSTRACT

For children living with cystic fibrosis, pronouncing the name of their disease often poses a challenge. Since 1965, the term "65 roses" has been employed by children of all ages to describe their condition. What started off as a mispronunciation, has now been adopted as the emblem of cystic fibrosis, fronting fundraising campaigns worldwide. Cystic fibrosis has been embraced by the scientific research community and has become a paradigmatic single-gene disorder in Ireland, a country that claims the highest incidence of CF worldwide.

Although youth affected by CF have chosen to simplify the name, it is crucial that the scientific community does not underestimate this disorder. Boasting almost 2000 identifiable mutations resulting in varying phenotypes, the CFTR gene has been a research giant, challenging both scientists and clinicians alike. However, despite massive advances in this field of study, significant gaps in knowledge and limitations in the management of CF remain.

INTRODUCTION

Despite cystic fibrosis' (CF) classification as a rare disease, CF is the most common life-threatening monogenic (single-gene) disorder in Caucasians. The estimated incidence of CF is 1 in 2500-4000 newborns and it currently affects more than 70,000 individuals worldwide.[1] Notably, Ireland has the highest incidence (per head of population) of CF in the world. Approximately 1 in 19 Irish people are said to be carriers of CF[2] and expectedly, CF is deeply ingrained in the Irish psyche and culture, despite its "rare" status.

Just like children with cystic fibrosis (CF) have simplified the name to "65 roses", there is a tendency to oversimplify this deceptively complicated single-gene disorder. At a basic level, we know the underlying genetic cause of CF. Similarly, at a clinical level, we know the features that characterise CF, particularly advanced lung disease, which is the primary cause of mortality in people with CF. Between these two extremes, the exact mechanism in which loss of CFTR function results in the CF phenotype remains somewhat uncertain.[3] Therein lie the thorns of cystic fibrosis.

Nevertheless, recent progress in elucidating the pathophysiology of CF has laid strong foundations for bridging this gap and has formed the genesis for new treatments. To understand this link between the molecular defects at the core of CF and the progression of CF symptoms, we must first revise a few key fundamentals.

BACK TO BASICS

CF is an inherited autosomal recessive condition caused by mutations in the CFTR gene, located on chromosome 7. This gene encodes an ion channel expressed on epithelial cell membranes, which mediates sodium and bicarbonate transport. In addition to controlling chloride secretion, this channel regulates the function of other membrane transport proteins. Collectively, these protein channels play an important role in maintaining homeostasis by controlling the movement of water through the epithelium, which is particularly pertinent for mucous membranes. Hence, CFTR malfunction leads to fluid hyperabsorption and dehydration of the epithelial surface, producing thick, dehydrated secretions.

Over 1900 CFTR mutations have so far been described. F508del is the most common mutation with an allelic frequency of around 90%.[4] These mutations impact protein synthesis and have been classified into six functional classes. Class II, home to the infamous F508del mutation, comprises mutants that fail to traffic the channel to the cell surface, due to protein misfolding and premature degradation by the cell's quality control system. However, the restriction of variants into a single class is problematic, as multiple processes can be affected by a single variant. For example, although F508del is categorised as a Class II mutation, in actuality, the effect this mutation has on CFTR synthesis and function, spans at least three functional classes.[5] Appreciation of the diversity of effects caused by a CFTR variant is important in the design of molecular treatments for CF, and represents just one thorn challenging the scientific community.

FROM MOLECULES TO MEDICINE – THE BIOLOGICAL CONSEQUENCES OF CFTR MUTATIONS

CFTR is primarily present in the epithelial cells of the airways, intestine and in cells with exocrine and endocrine functions. In organs and tissues implicated in CF, absence or dysfunction of CFTR results in an ionic imbalance that leads to dehydrated mucus. Thus, CF pathogenesis is characterised by the build-up of a thick, sticky mucus in multiple organs, such as the lungs, pancreas, intestine, sinuses, and reproductive organs.[5]

MUCOCILIARY ESCALATOR: OUT OF ORDER

Although CF affects several organs, the most significant clinical manifestations are seen in the lungs and airways. In bronchial tissue, the CFTR channel is found in submucosal glands and ciliated epithelial cells. The ciliated cell is the workhorse of the mucociliary escalator, a protective mechanism which clears excess secretions from our lungs. CF patients have a defective or absent CFTR and as such lack the ability to sufficiently hydrate the airway surface layer: an important mucous layer that lines the airway tract. The dehydrated mucous layer draws water from the protective coating on the cilia. Eventually, the cilia collapse as a result of the aberrant osmotic gradient and the mucociliary escalator ceases. Mucous stasis eventually leads to airway plugging, chronic bacterial infections, inflammation and airway tissue damage, in the form of bronchiectasis.[6]

As mucociliary clearance is an important defence mechanism against pathogens and dust particles, its reduction in CF patients leads to chronic infections by a restricted group of pathogens: *Pseudomonas aeruginosa*, a hallmark of CF which is found in 80% of patients by the age of 18 years.[1]

INTESTINAL CHANGES

The most serious acute complication of the CF intestinal phenotype is the obstruction of the terminal ileum or proximal large intestine, referred to as meconium ileus. Additionally, abnormal GI microbiota and inflammation may contribute to mucosal damage and ulceration. A new endoscopic technique relying on a swallowed capsule (PillCam) reported 63% of patients investigated had various lesions, including ulcers.[7]

CFTR AND THE PANCREAS

In healthy individuals, the pancreatic ductal epithelium secretes 1-2L/day of alkaline fluid, which flushes digestive enzymes into the duodenum neutralising acidic chyme. Decreased CFTR function leads to a lower fluid volume and increased acidity, precipitating protein rich secretions that plug smaller ducts. This results in progressive damage to the exocrine tissue of the pancreas. A lack of digestive enzymes leads to malabsorption of nutrients, and in its most severe form, pancreatic insufficiency.

In CF-related diabetes (CFRD), the aetiology is complex and the involvement of CFTR in the pathophysiology remains a contentious issue. Whilst the exact mechanism of CFRD continues to be debated, it is widely accepted that expression of abnormal CFTR channels in the exocrine part of the pancreas, is to blame for endocrine dysfunction and this may be due to reduced blood flow to islet cells.[8] Regardless of the aetiology, abnormal glucose regulation adds to the complexity of this "simple" monogenic disorder.

TREATMENT LIMITATIONS

CF is a complicated disorder for several reasons. As previously noted, almost 2000 CFTR gene mutations have been reported so far. This is further complicated by the presence of "complex alleles" i.e. those containing more than one CFTR mutation. Secondly, the CFTR genotype is often a poor predictor of the full spectrum of clinical phenotypes and multi-systemic consequences. Thirdly, an increasing number of CFTR mutations are associated with isolated disease characteristics such as disseminated bronchiectasis, chronic pancreatitis, chronic sinusitis, or male infertility; the distinction between these CFTR-opathies and CF is not always straightforward. Finally, it has been proposed that CFTR plays several other roles in the cells but it remains unclear whether correction of the primary function of CFTR will also restore these additional "secondary" functions.

PLAYING IT SAFE – CONVENTIONAL THERAPY LIMITATIONS

Conventional therapies for CF include antibiotics, chest physiotherapy, mucolytics and nutritional supplementation. These therapies are chiefly destined to manage CF symptoms and disease complications. Failure to treat the underlying molecular defect is a major limitation of this approach. These therapies are costly and time consuming, further limiting their success in combatting CF. Antimicrobial resistance and compliance issues are two omnipresent challenges in CF treatment.

Antimicrobial resistance

Despite improvements in outcomes, many CF patients still die from pulmonary complications. Treatment of bacterial lung infections remains one of the primary goals of CF care. Management of these infections involves complicated antibiotic regimes. Antimicrobial resistance poses a continuously evolving limitation to this conventional therapy. Known pathogens such as *P. aeruginosa* and *B. cepacia* continue to affect CF disease progression and over the last decade MRSA has demonstrated a notable increase in prevalence, increasing from 4% in 1999 to 25.7% in 2010. Recent research has demonstrated that chronic MRSA infection in CF is an independent risk factor for death, not just a marker of disease severity or end of life in individuals with CF.[9] Given this affirmation of the clinical significance of MRSA pulmonary infection in CF, tackling increasingly resistant pathogens with dwindling new antimicrobial options represents a limitation of conventional therapy.

Adherence to complicated CF medical regimens

Between the use of inhaled mucolytics, inhaled antibiotics, airway clearance, nutritional enzymes, supplements and equipment maintenance, many individuals with CF spend hours each day on their treatment regimens. Adherence to these complicated CF medication regimens is only approximately 50%[9]. Recently, a YouTube video of a six year-old boy taking his daily CF medications went viral, amassing almost one million views in less than one week. His daily pill count was 45.[10] Current research has highlighted both the challenge of adherence to these complicated CF treatments and the resultant impact on clinical outcomes. Two studies have demonstrated that poorer adherence to inhaled tobramycin was associated with an increased risk of hospitalisation and increased health care costs.[11]

WHY TAKING IT PERSONALLY MATTERS

In recent times, CF has become the 'poster-child' for personalised medicine. It is evident that symptom management, rather than correction of the underpinning molecular defect, is the overarching limitation of conventional therapies. Effective treatment of CF at the molecular level requires restoration of CFTR function in affected tissues. New personalised therapies are under development, targeting either the dysfunctional gene or protein. This new era shines a beacon of hope for curative strategies, rather than focusing on end-stage disease management of affected organs.

PROTEIN THERAPY

Protein therapies are aimed at correcting the dysfunction of CFTR, targeting specific mutation classes to personalise the treatment. One of the major limitations of these therapies are the vast range of mutations in the CFTR gene, and the heterogeneity of their effects. The pharmaceutical Lumacaftor, which allows CFTR to be expressed at the cell surface, was developed to tackle F508del.

However, phase II clinical trials indicated that restoring CFTR expression was not sufficient, and CFTR function had to be promoted by a potentiator. Consequently, a clinical trial that combined Lumacaftor, with the potentiator Ivacaftor showed significant improvements.[9] Thus ORKAMBI, a Lumacaftor/Ivacaftor combination recently licensed by the European Medicines Agency was born. The identification of the effects of each individual mutation and the creation of multiple targeted drugs are essential to effectively treat CF.

GENE THERAPY

One hopes that, in the future, gene therapy will be the gold standard treatment for patients with CF. The concept of gene therapy in CF involves adding a correct sequence of CFTR in a way that is incorporated into the patient's cells and is able to circumvent the CFTR mutation. Vector options include both viral and synthetic. Unfortunately, viral vectors studied for gene transfer induced an excessive inflammatory response or showed poor efficacy in CF. Therefore, weakly immunogenic synthetic vectors have become an attractive alternative. Currently, a phase III clinical trial of an inhaled gene therapeutic is ongoing in the UK with the use of a synthetic lipid vector but no results have been published to date.

Deliverance

Another limitation of gene therapy in CF is that thus far, agents have been delivered only to the lungs (via inhalation) and hence would have no benefit to other organs. Another challenge posed by this 'thorny rose' is access to the site of delivery, as thick respiratory mucus may prevent a favourable bioavailability. Issues may arise with chronic administration, even with a low immunogenic system.[9]

Cost

When the drug KALYDECO (Ivacaftor) came to market, the Irish government was caught in a precarious position. With a price tag of €234,000 per patient per year the National Centre for Pharmacoeconomics (NCPE) initially recommended against its sanction for use. However, after receiving criticism from patient advocacy groups, the government negotiated a reduced price with the manufacturing company and KALYDECO has since been approved.

Presently the government is facing a similar situation as ORKAMBI has recently been rejected by the HSE and NCPE as being "unjustifiably expensive and not cost effective",[13] although negotiations with the pharmaceutical company Vertex are ongoing. With the availability of new innovative therapies for CF on the rise, this situation is almost certainly to be repeated.

CONCLUSION

Despite being a 'simple' monogenic disease, CF has provided many lessons of complexity to the field of biomedical science. Cloaked in the guise of apparent simplicity, CF is indeed the monogenic disease paradigm, greatly contributing to the advancement of both scientific research and clinical practice.

As Jack Riordan, who together with Lap-Chee Tsui and Francis Collins made the original CFTR discovery, stated in a recent publication for the 20th anniversary of the discovery "*the disease has contributed much more to science than science has contributed to the disease*".[1]

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Maternal Sepsis *and patient safety*

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ABSTRACT

Sepsis is a serious issue both in the general clinical and maternity setting, though the consequences of maternal sepsis are often more detrimental. Not only are high morbidity and mortality rates associated with sepsis, but the infection also incurs high costs. Patient safety is a priority in maternal sepsis cases in Ireland and worldwide. In order to enhance safety, healthcare professionals should have sufficient knowledge of pathophysiology, aetiology, and risk factors related to maternal sepsis. One of the most effective and common methods in assessing pregnant women's well-being is through the use of Irish Maternity Early Warning System (IMEWS), which allows for early recognition of signs of deterioration that accompany a sepsis diagnosis. This facilitates quick and effective treatment, thus improving patient outcomes and safety. Healthcare providers caring for pregnant women, particularly those at higher risk of sepsis, must possess the necessary skills and training, as possible consequences of insufficient care, as in the case of Savita Halappanavar, can be disastrous. Furthermore, neonates that are born to mothers with sepsis are at risk of acquiring sepsis from the mother, while the same risk factors putting mothers at threat of sepsis put neonates at increased risk of developing early onset neonatal sepsis (EONS), with antibiotic prophylaxis being crucial in both cases. To conclude, maternal sepsis must be treated as an emergency and healthcare providers should be familiar with prevention strategies and the importance of early recognition and treatment.

INTRODUCTION

Sepsis can be defined as lethal organ dysfunction, which results from dysregulated immune response to infection.[1] It may also cause Systemic Inflammatory Response Syndrome (SIRS) and Multiple Organ Dysfunction Syndrome (MODS). When not immediately diagnosed and treated, it may progress into septic shock and eventually be fatal.[2] Hospitals are using more aggressive management strategies to improve its control and treatment,[3] but the incidence within the healthcare setting is still high. Approximately 102,000 suffer and 37,000 die from sepsis every year in the UK. From an economic standpoint, each case of sepsis in the developed world costs around £20,000, which leads to approximately £2 billion (€2.3 billion) spent on sepsis by the UK healthcare system every year.[4] In Ireland in 2015 alone there were 8,888 cases of sepsis, a 37% increase from 2011. The incidence of pediatric and maternal sepsis has increased from 737 pediatric and 190 maternal cases in 2011 to 766 pediatric and 308 maternal cases in 2015.[5] This demonstrates the scale of the issue and highlights the importance of prevention and effective treatment in order to decrease morbidity, mortality, and cost.

SEPSIS AND PREGNANCY

The exact pathogenesis of sepsis is not fully understood, though ongoing research continues to further our knowledge. It is thought that sepsis is the body's inflammatory response to infections of microbial origin.[6] In some cases, sepsis can be diagnosed clinically without a positive culture for pathogens.[7] Diagnosis of severe sepsis occurs when organ dysfunction or failure is present. Septic shock is the addition of hypotension despite adequate fluid resuscitation.[8]

Normal physiological changes during pregnancy tend to mask the clinical and laboratory symptoms of sepsis, making it a challenge for healthcare professionals to effectively diagnose and treat.[3] During pregnancy, blood pressure changes due to vasodilation induced by pregnancy hormones. There is a significant drop in diastolic blood pressure and, to a lesser extent, systolic blood pressure. This usually settles towards the end of pregnancy.[9] White cell count (WCC) rises due to stress, leading to leukocytosis. This is particularly evident just prior to delivery, when the WCC can fluctuate between 9,000 to 25,000 mcL. Normal values range between 4,000 and 11,000 mcL.[10] This demonstrates how the normal physiological changes during pregnancy can cause abnormal readings or laboratory results when compared with the non-pregnant population, potentially leading to a missed diagnosis of sepsis.

It is evident that maternal sepsis is a massive patient safety issue, affecting maternity units and hospitals worldwide, with drastic consequences that must be addressed. The MBRRACE[11] report states that overall maternal deaths are decreasing in the UK and Ireland (from 11 to 10 per 100,000). However, in Ireland in 2011, sepsis was the cause of severe maternal morbidity in 25 cases; in 2012 this number increased to 41 cases.[12] Furthermore, sepsis was responsible for 25% of maternal deaths between 2009 and 2012,

in Ireland and the UK. In the USA, maternal sepsis was the leading cause of maternal death (20.6%) between 2003 and 2011[13]. However, a study of pregnant women between 1993 and 2006 in the Netherlands showed the maternal mortality rate caused by sepsis to be only 0.73 per 100,000[14], indicating that the Irish and British health services have significant room for improvement, which was also supported by an Irish study by Knowles *et al.*.[15] Despite the significant impact of sepsis on patients, many symptoms continue to go unnoticed and cases are not detected quickly enough for efficient treatment. If symptoms of sepsis are detected early and managed immediately, patient outcomes improve dramatically.[16]

Group A streptococcus is the main bacterial cause of sepsis, implicated in over half of maternal deaths.[16] Consequently the majority of guidelines regarding identification and treatment are related to this pathogen.[15] However, Abir *et al.*,[3] stated that Escherichia coli bacteria was responsible for the majority of cases in their study, showing there are inconsistencies in bacteriological origin. Other organisms related to maternal sepsis comprise of: Listeria monocytogenes, anaerobic bacteria, Staphylococcus aureus and Group B Streptococcus (GBS),[15] which is also associated with sepsis and meningitis in new-borns, that can usually be prevented by treating GBS positive mothers during intranatal period with antibiotics.[17] Approximately 1 in 5 women carry GBS, however there is no universal screening for it during pregnancy either in Ireland or the UK.[17]

The rapid onset of sepsis leaves very little time for error. Thus, all potential risk factors, such as repetitive vaginal examinations without rationale or prolonged rupture of membranes,[18] should be considered when assessing patients. Acosta *et al.*,[2] stated that factors such as obesity, operative vaginal delivery, and age above 25 years can also increase this risk. Sriskandan[16] compared the different risk factors for women in developed and developing countries. In developed countries, risks for maternal death from sepsis were: emergency caesarean section, prolonged rupture of membranes, retained products of conception, premature labour, history of infection, excessive vaginal examinations, low income, diabetes, anaemia, recent upper respiratory tract infections in family, and giving birth during the winter months. Similar to Acosta *et al.*,[2] obesity was mentioned as risk factor. Each woman should be individually assessed antenatally, during labour, and postnatally, to ensure that the risks are adequately controlled and managed.

One of the most common ways to assess health status during pregnancy, labour, and throughout the postnatal period (42 days after birth) is by checking vital signs. The Irish Maternity Early Warning System (IMEWS) is widely used in maternity services in Ireland where routine vitals such as pulse, respiration rate, oxygen saturation, temperature, blood pressure, neurological state and pain score are noted.[19] Similarly, The Modified Early Obstetric Warning System (MEOWS) is used in the UK, which was recommended by the CEMACH 2003-2005 report. Singh *et al.*,[20] wrote that MEOWS is “cost effective, safe, and validated”. In their study, 676 cases involving the use of MEOWS were assessed and no deaths were reported.[20] However it is suggested that use of MEOWS is limited in the cases of chorioamnionitis, an infection of the amniotic fluid acquired through introduction of bacteria into the uterus through the birth canal and severe infections.[19] Measurement of a woman's blood pressure prior to 10 weeks' gestation, upon her first antenatal check-up, provides a baseline for the remainder of her pregnancy.[21] This baseline allows healthcare professionals to more accurately judge abnormally high or low blood pressure readings for the individual patient. If IMEWS is triggered, it indicates that the underlying cause of the change

in blood pressure needs immediate attention. As well as recording vitals, it aids in the identification of abnormalities, assists in further assessment and referral.[19]

Furthermore, 82% of sepsis, 100% of severe sepsis, and 86% of septic shock cases are diagnosed postnatally, with the most common point of origin being the genital tract.[3] In most hospitals, women are discharged within 24 hours of giving birth. However, an increasing number of women choose the ‘Early Transfer Home’ option available in Ireland, and return home as soon as 12 hours after delivery.[22] This quick turnover of patients provides midwives only a short window of opportunity to recognise sepsis and implement appropriate treatment.

DISCUSSION

Certain symptoms of sepsis cause abnormal vital signs. When this occurs, IMEWS or MEOWS automatically highlights the issue and alerts the healthcare provider. This allows for rapid action and referral of the patient for appropriate further screenings.[19,20] Such warning systems simplify this process by providing a clear escalation protocol for deteriorating patients. This early detection is especially crucial due to the rapid spread of maternal sepsis.

Despite IMEWS and MEOWS providing a great guiding tool for healthcare providers, they themselves must be able to take and interpret vital signs, consequently follow appropriate actions. Healthcare providers also need to follow strict, evidence-based guidelines when dealing with patients with maternal sepsis, such as NICE[23] guidelines on recognition, diagnosis and management of sepsis and RCOG[24] guidelines on bacterial sepsis in pregnancy and their own local hospital policies. Such guidelines aim to ensure patient receive the best care possible. In 2013, The Health Information Quality Authority (HIQA) published the report of their investigation into a maternal sepsis death in an Irish hospital in 2012. The investigation identified a failure in the provision of basic elements of patient care and a failure to recognize and act upon signs of clinical deterioration in a timely and appropriate manner.[25] The report made several recommendations, including the development and implementation of a national clinical guideline on the management of sepsis which has been made to aid healthcare professionals in detection, recognition and treatment of sepsis. National clinical guidelines on IMEWS have also been created and implemented after the HIQA report,[25] to assist clinicians in identifying deteriorating pregnant patients as opposed to National Early Warning Score (NEWS) which focuses on deterioration of non-pregnant adult patients. Another aim of these guidelines was to standardise care and provide consistency across maternity units throughout Ireland.[26] Since the introduction of IMEWS in 2013, an enhancement has been noted in consistency and documentation of vital signs particularly the respiratory rate,[27] which is considered as the first warning sign of deterioration.[26] However, the study by Maguire *et al.*[27] had a small sample size, meaning that further investigation is necessary. Lastly, the biggest change involved is the development of National Maternity Strategy 2016-2026. The strategy is intended to improve and standardise both maternity and neonatal care, ensuring that all pregnant women in Ireland can make informed choices regarding their care, and have access and support to all facilities necessary.[28]

Cross transmission of infection is another important patient safety issue contributing to maternal sepsis. Infections can easily spread between patients, thus special care must be taken when treating women with maternal sepsis. To prevent cross transmission of infection when conducting certain procedures such as administration of intravenous fluids, aseptic techniques must be used correctly. All staff involved in the care of a patient with maternal sepsis should be made aware of such cross transmission issues and take the necessary precautions. The World Health Organization's five moments of hand hygiene should be followed. Further, isolation of patients with multidrug resistant organisms is recommended where possible.[16] Prophylactic antibiotics are recommended for neonates born to mothers with severe sepsis, though transmission of sepsis from mother to baby is rare.[16] There is evidence that the risk factors for the mother also put the neonate at increased risk of early-onset neonatal sepsis (EONS), which develops in first 72hrs of life.[29]

CONCLUSION

Maternal sepsis must be regarded as a major obstetric emergency which all hospital staff should be trained to handle. Healthcare professionals should be aware that maternal deaths caused by sepsis, although low in number, are increasing. Methods of prevention include minimising invasive interventions, early diagnosis with tools such as IMEWS/MEOWS, adequate interpretation of vital signs, appropriate referral, and adherence to infection prevention and control precautions. If healthcare practitioners, from midwives to obstetricians, take appropriate steps in recognising the early signs of maternal sepsis and take the correct actions and precautions thereafter, patient outcomes should improve. Wider education and research regarding maternal sepsis is recommended, focusing on its cause, transmission, and development of best practice guidelines for prevention and treatment.

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Pharmaco-genomics and the application of technology *in Anaesthetic practice in the 21st century*

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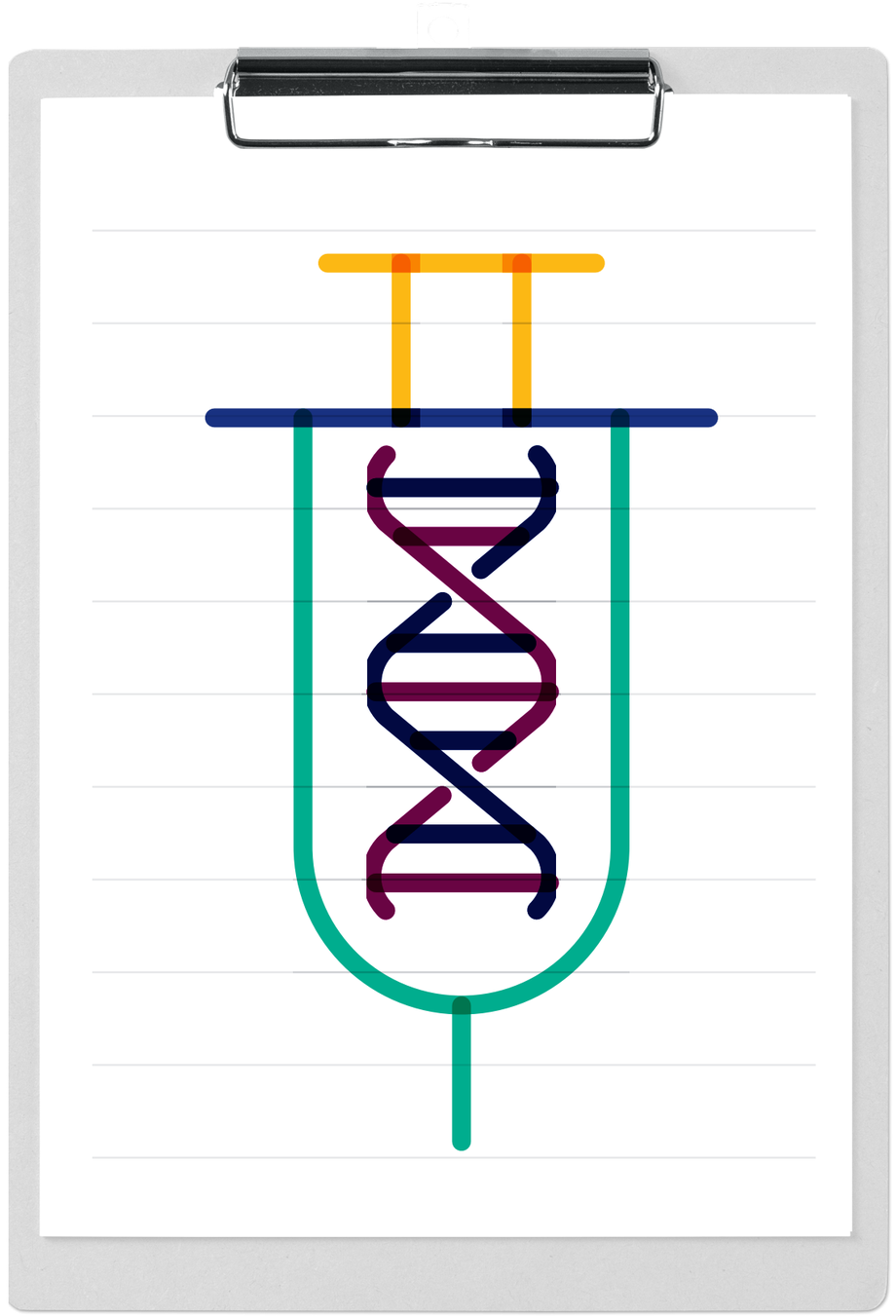

ABSTRACT

Genetic factors have been known to influence the individual's response to anaesthetic drugs for nearly 60 years. Advances in genetic sequencing have allowed researchers to identify many more variations within individual genes that can affect a person's response to drugs, including many of those used in anaesthesia. Since the first sequencing of the human genome in 2003, it has now become possible for researchers to study the effects of multiple genes, or even an entire genome, on individual pharmacodynamics and pharmacokinetics. The historically high cost of genetic sequencing has meant that pharmacogenomics has seen little clinic application, but this soon may change. In March 2016, the $1000 genome became a reality. This was long considered to be the benchmark for routine, affordable personal genome sequencing. This then raises the question of how this developing technology may impact anaesthetic practice in the centuries ahead. What follows is a brief review of pharmacogenomic literature that relates to the classic three components of anaesthesia: hypnosis, muscle relaxation, and analgesia, and aims to give an idea of what may be possible.

INTRODUCTION

In the first two decades of the 21st century we have already seen new technologies make a significant difference in anaesthetic practice. These have included the use of ultrasound in regional anaesthesia, video laryngoscopy for difficult airways, and EEG monitoring to measure the depth of anaesthesia, to name only a few. If the current trends of falling production costs and increased investment in research and development are sustainable, it seems likely that technological advances will continue to have an exponential impact on anaesthetics throughout the rest of the century. Thus, it is difficult to imagine what technologies will have made the greatest difference by the end of the 21st century. It is possible, however, to speculate about what technologies the next two decades are likely to bring. This review will examine one such up-and-coming technology: pharmacogenomics, the study of how a person's genome affects that person's response to drugs.

PHARMACOGENOMICS: THE RELEVANCE FOR THE ANAESTHETIST

Pharmacogenomics will have implications for all of medicine, but anaesthetics is one of the few specialties in which powerful and potentially dangerous drugs play such a central and regular role. Modern anaesthetic practice owes its origin to the discovery of drugs capable of affecting general anaesthesia in the 19th century.[1] Moreover, many of the major developments since have been driven by the isolation of compounds capable of having other profound effects on the body's physiology, such as neuromuscular blocking drugs. Needless to say, the medicines in the armamentarium of today's anaesthetist have changed considerably since the specialty's inception, and continue to be refined to this day. Furthermore, advances in patient monitoring and drug administration have enabled drugs to be used with greater and greater care. Nevertheless, not all the drugs work for everyone, and they can also cause serious harm. If we are to continue to make progress in this area, we need to look more to the other variable of the drug-patient interaction, that is, we need to know more about the drug needs of our individual patients.

We have long since realized how important it is to take into account factors such as age, sex, tolerance, and co-morbidity when predicting a patient's response to drugs – but we are left with poor surrogate markers for a person's genome such as family history and ethnicity. This is a problem because we know that, for some drugs, a person's genes make a significant, or the most significant, contribution to how they will respond to those drugs. For example, up to two-thirds of the variability in the inter-individual response to morphine has been attributed to genetics.[2] A person's genes can also predispose a rare but serious adverse reaction to a drug: for example, mutations in the ryanodine receptor gene *(RYR1)* are associated with the dangerous complication of malignant hyperthermia.[3] Hence, pharmacogenomics has particular relevance for optimizing anaesthesia for individual patients and for avoiding serious adverse outcomes.

THE CENTURY OF PERSONALIZED MEDICINE

Genetic factors have been recognised to influence individual patient response to drugs used in anaesthesia for nearly 60 years.[4] The concept of pharmacogenomics is considerably older still, with some arguing the modern concept can be traced back as far as 510 BCE, when the ancient Greek philosopher Pythagoras noted that ingestion of fava beans resulted in a potentially deadly reaction in some, but not all, individuals.[5] The basic science and theory of pharmacogenomics, therefore, are not new. However, the cost of sequencing a human genome has been falling exponentially since the turn of the century;[6] the Human Genome Project completed the first sequencing of a human genome in 2003 at a cost of $2.7 billion,[7] and in March 2016, the $1000 genome became a reality – long considered to be the benchmark for routine, affordable personal genome sequencing.[8] Consequently, the notion of pharmacogenomics as a technology with widespread clinical application will soon be viable. Furthermore, Barack Obama launched the Precision Medicine Initiative in his State of the Union Address on January 20, 2015,[9] the mission of which is to enable an era of personalised medicine whereby treatments and approaches are tailored to individual patients and their genes. Soon, whole genome sequencing could be performed as quickly and as easily as any other standard blood test. The 21st century, therefore, looks set to be the century of personalised medicine – and of personalised anaesthesia.

What follows is a review of some of the pharmacogenomic literature that relates to the classic three components of anaesthesia, namely: hypnosis, muscle relaxation, and analgesia. We will look at a selection of drugs under the headings of drug metabolism, receptor variability, and other genetic factors.

Drug metabolism

The Cytochrome P450 (CYP) family of isozymes is by far the most important enzyme system in terms of drugs metabolism, with approximately seven clinically re§levant CYP enzymes responsible for the metabolism of the majority of currently used drugs. A number of different CYP genes encode for the respective CYP enzymes, and there are many variations or alleles within each of these genes in the population. The result is that the effectiveness of each of the CYP enzymes can vary greatly from person to person, depending on how many copies of and the specific alleles that they inherit.[10]

With regards to the CYP2D6 enzyme, which is responsible for metabolizing many opioids, persons can be classified as *normal metabolisers* (NM), *intermediate metabolisers* (IM), *poor metabolisers* (PM), or *ultrarapid metabolisers* (UM).[11] As the name would suggest, most persons are *normal metabolisers*, as mutant alleles that increase or decrease the activity of the enzyme are, by definition, relatively rare compared to the normal "wild-type" alleles. For those who are not NMs, opioids can have a very different effect to that which is intended. Codeine, for example, is a prodrug that must be metabolised by CYP2D6 into its active form, morphine, in order to have any significant affinity for the μ receptor. This means that PMs who are given standard dose paracetamol and codeine are, in effect, only receiving paracetamol, while with UMs the result might be dangerously high levels of morphine.[12] Similar concerns apply with regards to tramadol and hydrocodone and CYP2D6, as the respective metabolites of these are much more potent than the original drugs.[13, 14] The analgesic effects of other opioids, such as oxycodone, also depend on the amount of certain metabolites present.[15] In other words, patients may receive opioid analgesics without receiving sufficient analgesia: Yang et al. (2012) looked at a group of post-op patients with acute severe pain and found that 71% were PM for *CYP2D6*.[16] Equally, standard doses of these opioid medications may actually be dangerous to some individuals.

Many hypnotic agents are also subject to CYP metabolism, though the research in this area has been less extensive. Approximately 5% of sevoflurane is metabolised by CYP2E1 to hexafluoroisopropanol and fluorides, with the remaining 95% being secreted unchanged.[17, 18] It is suspected that these fluoride metabolites may exhibit nephrotoxic action.[19] Thirteen variants of the CYP2E1 gene, with varying frequencies in the population have been described.[20] It is therefore conceivable that such variations may result in a larger or smaller percentage of sevoflurane undergoing biotransformation, resulting in more or less nephrotoxicity.

Enzymes other than CYPs are also involved in the metabolism of certain drugs. Approximately 70% of propofol metabolism, for example, is performed by UPD-glucuronosyltransferase, encoded for by UGT1A9,[21] a non-CYP gene, while CYP2B6 and CYP2C9 are responsible for the rest of propofol metabolism.[17] Experiments have indicated a relationship between a person's response to propofol and alleles of *UGT1A9* and these *CYP* genes. [17, 22, 23, 24, 25, 26, 27, 28]

Suxamethonium, a depolarizing muscle relaxant, owes its short duration of action to its normally rapid metabolism by nonspecific plasma cholinesterases. However, plasma cholinesterase activity can be reduced in some persons, again due to genetic variation, resulting in a prolonged duration of neuromuscular block. The normal (Eu:Eu) genotype is present in 96% of the population, with the remaining 4% having one abnormal gene (Ea, Es, Ef), or various combinations of two abnormal genes. All of the abnormal genes result in a longer duration of neuromuscular block, ranging from 20 minutes up to several hours, depending on the combination.[3]

Receptor variability

The effectiveness of opioids is also subject to inter-individual variation in the genes that encode for the various opioid receptors. For instance, genetic variations in the μ opioid receptor gene *OPRM1*, have been shown to correlate with the amount of morphine required after lower abdominal surgery. Liu and Wang (2012) reported that persons carrying the GG genotype (10.4% of the population) required much higher opioid doses to achieve pain relief.[29] In addition, variations in *OPRK1*, which encodes for the kappa opioid receptor, have been demonstrated to influence the risk of opioid addiction.[30]

The ryanodine receptor is located on the membrane of the sarcoplasmic reticulum, and isoform 1 (RYR1) is located primarily in skeletal muscle. Variations in the *RYR1* gene have long been suspected to be the culprit in malignant hyperthermia (MH), a rare life-threatening condition that is usually triggered in response to suxamethonium and volatile anesthetic agents. The RYR1 receptor functions as the primary Ca2+ channel, allowing stored Ca2+ from the sarcoplasmic reticulum into the cytoplasm, which in turn triggers the contractile mechanisms within the muscle cell. Abnormal RYR1 receptors, however, allow excessive amounts of Ca2+ to pass, resulting in generalized muscle rigidity. ATP is consumed rapidly, as it is used in the process to return Ca2+ to the sarcoplasmic reticulum, and the result is an increase in CO2, heat, and lactate production. Unless treated promptly with dantrolene, the inevitable result is break down of the muscle cells, resulting in myoglobinaemia and hyperkalaemia 3. Unfortunately, this disorder has eluded a simple genetic test: at least six different loci on the *RYR1* gene are known to be involved, each of which can contribute a large number of variations, and MH is also associated with variations in other genes.[31] However, such a complex genetic phenomenon is precisely the type of problem that the pharmacogenomic approach is designed to solve: in time, we should be able to predict a person's risk of MH based upon the number of contributing variations present in their genome.

Other genetic factors

There are other genetic factors still that may influence an anesthetist's prescribing: it has been established, for example, that a person's pain perception and disposition to pain are also partly hereditary. Take the enzyme *Catechol-O-methyltransferase* (COMT), which metabolises catecholamines: it has been estimated that approximately 10% of the variability in pain sensitivity is related to single nucleotide polymorphisms (SNPs) in this gene.[32] Hence, a person's genome may influence their need for, as well as their response to, analgesics.

CONCLUSION

The value of a pharmacogenomic approach to anaesthetics is clear: it would enable us to take into account the contributions of many different variations, in many different genes, that influence the pharmacodynamics and pharmacokinetics of a particular drug to optimize the experience of an individual patient. When widespread whole genome sequencing becomes a reality, it will enable genome association studies with larger sample sizes than ever before. Thus, greater use of the technology will drive research, and in turn, the results of that research will drive greater use of the technology. Moreover, not only will it transform the use of drugs employed in anaesthetic practice today, but it will also have implications for drugs currently in development and drugs not even yet discovered or conceived of. The future impact of pharmacogenomics cannot be underestimated, and anaesthetics has the potential to lead the way.

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In the Patient's Shoes: *A Medical Student's Experience with Crohn's disease*

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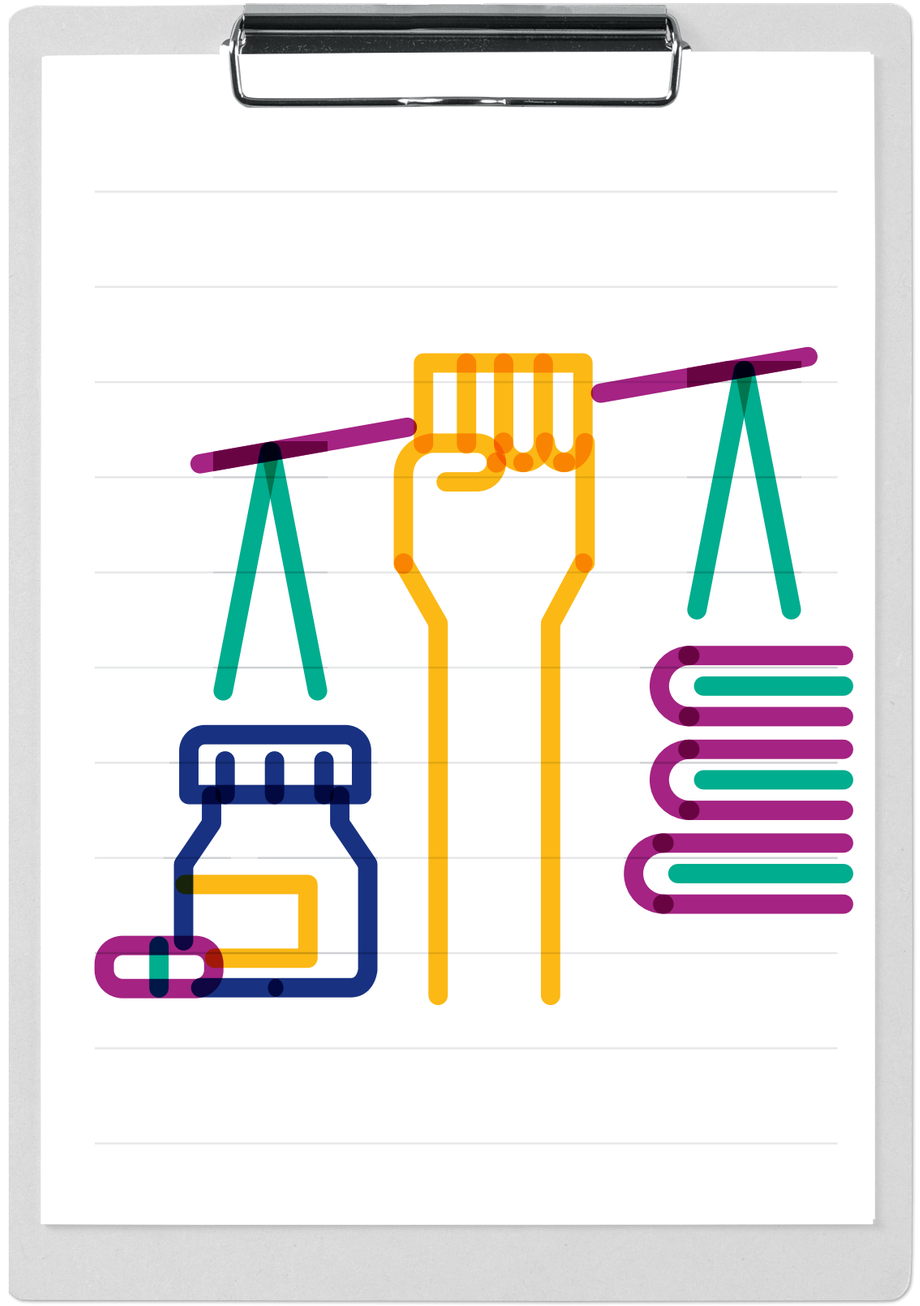

The journey to becoming a doctor begins in the classroom. You begin by attending lectures and reading through piles of textbooks, hoping that you will retain even a portion of the information. As you move into the upper years, you explore pathology and realise how vulnerable the human body is to a vast spectrum of diseases. I often found myself wondering how I could be sitting in class or at home and feel perfectly healthy. It is not uncommon for lecturers to speak to us about various illnesses and then tell us that "one in four" of us in the audience will develop cancer or another serious disease within the course of our lifetimes. From experience, I know that as medical students, we tend to brush off such statistics. The notion that "it won't happen to me" seems to circulate through everyone's mind. I was no different. I was like many of my peers, who too often took their own health for granted.

As a 23-year-old student, my mind was focused only on my studies, my friends and my future career. More often than not, I neglected my own health and passed off illnesses I experienced as transient. This is a story, not about my journey as a student doctor, but as a patient within the healthcare system. I hope to give you a unique insight into the emotional toll and struggles that comes with being a patient, as well as the investigative process used to reach a diagnosis.

It began with severe abdominal pain during the winter exam session of 2015. The pain – a burning, distended, deep-seated pain – was not new to me. In previous years a similar pain had afflicted me, but it was fleeting. This time, it was different. The pain never went away. Granted, I was concerned but instead of seeking help immediately, I focused on my exams. Studying was not easy; the pain had no pattern and would sporadically worsen and subside without warning. A week prior to my first exam, I realised my legs were swollen and had pitting oedema. I saw a GP that day but she passed it off as something idiopathic. I was unconvinced, but with a week until exams I endured the added level of excruciating pain and continued to study.

When exams were conquered, I focused my attention on my health. After seeing a dermatologist, the lesions on my legs were thought to be due to the rare condition erythema nodosum. However at this point, no physician knew what relation that had to my poorly localised abdominal pains. First my GP treated me for irritable bowel syndrome with no improvement. Then they tried to treat for a duodenal ulcer, but again to no avail. A month later, I attended a gastroenterology clinic at St Vincent's Hospital. They ordered a variety of blood and faecal tests as well as CT imaging studies. A few weeks later the radiology report was in and showed an area of small bowel thickening and enlarged mesenteric lymph nodes in the same region. This is when I began to worry. Was it a lymphoma? Would I be able to continue with medical school? Would everything I had been working towards come to an end?

My worries became my family's worries. To make matters worse, they had the added stress of being unable to physically be here for me since they lived overseas, in Toronto, Canada. They tried their best to hold back the tears when we spoke on Skype. Their reassurance that "everything is going to fine" and the "doctors will get you feeling better in no time" didn't make me feel better; rather, it made me feel vulnerable. My health was now in the hands of doctors. Don't get me wrong, I know how well doctors are trained, but the notion that I, the patient, would have to rely on a team of complete strangers to manage my health was unsettling. What if they miss something? What if they don't order the right tests? What if they can't make me better? For me, the feeling of hopelessness reigned in moments like these.

Shortly after the imaging results, the doctors decided that the only option was to refer me over to the surgery team for a diagnostic laparoscopy. This was to take place in September of 2016. As a student, I had always been interested in surgery and took every opportunity to scrub into theatre to watch. Having said that, I was more nervous than I had ever been before. I had never thought that I would be under the knife, especially not now and this far from home. The summer leading up to my surgery was difficult. I not only had the image of me on the operating table ingrained into my mind, but I also had to study for the first part of the United States Medical Licensing Exam. I spent my summer studying 6 to 8 hours a day while enduring the pain of which the origin was still unknown.

Soon September arrived and my surgery was just around the corner. On the day of the surgery, I arrived at the surgical reception area. I changed into a gown and lay on a bed awaiting my operation. My anxiety levels were high. I didn't know what time the operation would be as I was told that the surgeon would decide on the order of his surgeries for the day that morning. As it turned out, I was the first. After being wheeled down to the operating theatre area, the anaesthetist inserted a cannula for intravenous anaesthetic access and explained the process of general anaesthesia. Then, I was brought into the operating room. A mask was placed over my face and I took deep breaths and counted backwards from 10 as the anaesthetics were administered. Before I reached 5, I was unconscious. The next thing I remember was waking up in the post-anaesthesia care unit. Once the nurses deemed my vital signs to be adequate, I was brought to my inpatient bed.

Later that day, the surgeon came to speak with me. He said "I have some news". Before he continued, I immediately thought the worst; was it a lymphoma? Do I have cancer? He told me that the good news was that the biopsy of some severely enlarged lymph nodes was negative for lymphoma or neoplasm. I was relieved. He then explained that I have Crohn's disease, an inflammatory bowel disease. As a medical student, I knew a lot about Crohn's disease; I knew it was due to an abnormal Th1 mediated immune response to gut bacteria causing transmural bowel inflammation. Knowing about a disease is one thing, but experiencing it is a different ballgame. With this diagnosis, I knew that many blood tests, faecal tests and a plethora of imaging modalities lay ahead. The road toward staging and treating my disease was about to begin and I wasn't sure what to expect.

So far, I have had more blood tests then I can count and have had an MRI and CT scan of my abdomen and pelvis. Currently, I am waiting on more procedures and ultimately a treatment plan that will help me to keep this lifelong illness at bay. To say it has been a struggle is an understatement. It has taken over 10 months just to arrive at a working diagnosis. Despite the struggle, I am optimistic about the future and about my future as a physician who will be able to care for and comfort other people with diseases similar to my own.

To all future healthcare professionals, and to those who are not in the healthcare field, I hope this article has given you more insight into the patient experience. It is vital to recognise and acknowledge the emotional toll that a patient endures from the onset of symptoms and throughout the diagnostic testing process. From the stress of undergoing testing, to waiting to be told what the results mean for them; results that can change the course of one's life. This is an unconscionably difficult time in a person's life and it is important to understand that. I have a better understanding of this now, which is something I will keep in mind when dealing with patients throughout the course of my future career.

Medical school teaches us about the importance of empathy through lectures and examinations. The problem is that empathy is not easily taught. It is a skill acquired by listening to a patient's story and understanding their emotional burdens. I had the opportunity, albeit unpleasant, to literally put myself in the patient's shoes. I hope none of you will ever be in that position, but I do hope that you have learned something about the importance of the medical process and more importantly, the impact of that process, on a patient's life.

Acknowledgements

I would like to thank my family, friends and peers for their ongoing support. As well I would like to thank the staff at SVUH who, through their display of exemplary professionalism and due diligence, were able to guide me through this difficult time in my life and arrive at a diagnosis and treatment plan in a timely manner. I would further like to commend the SVUH staff for their compassionate care and for practicing medicine to the highest of standards.

Emerge Better: *Completing an Elective in Emergency Medicine*

Written by Tiarnán Byrne

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Introduction

Elective placements are a feature of most undergraduate medical programmes throughout the world. They are characterised by a period spent in a clinical speciality and setting of the student's choice and are usually undertaken during the final year of medical school. Some see this as an opportunity to make a declaration of intent regarding their postgraduate careers, with budding surgeons entering the operating theatre and enthusiastic medics, the wards of their coveted speciality. Others, perhaps less sure of their path, may see it as a time to sample different specialities or different healthcare systems. However, as more barriers to practical learning emerge within the clinical environment, many are beginning to view their elective period as an opportunity to experience the type of clinical exposure that their core clerkships may have struggled to provide.

It is in this context that emergency medicine has emerged as a favourite amongst medical students undertaking clinical electives. A fast paced and dynamic speciality, it offers a combination of a strong teaching culture and a unique clinical environment that enables students to consolidate and improve their clinical skills before entering practice.

For my own elective I travelled to Westmead Hospital in Sydney, Australia where I trained in both a busy emergency department and with a pre-hospital emergency medical team. The experience not only improved my clinical skills, but also changed my understanding as to how and why I learn. Based on this experience, I intend to lay out some of the specific reasons why an elective in emergency medicine can provide a high quality learning experience.

ELECT FOR EMERGENCY MEDICINE

"For days and days, you make out only the fragments of what to do. And then one day you've got the thing whole. Conscious learning becomes unconscious knowledge, and you cannot say precisely how."
– Atul Gawande, Complications.

Over the course of the last five decades emergency medicine has transformed the treatment of acute illness. From a collection of ad hoc processes performed to inconsistent standards, it has morphed into a highly effective and evidence-based system of urgent care, whilst still maintaining an ethos of multidisciplinary teamwork and proactive change at its core. Furthermore, in emergency medicine the number and diversity of learning opportunities that exist for the motivated student to take advantage of is unrivalled. For the purposes of this discussion we can categorise these opportunities into one of five 'P's'; patients, presentations, practitioners, procedures and performance.

PATIENTS AND THEIR PRESENTATIONS

The emergency department receives patients from across the clinical spectrum. They range from the intoxicated, but otherwise healthy persons, to older persons with extensive co-morbidities and complex social support needs, to patients with serious injuries in need of urgent resuscitation. For the medical student this represents a valuable introduction to the heterogeneous and often complex nature of treating real patients in the earliest stages of their care.

Simple, single-system complaints, such as those often found in minor injury units or urgent care clinics, allow students to practice focused history taking and examination as well as familiarisation with common clinical signs and symptoms. Here students can also experience the overt progression through the process of forming a differential, ordering investigations, making a diagnosis, and initiating treatment.

More complex presentations such as acute exacerbations of chronic diseases, particularly in patients with multiple co-morbidities, can expose students to the multidisciplinary and often assiduous nature of organising the constellation of interventions. Such interventions may be both immediate and long-term, and are commonly required to arrest disease processes, restore patient function and prevent readmission, to whatever degrees these objectives might be possible.

Patients with life-threatening illness and injuries, such as those with major trauma, may not be as physically accessible to medical students as others in the department. Nonetheless their management represents an important opportunity to witness emergency teams in action and the crucial role that strong leadership, efficient communication and other team dynamics play in influencing patient outcome. One of the most impactful moments of my medical training so far was witnessing the mantra of 'Airway, Breathing, Circulation' applied in stressful and complicated clinical circumstances by multidisciplinary teams in Sydney.

PRACTITIONERS AND PROCEDURES

Another key reason for my positive experience in Australia was my working alongside many different types of clinicians, the vast majority of whom were motivated to provide high quality supervision and instruction. While the levels of staffing that is typical of Australian hospitals facilitated this, it was the willingness of the staff to teach that was the most important factor. This was an attitude I had also recognised from prior clerkships in emergency departments in Ireland. Their support is of immense benefit for students as it quickly reveals gaps in their knowledge and training and deliberately remedies them with expert guidance. In my case it was often basic clinical tasks such as the interpretation of electrocardiograms, administration of intravenous medications and clinical examinations where I found myself to be wanting and where subsequently I made concentrated efforts to improve.

Another benefit of the strong teaching culture is the number of opportunities to practice basic procedures and clinical skills, limited only by time and stamina. Competency in many basic procedures, for example intravenous cannulation, can be achieved quickly in the emergency department provided one is proactive and prepared. Exposure to more complicated procedures such as fascia iliaca block for patients with hip fractures is also common. Familiarisation with constituent tasks, such as aseptic technique or ultrasound guidance, alongside time with clinicians from different specialities such as anaesthetics and cardiology, provides invaluable holistic training. Witnessing rare and dramatic procedures, such as an emergency thoracotomy, can prompt reflection as to how practitioners decide and carry out these types of procedures under significant pressure, which brings us to our next topic.

PERFORMANCE

As I progressed through my elective my thoughts turned toward improvement as I gained further insight into my own strengths and shortcomings. Scarcely fifty years old as a speciality, emergency medicine has always had continuous individual and collective improvement at its core and draws widely from the contemporary theories of other sciences such as psychology and performance. Through both formal and informal discussions with clinicians and peers, and independent yet guided exploration of the literature, I came to better understand some of the factors that were affecting my performance.

The term 'Cognitive Bandwidth', for example, refers to a person's capacity to process information, make decisions and perform tasks. It is of interest to emergency physicians due to the psychological and environmental stressors that they often encounter. These stressors can reduce this 'bandwidth' and lead to poor performance and patient outcome. What I found enlightening was how principles such as cognitive bandwidth also applied to students. Take, for example, a student performing a relatively simple procedure, like placing a urinary catheter for the first time. Minor stressors such as patient or supervisor dissatisfaction, can nonetheless produce as strong a stress response in the student. In the same way, this can reduce their cognitive bandwidth and therefore their ability to perform. It is also interesting to note how theoretical preparation and practical familiarisation with a given procedure, perhaps by utilisation of techniques such as simulation or visualisation, could tangibly reduce a student's stress response and improve performance.

CONCLUSION

An elective offers opportunities that translate into a greater likelihood of experiencing many of the important 'firsts' that may have passed a student by during previous placements. Some of these may be dramatic, such as assisting in the performance of compressions during cardiopulmonary resuscitation. Others can be more mundane, like ordering a full blood count. All however, are equally as important for your future career.

Sir William Osler, the first Professor of Medicine at John Hopkins Medical School, understood and championed the importance of a hands-on, immersive approach to medical education. He once wrote; "He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." Increasingly, it seems that students are at risk of finding themselves stranded on the quayside. Though the reasons for this may be complex, multifaceted and largely beyond a student's control, ultimately it is the student who must take responsibility for their own learning. In this context the elective placement can adopt a redemptive role, affording students the much needed immersion into modern clinical practice.

I would never argue that emergency medicine enjoys a monopoly for enthusiastic clinical teachers who can facilitate high quality learning. One need only search social media for the term '#foamed', free open-access medical education, to find evidence of the many dedicated clinicians and academics who are eager to share knowledge of their own branches of healthcare. Personally, the frequency with which I have met teachers of this type during my time in the emergency department, coupled with the abundance of opportunities I encountered there, made my elective the most valued experience of my training so far. I firmly believe that for students who wish to truly test themselves and build on what they discover, an elective in emergency medicine is one of the surest ways of doing so.

Acknowledgements

I am indebted to all of the clinicians, of all professions and specialities, who took time to teach me part of their craft. In particular I would like to acknowledge the staff at the Emergency Departments of St. Vincent's University Hospital in Dublin and Westmead Hospital in Sydney, as well as the staff of the Greater Sydney Area Air Ambulance. Their generosity of time and knowledge served as the inspiration for this article. I would also like to thank Mr. James Condren for his honest and insightful advice.

International Opportunities with the *Association of Medical Students, Ireland*

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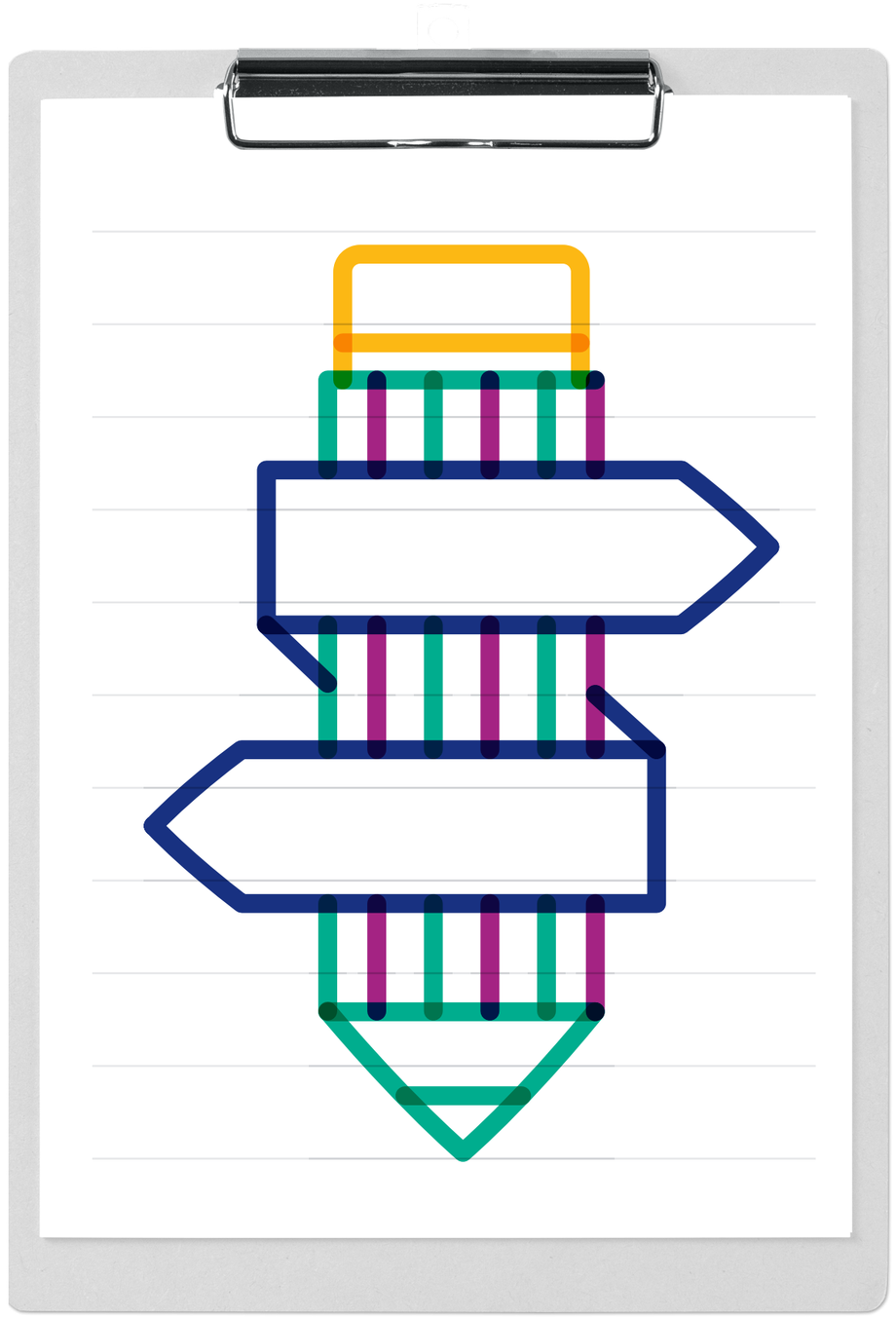

The Association of Medical Students, Ireland (AMSI) is the National Member Organization (NMO) to the International Federation of Medical Students Associations (IFMSA). Founded in 2013, AMSI engages with an inspiring and engaging network of thousands of students from all 7 medical schools in Ireland. One of our aims is to bring medical students together from around the globe to exchange, discuss and initiate projects to create a healthier world, thus, providing them with the skills and resources to become future health leaders.

AMSI is proud to be part of two programs initiated by IFMSA – Professional Exchanges (SCOPE) and Research Exchanges (SCORE), both of which are endorsed by the World Federation of Medical Education (WFME), the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA), the Federation of European Neurosciences Societies (FENS) and the European Society for Emergency Medicine (EuSEM).

Post-World War II, IFMSA founders came together in a period of history where growing disparities in the socioeconomic and political arenas challenged the health and wellbeing of people around the world. IFMSA was created to foster cooperation and collaboration among medical students by breaking down social barriers through promoting opportunities for dialogue and creating clinical exchanges via the Standing Committee On Professional Exchange (SCOPE) (1951) and Standing Committee on Research Exchange (SCORE) (1991).

Ever since the program's establishment, over 13,000 medical students have been given the unique opportunity to embark on a journey to explore healthcare delivery and health systems in different cultural and social settings each year. This is achieved by providing a network of locally and internationally active students access to research and clinical exchange projects, which usually last four weeks. UCD-AMSI is proud to be part of this international platform for clinical and preclinical exchanges within the medical student global community.

All exchanges are carried out in a bilateral basis, where each participating country exchanges one of its students with another. The students are offered a place in the department or on the research project of their choice, as well as accommodation and social programs. Participating students will be assigned to a mentor during their entire exchange to ensure that they are able to achieve their maximum potential.

The SCOPE program is a quality educational and global experience where medical students in their clinical years are given the opportunity to participate in a 4-week clerkship in a chosen medical field in various hospitals across the globe. The language of instruction is either English or the language of the host country. In order to complete the clerkship, the exchange student must show adequate knowledge of the English language or the native language of the host country.

Presently, the SCORE program involves more than 65 active NMOs, offering over 3000 research projects to medical students worldwide. Providing the opportunity to learn the basic principles of medical research such as literature studies, data collection, scientific writing, lab work, statistics and ethical applications. Types of research projects presently offered include basic research laboratory projects, clinical research projects, and global action projects.

If you would like to get involved in either of the above programs – please contact us at leo.amsiucd@gmail.com. We would love to hear from you.

Storage Spaces *for the Homeless*

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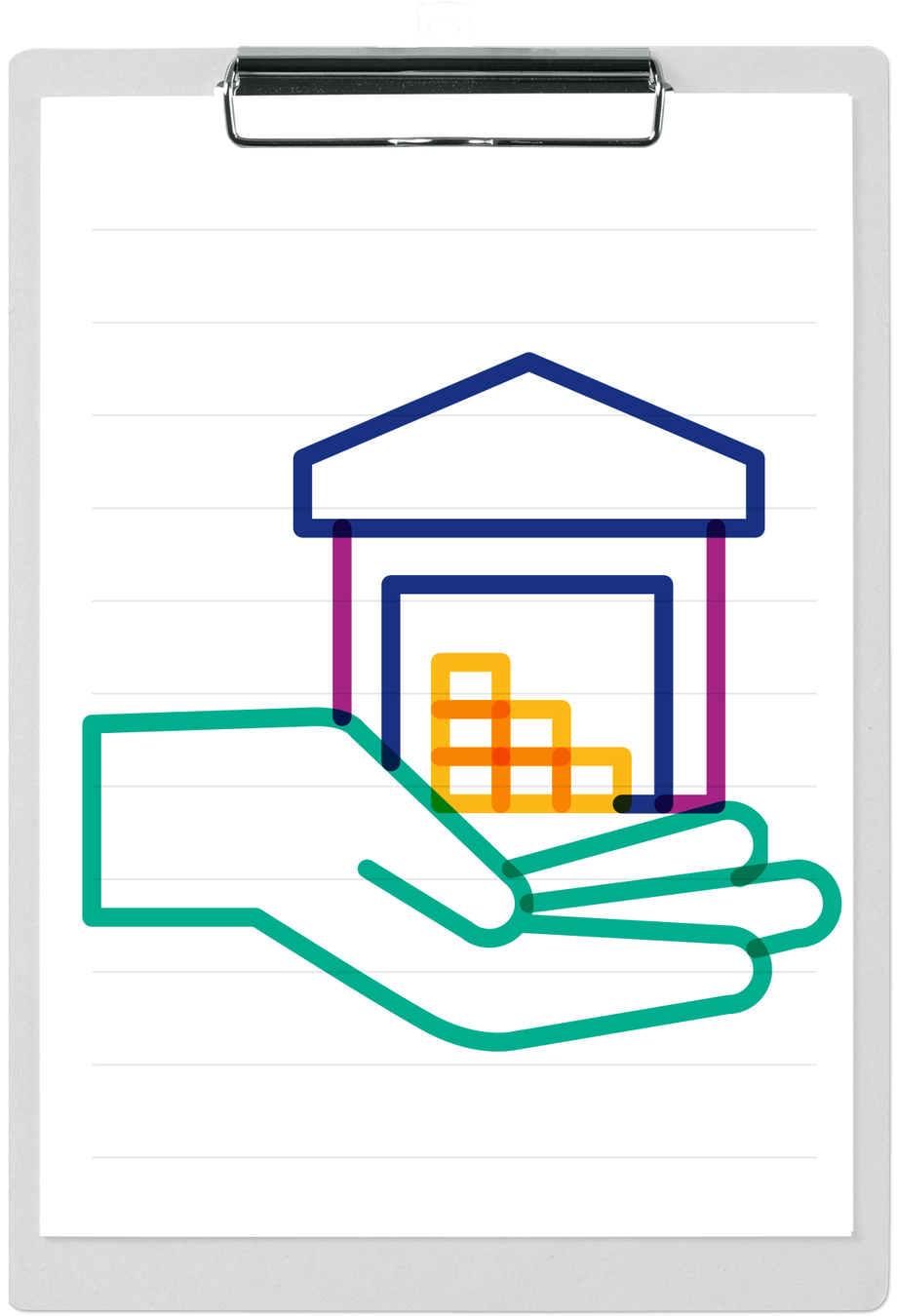

Written by Stéphane Blouin
Daniel Gourlay
Riya Varman

This year, the newly founded, student-run UCD Social Medicine Society hosted an interfaculty competition in which four teams had to come up with and present innovative solutions to this year's question at the inaugural Ideas for Change event: "How do we improve the health of homeless people in Ireland?"

Homelessness is becoming increasingly prevalent in Ireland. As of December 2016, the number of homeless people, in emergency accommodation, temporary services and homeless families, in Ireland has risen to approximately 7,148.[1] It is important to note that this number does not include rough sleepers or people living in squats.

Studies demonstrate that homeless people tend to engage with primary health care services less, and often present acutely in emergency settings.[2] A report by Crisis, a British organisation, found that homeless people are almost 40 times more likely to not be registered with a GP than the general population. 79% turn to the emergency department, with 10% using the emergency service once a month.[3]

Homeless people have a greatly reduced life expectancy, estimated as 47 years of age in one study[4] and suffer from a greater number of co-morbidities[5] than the general population. Additionally, a study looking at the rate of suicide and self-harm among the homeless in Ireland found that a significantly higher proportion of homeless people (24.8%) engaged in repeated self-harm acts compared to those with a fixed residence (15.1%) with 5,487 (15.3%) engaging in one or more repeated acts of self-harm during the 12 month follow up period since the time of the index self-harm act.[6] The key finding in this study demonstrated that homeless patients were less likely to be offered an outpatient appointment compared to patients with fixed residences.[6] The report states that the primary reason for this was lack of fixed address and general unpredictability of a patient's living arrangements.[6]

In efforts to tackle the problem of housing shortage, the €5.35 billion 'Housing initiative: Rebuilding Ireland – Action Plan for Housing and Homelessness', aims to build 25,000 houses per annum from 2017 to 2021. A housing first policy is undoubtedly the most effective intervention that can improve the health and quality of life of homeless people. In the meantime, measures to address the health care issues of the homeless need to be implemented.

Our Ideas for Change 2016 proposal was to provide homeless people with access to secure storage facilities for their personal belongings. It is important to bear in mind that the homeless population in Ireland is a heterogeneous group comprising homeless families, people with mental disorders, people with drug addictions etc. As such, our service is designed to operate on two separate tiers to target what we perceive to be different needs present within distinct homeless populations.

The first service from our proposal is targeted towards families and people transitioning through emergency accommodation or on the brink of homelessness. It is essentially a secure area composed of individual storage units to allow for the safekeeping of the bulky furniture and everyday objects that are inevitably lost when one becomes homeless. Having a secure place to keep these belongings would help alleviate some of the stress and anxiety that are associated with becoming homeless. A large part of a person's identity is bound to their personal belongings and the emotional value that they attach to them. This facility would mean that just because someone loses their home does not mean that they must go through the further step of losing all of their possessions. Once these people transitioning through homelessness are rehoused, the ability to move their possessions into their new accommodation would reduce the financial strain of refurnishing their new home. This service is intended to be only a temporary measure to help tide over the people who are spending a limited time without a home. It is not supposed to become a long-term storage area that gradually accumulates clutter. Therefore, care will have to be taken to make sure that the system is not abused.

The second part of our idea applies to a broader section of the homeless population. It is to offer secure personal storage spaces, such as lockers, to individuals for the preservation of their personal belongings. Along with a locker, people would be assigned a case manager who would help them engage with healthcare and welfare services. There is currently very limited access to lockers and storage spaces for homeless people in Dublin and no service utilises case management and engages the homeless population in the way that we envisage. The storage lockers would be mainly used to store medications, a clean change of clothes and small objects that may be lost or damaged in the turbulence associated with day to day living as a homeless person. This should help keep people's belongings safe from theft, damage from exposure to the elements, or simply loss.

Theft is a huge problem in a population that already suffers from a higher rate of comorbidities. A study by Crisis in 2004 found that 67% of homeless people had been victims of theft.[7] Adherence to prescriptions is estimated to be 50% amongst patients from the general population. Homeless people have higher rates of non-adherence due to problems such as theft, loss, lack of storage space and social isolation.[8,9,10] Having a secure area to store these medications would hopefully help to address this issue.

Access to a place to store a clean change of clothes would also be of enormous benefit for people without a home. It offers not only an improvement in quality of life and hygiene, but an infection control benefit. The ability to wash and change clothes is essential in preventing infections such as scabies, which are rife in the homeless community.

Active case management is integral to this plan; case managers would be assigned a small number of people using the lockers with whom they would be in direct contact. As people will be accessing these lockers on a regular basis they should be easy to get a hold of, which is characteristically a problem in homeless healthcare. The case manager would remind people to attend appointments, clinics, promote health seeking behaviour and help them engage with services. It has been shown previously that active case management improves health outcomes amongst homeless people.[11] By combining case management along with secure storage of prescribed medications, we hope to reduce loss of homeless patients to follow-up and hopefully lead to less people with chronic conditions deteriorating and presenting acutely. We would therefore argue that this intervention is not only beneficial to the health and wellbeing of the population that it serves, but is also of benefit to the health service. If proven to be effective, this relatively inexpensive intervention could reduce the financial burden of acute presentations and hospital admissions of the homeless population.

People using the locker service would also be able to use it as a postal address for appointments and correspondence to be sent to. Not having a fixed address is a major obstacle that homeless people encounter in their interactions with the health service and various government bodies. The ability to provide an address where they could be contacted should help resolve part of that problem.

Similar interventions have been carried out in different cities across the world such as Los Angeles and Paris.[12,13] Although there have been no academic studies on the impact these interventions have had on homeless health, first-hand reports from the service providers and users have been largely positive. We do understand however that there are practical issues that must be addressed before such a plan can be implemented in Ireland.

One obstacle is finding a suitable location for each of the storage spaces, with the lockers ideally being located on the site of an existing homeless service. This would keep the cost down to the purchase of lockers and wages of staff. Purchased new, it would cost approximately €2,742 for 30 lockers,[14] which would suit a pilot programme to determine the appropriateness of the scheme for wider implementation. The larger long term space can be situated more remotely, with access being prearranged with a coordinator. The risk of the service being abused must also be noted and our solution to this would be to control access to the facility, monitor the rooms with surveillance cameras, and implement a zero-tolerance policy for anyone misusing the facilities resulting in denial of access.

Our idea to improve the health of the homeless population of Ireland is a simple one: fulfil a basic need by providing the ability to store important belongings in a safe, dry, and clean space. Storage spaces would be hugely beneficial to this marginalised section of society and we believe that with the additional support of a case manager, the lockers and storage spaces can be used responsibly and have a tremendous impact on the health and wellbeing of the homeless population of Ireland.

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An Interview with *Dr. Trish Scanlan*

Written by Eimear Byrne

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Dr. Scanlan graduated from UCD Medicine in 1997 and went on to practice at Our Lady's Children's Hospital Crumlin. After relocating to Dar es Salaam in Tanzania in 2007 to work on the children's oncology ward at the Ocean Road Cancer Institute, Dr. Scanlan had to transition from circumstances where a 90% childhood cancer survival rate is the norm, to where 90% of children attending her hospital died. Dr. Scanlan helped to create a national strategy for paediatric oncology and established the National Paediatric Oncology Centre at the Muhimbili National Hospital. Over the following years, survival rates have been transformed under her constant guidance.

→ What originally inspired you to relocate to Tanzania in 2007 and subsequently set up the National Children's Oncology Centre?

The first time I went to Africa was to Kenya with MSOR (Medical Students Relief Overseas) as a UCD medical student and what struck me immediately was how it's just a different pace, a different world, with different needs. In my masters, my thesis had to be based in an area I was training in, which for me was paediatric oncology. I did a quick google search and found a charity INCTR, that had the link with Tanzania so that's how I ended up there.

I was originally just in Tanzania for 6 weeks in 2006 to complete my thesis. For my thesis I did a needs assessment of the children who had been there in 2005 and 2006 - a snapshot of what was going on in the ward - and the situation was extremely sad. What wasn't sad, however, was how amazing the doctor and the nurses were, and how open they were to suggestion and implementing changes.

I finished my masters, finished my SpR (Specialist Registrar), and then returned to Tanzania and I haven't left since!

→ What were the main differences in the standard of care for childhood cancers in Tanzania compared to Ireland back in 2007?

When I arrived, Tanzania had a population of approximately 40 million people and about 50% of those were under 18. The population was largely poor and largely rural, with approximately 80% of the population living in the countryside. This made it incredibly difficult to deliver care when 80% of the population are scattered all over the country.

A couple of years prior to my arrival, they had only just opened the first children's cancer ward in the whole country. The government had announced that it was to be free care for all of its citizens, children and adults, which is why they opened the first cancer institute. However, the problem was that the cupboards were bare - if you didn't have Burkitt's lymphoma there were no drugs. This lack of drugs was certainly the biggest issue.

Here in Ireland, if you were sick, within one contact you'd be with a specialist, whereas in Tanzania it could take them up to 6 contacts, and potentially over 6 months to get to a specialist.

Things are changing in Tanzania. In 2005 the original children's cancer centre saw 100 new children out of potentially over 3000 – this is an estimate as nobody knows for sure how many are dying of childhood cancer in the villages. Now more than 500 children are treated at the Upendo (the Swahili word for love) Children's cancer Ward at Muhimbili National Hospital.

→ The success of your team has been reflected in the incredible increase in survival rates, from 12% to 60%. How will you work to further this progress?

It's true that we have improved the survival rates for those who are curable. The biggest problem and the saddest part of it is that for 35% of the children, by the time they cross the threshold into our care they are already palliative. The main reason for this, as I've said before, is the huge delay in reaching our centre.

We are now working with 2 centres in two different parts of the country. We plan to accept all children – stabilize, diagnose stage, and plan the treatment. Once the children are stabilised they will be returned to the local hospitals with all chemotherapy and supportive care medications to complete their treatment locally. Then we can treat more and more children with these shared care centres.

→ How has the Tanzanian government supported you throughout your work despite their limited resources?

70% of the clinical care that these children get is covered by the government; we cover the cost of the remaining necessary care, which includes chemotherapy, supportive care drugs and much of the pathology testing. On the psychosocial side, the Tanzanian government gave us the plot for the centre and pay the electricity and water bill, provide three meals a day for each child and carer and have given us two teachers.

→ Does research play an important role in improving the rates of children's cancer?

Absolutely! Research is why we know anything we know about any cancer. Of all oncology research, paediatric research has led the way from the beginning – always collaborative, brave and innovative.

Obviously, moving forward, research is the key. There are roles for all manner of research. I am not a scientist, I'm a clinician and so the research we have been doing so far on the ward has been clinical audits which, though simple, are very powerful and very valuable and have changed many of the things that we do.

The one gap in what we are doing right now is in implementing clinical trials or other more complex studies of genetics and molecular biology. I recognise the value of these more complex studies and hope to connect with scientists and specialists who will be able to help us in this area in the coming years.

→ Recently a charity known as Their Lives Matter or TLM has been established – could you tell us a bit about what this does?

In Ireland and the UK it's called Their Lives Matter– it has only been set up in the past 12 months and its aim is to support all of the activities in Tanzania, largely fundraising and coordinating volunteers. We have a charity board including a number of inspirational people who have been incredibly helpful, supportive, and generous in this project all the way along. The charity has a sister group in Tanzania called "Tumaini la Maisha" set up in 2011, which means "Hope for Life" that runs this whole service – the hospital, transport, school for the children, fundraising locally. Together they're all called We Are TLM.

We are keen to develop more as we expand our vision – to reach every child with cancer in Tanzania in the next 5 years.

→ What advice would you give to any medical student who wishes to work in the Children's Oncology Centre in Tanzania?

We have many medical students that come out to us every year. UCD was the first medical school to come out, back in probably 2008 or 2009. The one thing about students from Ireland is that when you ask them to do something, they'll always have a go, which I really love about them – they're remarkably hard working and have the right attitude working in an environment which is certainly not always easy.

The children we have in our centre really are so sick. We often say that if you look at a textbook, that last paragraph in the textbook is where medicine begins in Tanzania. We are hoping that will change over time and we can get the children in at an earlier stage.

Certainly medical students are very welcome. If they would like to get involved they should contact me through the website www.wearetlm.org or like and comment through our facebook page 'We Are TLM'.

→ Finally – what are your hopes for the future?

I will be happy when we see that every child who has cancer has access to the appropriate level of care in a timely fashion and I do not think it's unreasonable to expect that that will happen. I think part of the reason these things don't happen is because people don't believe that they can. I truly believe we will access every child in Tanzania with cancer in the next 5 years.

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