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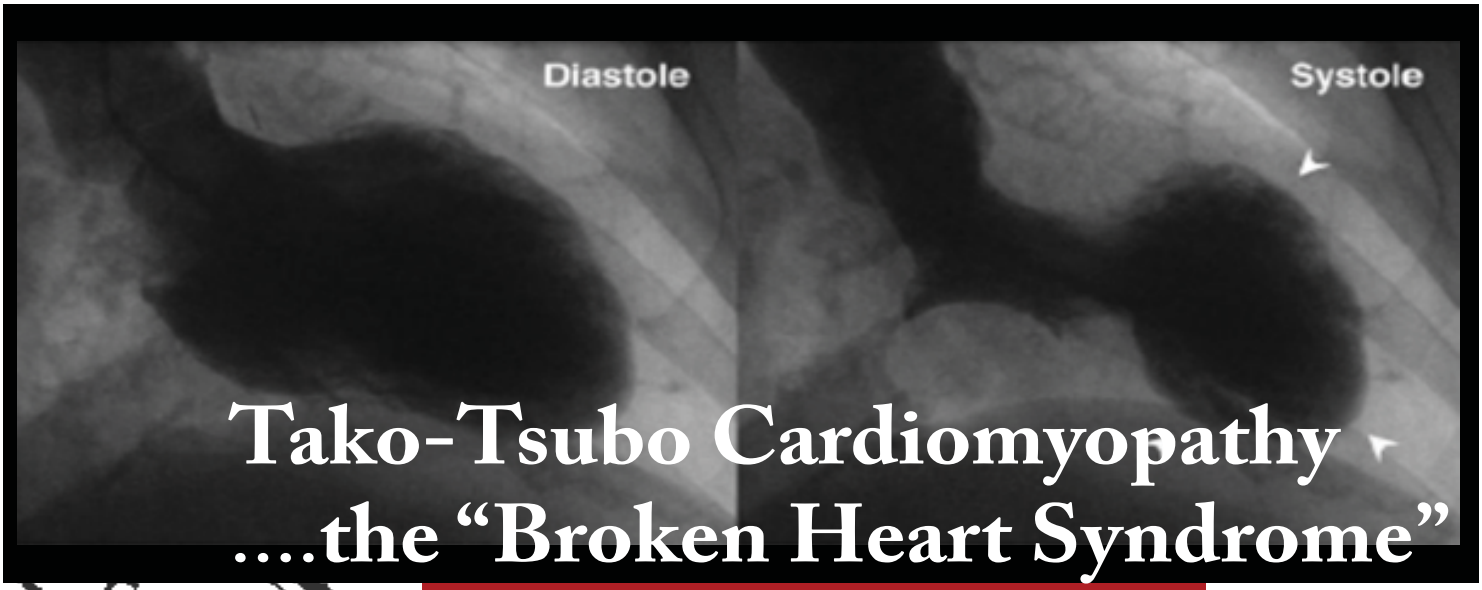
TSMJ
TRINITY STUDENT MEDICAL JOURNAL



Tako-Tsubo Cardiomyopathy ....the "Broken Heart Syndrome"

PLUS...

The Cervical Cancer Vaccine:
Protecting Young Girls Across Ireland

Adult Neurogenesis:
Hope or Hype?

Taming the Escalating Costs of
Ireland's Community Drugs
Schemes

Literature Reviews | Original Research | Case Reports | Interest Articles

The Trinity Student Medical Journal is intended to provide an inclusive vehicle for students to communicate current medical research, opinions and thoughts to other students, faculty members and faculty of affiliated hospitals and institutions. We publish articles relating to many aspects of medicine including scientific research and clinical experience. Articles are accepted from students in medicine and other related fields, as it is our view that medicine is the meeting point of any disciplines. The aim of the Journal is to provide a medium that is responsive to the rapidly changing face of contemporary medicine, and is able to grow and expand as rapidly as the subject.

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Abbreviations
TCD: Trinity College, Dublin
RCSI: The Royal College Of Surgeons, Ireland
UCC: University College, Cork
AMNCH: The Adelaide and Meath Hospital incorporating the National Children's Hospital
CWIUH: Coombe Women and Infants University Hospital

Letter from the Director

Dear Reader,

Welcome to the 2010 edition of the Trinity Student Medical Journal. It has been a busy year for the TSMJ team, with unprecedented numbers of submissions and a mini tour of the country spreading the word about the journal. I am proud to say that the result is a great edition of the TSMJ that I hope you enjoy reading as much as we enjoyed producing.

I want to thank the indefatigable committee; our editors for their many hours spent pouring over rough drafts, the sponsorship team for balancing the books, the conference coordinators for masterminding the launch, the production team for making the journal a reality and our predecessors for all their help and guidance.

This peer-reviewed medical journal is an indispensable outlet for the presentation of original research, academic review and personal opinion for Health Science students across Ireland and none of this would be possible without the generosity of our sponsors, patrons and advertisers. The Trinity College School of Medicine has been a constant support and as always St. James's Hospital, AMNCH, CWIUH and the TCMA have dug deep in their coffers to sponsor our annual scholarships and prizes. Yet again we have been humbled by the support of our consultants and GPs in what has proven to be a very financially challenging time globally.

With this continuing support the TSMJ has grown year on year and evolved from what was originally a publication for only Trinity medical students to an all-Ireland journal. We want the TSMJ to not only be an outlet for undergraduate writing but also a guide and an encouragement to students to get involved in original research.

Evidence based medicine and medical research are becoming more and more integral to all health science courses. We are committed to making the TSMJ, and research in general, more accessible to students. We continue to offer awards for Best Research and Best Article within the journal and also prizes for best Research Poster at our annual launch. This year, however, we have become a bit more proactive. The TSMJ Tercentenary Research Grant is a grant available to undergraduate medical students to fund a six week research project in a Trinity associated laboratory or clinical directorate.

"Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided." Paracelsus

This grant has been set up in the hope that it will provide a framework for other students approaching research in the future and we hope that we can continue to offer the grant in coming years.

The TSMJ is never happy to just sit on its laurels; the future will bring many challenges and opportunities for us but we hope to make the TSMJ bigger and better. As we proceed into our second decade of production we have come a long way and we hope that the hard work and dedication shows in this, our 11th TSMJ edition.

Best wishes,

Libby Ennis
Director 2010

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Trinity Student Medical Journal 2010

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Editorial

The world is in a perpetual state of flux. Each day, people's lives are affected in unimaginable ways by unpredictable events, from natural disasters to economic recession. Amidst this environment of uncertainty, one thing remains certain: our health is of central and utmost importance. In fact, some might say our health is synonymous with our wealth. Nevertheless, our health care systems are strongly impacted by economic and political developments. Over the past few years, the world has experienced a recession of historic proportions. Some countries are on the road to recovery while others have suffered more enduring consequences. Recessionary times have led to stringent budget cutbacks and new policies for the allocation of scarce resources, ultimately affecting the quality and provision of health care. This edition of the TSMJ explores the current economic reality in the context of the Irish health care system. For example, a review of recent trends in drug prescribing reveals Ireland's struggle to offer an effective system for delivering medications to those in need given a shrinking healthcare budget. Furthermore, this issue of the TSMJ raises the question whether the current focus on budgets and figures is impeding the successful delivery of high quality, personalized health care. One of our authors considers the potential risks of budget cuts for the mental health care sector while another author discusses the nearing extinction of the GP house call in rural Ireland and the transformation of GPs' offices into "mini hospitals".

In these times of economic hardship and instability, the fact remains that our health requires priority attention. As physicians, we cannot ignore the implications of recession on both our patients and our society as a whole. If ever there was a time to remind ourselves of the importance of the personal side of medicine, now is that time.

Likewise, in this climate of cutbacks and compromise, we must not forget the value and importance of medical research. Ongoing research facilitates advancements in medical knowledge, technology, diagnostics and therapeutics, which in turn allow us to deliver a system of health care that is efficient, high quality and responsive to our evolving world. The TSMJ promotes continuing medical education by offering students the unique opportunity to participate in and learn from the research process. Throughout this edition of the TSMJ, it is evident that current research is expanding our knowledge and changing our approaches to treatment. New concepts such as inducing hypothermia to treat cardiac arrest and the introduction of vaccines to prevent cervical cancer are reviewed in this edition. In addition, new insight into the treatment of hyponatraemia and trigeminal neuralgia are addressed and serve as a testament to the value of evidence-based research and lessons learned in the clinical context. Interesting developments in the complex areas of hippocampal neurogenesis, cardiac rehabilitation programs, and atopic disease illustrate the far reaching and diverse impacts that research has on our current and future health care systems.

As medical practitioners, we can do our part to ensure that the quality of health care is not compromised by investing time and energy in our professional development. Medical students are constantly taught and tested on the more common medical afflictions. While these conditions contribute to a vast majority of medical diagnoses, as future medical practitioners we must not overlook the weird and wonderful medical illnesses we may encounter. By committing to continual learning and staying abreast of research developments, we increase our ability to recognize new and rare conditions, often misdiagnosed as more classic conditions, thereby ensuring appropriate management. In this edition of the TSMJ, we explore the diagnosis and management of new and rare conditions such as congenital long QT syndrome, broken heart syndrome and eosinophilic oesophagitis.

Over the past decade, the TSMJ has expanded to include student works from all fields of health care and all of Ireland's medical schools. We received an overwhelming number of submissions this year, and we are proud and excited that the student community has demonstrated such a keen interest in the journal and in research as an entity. We thank all of this year's authors and editors for their hard work and commitment to the TSMJ. We extend our appreciation, as well, to all students who submitted articles and we encourage and welcome your submissions to future publications. We hope that, as medical students and future physicians, you will strive to question what you hear, validate what you learn and consecrate your knowledge through evidence-based research.

Samara Kraus and Erin Hanley
Co-Chief Editors

LITERATURE REVIEW

Best Article

Taming the escalating costs of Ireland's community drugs schemes

Duncan Fortescue-Webb (*Third Year Medicine, TCD*)

CLINICAL POINTS

- The Community Drugs Schemes provide prescription drugs to patients through community pharmacies, and cost €1.9 billion in 2008.
- Minister Harney has recently implemented legislation to reduce the cost of the Community Drugs Schemes by reducing payments to drugs manufacturers, wholesalers and pharmacists; and requiring patient co-payments for all prescriptions dispensed.
- Future legislative reform is likely to include introduction of reference pricing, pharmacist-led substitution, renegotiation of prices with manufacturers, and disinvestment of ineffective drugs.
- Prescriber initiatives to reduce drugs expenditure can significantly ease the healthcare budget and forestall cutbacks to services.
- Generic prescribing continues to have an important role in improving patient safety and reducing drugs costs.
- Prescriber comparison of the prices of competing drugs and brands for the same indication can improve cost-effective prescribing.
- One third of prescriptions for the over 70s contain potentially inappropriate items. The most frequent include: PPIs at full therapeutic strength for over 8 weeks, NSAIDs for over 3 months, long-acting benzodiazepines for over 1 month, and duplicate drugs.
- Use of antibiotics to treat illnesses that are not likely to be bacterial is ineffective, causes adverse effects in one fifth of patients, and leads to antimicrobial resistance.

ABSTRACT

A reduced public budget has increased pressure to improve the efficiency of healthcare provision in Ireland. Legislative changes to reduce margins throughout the drugs supply chain and increase patient co-payments have recently been implemented. The background and implications of these changes are considered for manufacturers, wholesalers, pharmacists, patients and the public purse. Together, the changes are predicted to reduce the cost of providing drugs in the community in 2010 by nearly €270 million (11% of the projected €2.4 billion they would otherwise cost). However, underlying growth trends in drugs expenditure, particularly in the burgeoning high-tech drugs market, mean that although recent changes should contain the cost of drugs in 2010 at a level similar to 2009, annual growth of 12% is likely to resume thereafter unless additional reform is implemented. Slated future legislative changes that could be worth a further €200 million or more annually include: reference pricing, pharmacist-led substitution, renegotiation of manufacturer prices, and disinvestment of non-cost-effective drugs from public schemes. Finally, ways to improve prescriber habits are considered that could save an additional €100 million annually. These include periodic and critical reviews of patient prescriptions, more judicious use of antibiotics, generic prescribing, prescriber awareness of drug prices, and provision of prescribing software.

INTRODUCTION

Health accounted for 27% of Ireland's total public current expenditure in 2008 and, therefore, is of central importance in any strategy to ease the public budget[1]. The Health Service Executive (HSE) provides most public healthcare and had a budget of over €14 billion in 2008[2]. €1.9 billion of this was spent on prescription drugs supplied through pharmacies via the Community Drugs Schemes[3]. The cost of these schemes has been growing lately by about 12% each year[3,4] (Figure 1), and quintupled during the last decade because of changing demographics, the introduction of expensive new therapies, and a bloated supply chain. The rate of increase is among the highest in Europe[5] and the burden on public finances has come under increasing criticism. Mary Harney, Minister for Health and Children, recently implemented cost-containment measures to reduce payments to manufacturers, wholesalers and pharmacists, and to increase patient co-payments. This paper will examine the background and effects of these changes, the potential for further cost-control legislation, and the role of prescribers in the development of an efficient drugs supply system.

OVERVIEW OF DRUG DEVELOPMENT AND SUPPLY IN IRELAND

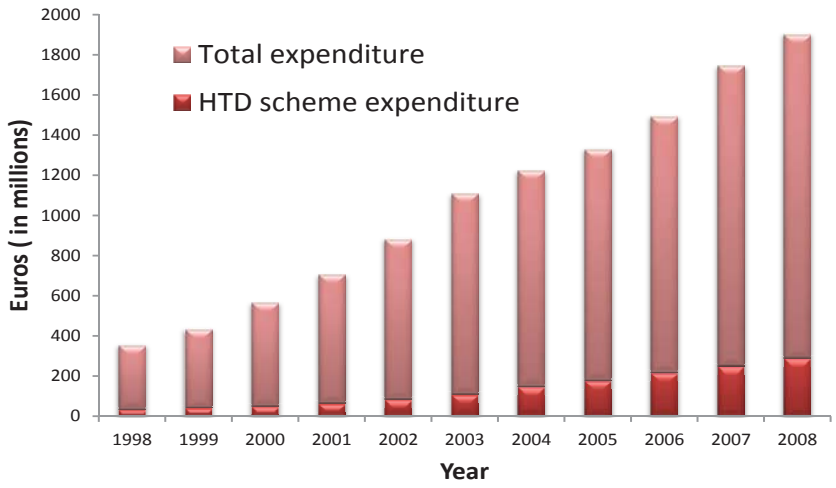
Drug research and manufacturing produces over half of Ireland's exports, employs about 24,500 people directly, and contributes over €1 billion in corporation tax[6]: it naturally also enjoys considerable political clout. To bring a new drug to market can take a research-based manufacturer upward of a decade and cost as much as €1 billion[7]. Once

chemical entities with promising biological activity are identified they must be assessed for safety, toxicity, pharmacokinetics, metabolism and efficacy via a series of in vitro, animal and human clinical trials. The vast majority of potential drugs fail. A twenty year patent is commonly granted to the originator company once a promising chemical entity has been identified. This patent typically lasts 8-12 years beyond the time required to bring the drug to market[7] and gives the company exclusive rights to manufacture and supply the drug. When the patent expires, generic competitors may enter the market.

Every drug has an International Nonproprietary Name (INN) granted by the World Health Organisation (WHO). The INN reflects the therapeutic mechanism of the drug and is used to refer unambiguously to a specific chemical entity (e.g. omeprazole). In addition, the originator company chooses one or more brand names under which to market the drug (e.g. Losec). When the patent expires other manufacturers may also market the same drug under generic brands (e.g. BySec, Lopraz, Losamel, Ulcid) or the INN. These generic manufacturers incur relatively low development and regulatory costs, and typically sell the drugs at a lower price than the originator company.

Once a drug has been approved for sale in Ireland, the HSE negotiates an ex-factory price with the manufacturer based on the average price in nine European countries[8]. The manufacturer sells the drug to wholesalers, who add a mark-up and sell it on to pharmacists and hospitals. Pharmacists then dispense the drug, adding any applicable mark-up and fees. A prescription that specifies a brand of drug cannot be dispensed as another brand, but a generic prescription (where only the INN is used) can be dispensed as any available brand. About 85% of all community prescription drugs are paid for by the HSE through the Community Drugs Schemes[9]; the remainder is paid for by patients.

There are four major Community Drugs Schemes in Ireland providing prescription drugs through pharmacies. The largest Community Drugs Scheme is the means-tested General Medical Scheme (GMS) which provides drugs to medical card holders for 50c an item. The Long-Term Illness scheme (LTI) provides drugs to treat any of fifteen chronic conditions (e.g. cystic fibrosis, epilepsy, diabetes) for 50c an item. Together, the GMS and LTI cover approximately one third of the population and account for two thirds of expenditure[3] (Figure 2). The Drugs Payments Scheme (DPS) is available to all residents and limits the drugs cost to a €120 co-payment per family per month. Finally, the High Tech Drugs scheme (HTD) provides certain high-price drugs such as chemotherapy adjuncts and biologic agents that would otherwise be provided primarily in hospitals, with patient co-payment dependant on eligibility under the GMS, LTI or DPS schemes. The HTD is the most rapidly expanding scheme, with costs increasing between 2004 and 2008 by 18% a year (Figure 1) (HTD historic cost data from M Barry; personal communication, 16 February 2010)[10,11,12].



▲ **Figure 1.** Expenditure under the Community Drugs Schemes, 1998-2008

Minister Harney has sought ways to control drugs costs while still encouraging future drug innovation and ensuring continuity of supply to patients. To achieve this she has recently undertaken extensive renegotiation of the agreements that govern costs throughout the drugs supply chain.

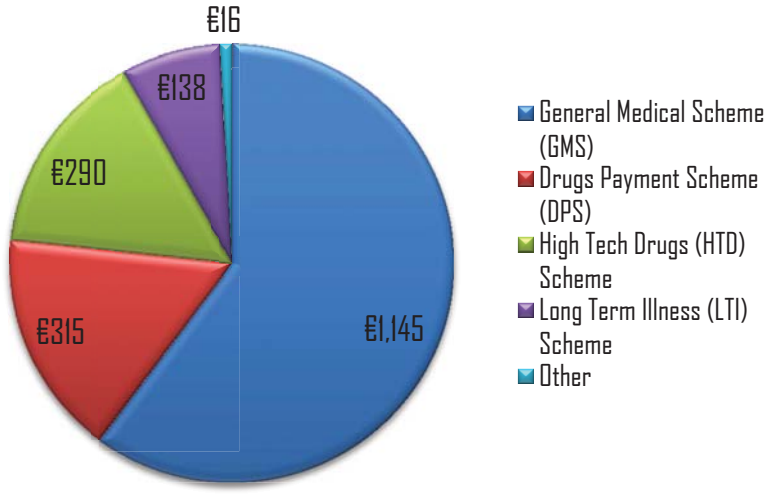
Recent legislative changes affecting the Community Drugs Schemes

In order to conserve scarce resources for home support and acute hospital activities, Minister Harney implemented several measures in 2009 and 2010 to reduce public costs throughout the drugs supply chain. The groups targeted to achieve this reduction include manufacturers, wholesalers, pharmacists and patients.

Since 2006, under the IPHA/HSE Agreement, when a drug's patent expires and a generic competitor enters the market, the price is reduced immediately by 20% and then by another 15% of the original price 22 months later[13]. The Irish Pharmaceutical Healthcare Association (IPHA) of research-based manufacturers have now agreed to reduce prices of nearly 300 off-patent drugs by a further 40% from February 2010[14], leaving these drugs at least 61% below their previous on-

patent price. Prior to February 2010, original branded drugs typically cost 10% more than their generic competitors[15]. Now, however, Ireland is in a unique situation with many well known proprietary brands of drugs from IPHA manufacturers costing about 30% less than equivalents from competing generic manufacturers.

In addition, IPHA manufacturers are required from February 2010 to pay the HSE a rebate of 4% of the ex-factory price for all other drugs sold under any of the Community Drugs Schemes. Previously a 3.53% rebate applied under only the GMS. Together, the 40% price reduction and the increased rebate are expected to save €94 million per year[14].



▲ **Figure 2. Expenditure by Community Drugs Scheme (in millions of Euros), 2008**

Legislative changes to wholesale and pharmacist mark-ups and fees were implemented in July 2009 to contribute to cost reduction. The wholesale mark-up has been reduced from 17.66% to 10%, which brings the price paid for delivery of drugs to pharmacies back towards the European average of 8%[16]. Previously about half of the wholesale mark-up was being passed from wholesalers to pharmacists as discounts[17]. The pharmacist mark-up applicable under the DPS and LTI schemes has also been reduced from 50% to 20%. Furthermore, the previous standard dispensing fee structures under the GMS, LTI and DPS (to cover miscellaneous costs such as spoilage and repackaging) have been replaced with a more generous single sliding scale: €5 for the first 1667 items dispensed by a pharmacy per month, €4.50 for the next 833, and €3.50 for any remaining items[18]. The standard patient care fee of €60.52 per month paid to pharmacists under the HTD scheme is unaffected. These changes in payments to wholesalers and pharmacists should save €141 million per year.

Finally, the maximum patient co-payment under the DPS has been increased by 20% to €120 per family per month from January 2010. Patient co-payments of 50c per item (capped at €10 per family per month) have also been introduced under the GMS and LTI schemes from April 2010. These co-payments should save €52 million per year[1].

Without intervention, the 12% per year growth trend of the Community Drugs Schemes would have brought their cost to about €2.4 billion in 2010. Altogether, the above measures recently introduced by Minister Harney are predicted to reduce the 2010 Community Drugs Schemes cost by €270 million (about 11%), minimising any cost increase over 2009.

Effects of recent legislative changes

Minister Harney's recent legislative changes will promote efficient healthcare and bring long term cost benefits. However, the disruption as the drugs market adjusts to these changes is likely to bring many indirect consequences which will erode the cost savings.

Minister Harney's recent changes will reduce revenues of IPHA drug manufacturers through the implementation of the 40% price reduction on 300 off-patent drugs and the 4% rebate for all other drugs. However, these manufacturers have secured two significant concessions by agreeing to reduce prices six months before their existing contracts were due to expire in September 2010. Firstly, renegotiation of prices for on-patent drugs (which account for about 75% of drug expenditure[19]) has been deferred 18 months until February 2012, protecting the largest part of the manufacturers' revenues from any further reduction. Secondly, the 40% price reduction will not automatically apply to drugs whose patents expire after January 2010[20]. Several blockbuster drugs will come off patent in 2011 including: atorvastatin (Lipitor) which cost €94 million in 2008, clopidogrel (Plavix) which cost €24 million, and olanzapine (Zyprexa) which cost €23 million[3]. Revenues from these drugs will therefore remain relatively high even once the patents expire and generic competitors can enter the market. These two concessions mean IPHA manufacturers will be able to maintain revenues from their most lucrative drugs for longer, offsetting the price reductions for their off-patent drugs and the increased rebate, and thereby diminishing the true savings to the Community Drugs Schemes.

However, non-IPHA generic manufacturers declined to match the IPHA 40% price reduction and 4% rebate. Their prices are now less competitive compared to IPHA manufacturers', and they risk losing significant market share. Many generic manufacturers may find that it is no longer profitable to operate within the Irish market and may cease operations in Ireland entirely, with adverse implications for employment and long-term competition. Additionally, the 2006 IPHA/HSE Agreement triggers a phased 35% price reduction when a drug comes off-patent only if a generic competitor enters the market. If fewer generic manufacturers operate in Ireland it is likely there will be a longer delay between patent expiration and generic entry, allowing IPHA manufacturers to maintain market dominance and high prices for their drugs that come off-patent.

The recent changes are also expected to bring wholesaler and pharmacist dispensing revenues down by about 30%[17], encouraging competition and efficiency. Between 2004 and 2010, the number of pharmacies in Ireland increased by 28% to 1705[21,22]. This boom is unsustainable in the face of such severe revenue cuts and the general economic downturn. Already many pharmacies are running at a loss, several have closed, and the Independent Pharmacy Ownership Scheme (which had minority holdings in nearly 150 pharmacies) has gone into liquidation[23]. There is a risk that patient access to services will be hindered if pharmacies in rural or deprived areas close. A further problem is that the Community Drugs Schemes provide a perverse incentive to pharmacists and wholesalers to fill generic prescriptions with the most expensive available drug in order to maximise their mark-up. With many pharmacies and wholesalers in financial difficulty it is likely some will resort to preferentially supplying more expensive brands, inflating the costs of the Community Drugs Schemes. Parallel imports, where pharmacists and wholesalers source drugs more cheaply from wholesalers abroad, allow greater profit margins and are likely to increase, bringing the hazard that counterfeit drugs may more easily enter the supply chain.

Changes to patient co-payments are intended both to raise revenue and to discourage unnecessary drug use by influencing prescriber and patient habits. However, the system of patient co-payments has two major flaws. Firstly, increased patient co-payments will cause some price-sensitive patients to reduce their consumption of drugs that have significant clinical merit for chronic conditions such as cardiovascular disease[24]. Reduced consumption will hinder disease management programmes, increase acute hospital admissions, and add to HSE running costs. Secondly, although the co-payments may ease the Community Drugs Schemes budget, they merely shift the costs onto patients. Therefore the overall proportion of the nation's wealth that is spent on drugs is not reduced, and so no net resources are freed for use elsewhere. Future reform should aim to reduce total drug expenditure across both public and private sectors.

Altogether, Minister Harney's recent reforms are intended to reduce the projected €2.4 billion cost of the Community Drugs Schemes in 2010 by €270 million. Assuming that market adjustments do not erode these savings significantly, this will be sufficient to restrain overall drug expenditure near 2009 levels during 2010. However, unless long-term strategies are developed to improve both price competition within the drugs market and prescribing habits, underlying growth trends of 12% per year will then resume. An emerging issue is the HTD scheme, which cost €290 million and accounted for 15% of the Community Drugs Schemes expenditure in 2008. Recent reforms fail to address the cost of the scheme beyond imposing a 4% rebate on the ex-factory price of these drugs, worth €14 million in 2010[3,18]. The cost of the HTD scheme has been increasing by 18% per year between 2004 and 2008, far more than the 11% increase of the other schemes (Figure 1). If this growth rate continues unchecked, the HTD scheme expenditure will approach €900 million in 2015.

Long-term control of the costs of the Community Drugs Schemes without compromising patient care requires ongoing reform from both legislators and prescribers. Several strategies to further reduce drug expenditure are available. Future legislative reform offers the chance to address some of the current shortcomings in current drugs market legislation as well as to implement entirely new initiatives. Educational efforts to improve the cost-effectiveness of prescribing while improving patient care could begin immediately but are likely to be relatively slow to show results.

Future legislative changes to the Community Drugs Schemes

Four major changes expected for the Community Drugs Schemes are reference pricing, pharmacist-led drug substitution, renegotiation of drug prices with manufacturers, and disinvestment of selected drugs.

Introduction of a reference pricing system has been proposed for 2011[11]. Under this system, a maximum reimbursement price would be agreed for groups of interchangeable drugs with the same active ingredient. For example, whether omeprazole is dispensed as the original brand, Losec, or as one of many available generic versions, the HSE will only reimburse at the stated reference price based on the cheapest alternative. If the patient insists on a more expensive branded product without medical justification, he must pay the price difference from his own pocket[25]. Reference pricing is an effective way to legislate for reduced drug expenditure without compromising prescriber autonomy or patient care[26], and is already in place in eighteen European countries.

Also proposed for 2011[11], obligatory pharmacist-led substitution would complement reference pricing by requiring that the cheapest available version of a drug be dispensed regardless of any brand specified on the prescription, unless the prescriber insists otherwise. There are situations when continuity of the same brand may be important and substitution is inappropriate. If the drug has a narrow therapeutic index between efficacy and toxicity, then small potential differences in bioavailability mean that continuity of a single brand for a patient may be important (e.g. ciclosporin, lithium). Also potentially unsuitable for substitution are medicines with modified release preparations, multiple ingredients, different administrative devices (e.g. between brands of inhalers or pre-filled syringes), different preparations with different indications, and products of biological origin[27].

Irish drug prices are about 20% above the European average[28], indicating that substantial savings are achievable through renegotiation of prices with manufacturers. Renegotiation with non-IPHA generic manufacturers will take effect in September 2010 when the current contract expires. Renegotiation for on-patent drugs has been deferred 18 months until February 2012. Drugs which are on-patent or lack generic competitors make up about 75% of the cost of the Community Drugs Schemes[19], meaning that even a modest 5% price reduction would save in the region of €100 million per year from 2012.

To reduce drugs costs further, certain drugs that have not been shown to be cost-effective should be disinvested from the Community Drugs Schemes. In 2008, €52 million was spent on clinical nutritional products[3] that have not been shown to bring long-term benefit in the community setting, and half of which are not consumed[29]. Over €5 million was spent on glucosamine for osteoarthritis without good evidence of benefit[3]. Disinvested products could remain available over the counter at the patient's expense.

A guiding principle for future legislation should be to simplify the supply and reimbursement of drugs. This would improve market transparency and competition, reduce perverse incentives, and lower administrative costs.

Prescriber initiatives to reduce drugs costs

Changes in prescriber habits could effect far-reaching improvements in healthcare efficiency without compromising patient care or requiring further legislation. Rational prescribing aims to use drugs most effectively while minimising risks and unnecessary costs, and is essential to efficient healthcare. Examples of rational prescribing habits include periodic and critical review of the drugs taken by every patient, judicious antibiotic use, generic prescribing, and cost-aware prescribing. To help improve rational prescribing habits, specialist prescribing software could be provided to GP surgeries and hospitals to automatically assess the quality of prescriptions.

Periodic and critical review of the drugs prescribed to every patient could reduce unnecessary expense, adverse drug effects, drug interactions and wastage. Over a third of prescriptions for those over age 70 have been shown to be potentially inappropriate, costing €46 million in 2007: 9% of the total drug expenditure for that age group. The main contributors to this include: proton pump inhibitors (PPIs) prescribed at full therapeutic dose for more than eight weeks, non-steroidal anti-inflammatory drugs (NSAIDs) prescribed for more than three months, long-acting benzodiazepines prescribed for more than one month, and duplicate drugs on the same prescription claim[30].

Ireland has been among the least successful of European countries at reducing unnecessary antibiotic use[31]. Prescribers often feel pressured to provide antibiotics even for viral infections such as colds and flu where they offer no benefit[32]. Unnecessary antibiotic use wastes about €41 million a year and leads to adverse drug effects for one fifth of patients[33].

It also threatens the health of the wider community by encouraging antimicrobial resistance, which leads to the increased morbidity, increased fatality and prolonged epidemics seen with multidrug-resistant Staphylococcus aureus (MRSA), Streptococcus pneumoniae and Haemophilus influenzae[34]. Redoubled education campaigns such as the European Antibiotic Awareness Day are required to change patient expectations and prescriber habits.

Generic prescribing, where drugs are specified by their INN, is usually seen as a key strategy to improve patient safety by avoiding potential prescriber, pharmacist and patient confusion over the diverse brand names that exist for the same drug. Fewer mistakes translate into fewer adverse drug reactions, better patient outcomes and reduced healthcare costs. Generic prescribing also has potential to reduce drugs costs (without waiting for reference pricing or pharmacist-led substitution to be legislated) by allowing the cheapest equivalent alternative brand of a drug to be dispensed. This in turn encourages price competition between manufacturers. In England nearly two-thirds of prescription items are dispensed generically[35], contrasting with less than one fifth here[4]. The low rate seen in the Irish system is driven by the marketing of branded drugs to prescribers, public perception that generic drugs are inferior, and prohibition of pharmacist-led generic substitution for branded prescriptions. The IPHA 40% price reduction for 300 off-patent drugs has temporarily created an anomalous situation in Ireland where many well-known branded drugs cost considerably less than their generic equivalents from non-IPHA manufacturers. This anomaly

will not persist if reference pricing and pharmacist-led substitution are introduced in 2011, or if non-IPHA generic manufacturers agree to reduce their prices from September 2010. Meanwhile, prescribers can maintain patient safety and ensure their patients receive the cheapest version of a drug by checking prices in an up-to-date Monthly Index of Medical Specialties (MIMS) and specifying both the least expensive brand and the INN on the prescription e.g. "BySec (omeprazole) 20 mg". However, if the pharmacist is out of stock of a particular brand of a drug, then specifying that brand on a patient's prescription may lead to a delay in dispensing while supplies are delivered.

Additionally, prescribers should be aware that competing drugs for a given indication may have very similar efficacy and safety, yet very different prices. For example, there may not be any medical reason to prefer a particular PPI over another for a patient with dyspepsia. Yet, despite evidence that esomeprazole (Nexium) and omeprazole are equally effective for most patients[36], the ex-factory price of Nexium is double that of the cheapest omeprazole because it is still on-patent. Nexium cost €37 million in 2008[3]. As Thomas Scully said while Administrator of the Centers for Medicare and Medicaid Services in the US: "You should be embarrassed if you prescribe Nexium," because it increases costs with no medical benefits[37].

Drug prices can also vary considerably between hospital and community settings. Hospital prescribers initiate over a third of GMS prescriptions, at a median cost 70% greater than those initiated by general practitioners[4]. In part, this reflects the differing morbidities of patients seen in hospital and by GPs. Also, however, hospitals are often offered discounts on certain drugs, which lead to these drugs' continued prescription in the community after discharge despite their community cost being significantly higher than competing drugs for the same indication. Hospital prescribing guidelines should be amended to reflect costs both to the hospital and to the Community Drugs Schemes[4].

These suggested changes to prescriber habits will require an ongoing investment in the education of prescribers and patients about best practices. Provision of prescribing software to general practitioners and in hospitals would facilitate analysis and feedback in relation to quality prescribing indicators such as dose, duration, potential drug-drug and drug-disease interactions, and generic prescribing rates[4]. If such software is able to save prescribers time, improve the quality of their prescribing, and prevent drug errors that harm patients and lead to lawsuits: it is likely to be received enthusiastically.

> **"You should be embarrassed if you prescribe Nexium, because you're screwing your patients and you're screwing the taxpayers."**

Prescribers control patient access to prescription drugs and therefore have a responsibility to ensure that they prescribe effectively based on best evidence and up-to-date cost data. Efforts to improve rational prescribing such as periodic patient drug reviews, more judicious antibiotic use, generic prescribing, and cost aware prescribing all offer improved patient care and more efficient drug use. This in turn will reduce the costs of healthcare.

THE OVERALL FINANCIAL EFFECT OF RECENT AND PROPOSED CHANGES

The cost savings from these recent and proposed changes are not trivially additive; ways to erode the savings will be found by those whose incomes are affected, investment will be required for reform, there will be knock-on effects throughout the supply chain, and secondary effects such as reduced antibiotic-resistant infections will alter healthcare requirements. However, simple summation does indicate something of the magnitude of savings available. Minister Harney's recent changes could save €270 million in 2010. Future introduction of reference pricing, pharmacist-led substitution, renegotiation of on-patent and generic drug prices, and disinvestment of ineffective drugs could save over €200 million more. Prescriber initiatives such as periodic prescription reviews, more judicious prescribing of antibiotics, generic prescribing, cost-aware prescribing and amended hospital prescribing guidelines offer another €100 million per year.

Minister Harney's recent reforms should be sufficient to restrain overall drug expenditure at 2009 levels during 2010 but, unless long-term strategies are developed to improve both prescribing habits and price competition within the drugs market, underlying growth trends will then reassert and growth of 12% per year will resume.

The magnitude of available savings still available for the Community Drugs Schemes indicates the significant direct benefit of renewed efforts to reduce drugs costs. The secondary benefits from resource reallocation, reduced drug-resistant infection and improved health that these policies could bring are difficult to quantify, but are perhaps even more valuable.

CONCLUSION

Public budget cuts provide an impetus to legislators and prescribers to overhaul the provision of healthcare. Efforts to improve the efficiency of the drugs supply in Ireland can both save public money and improve patient care. Recent changes to the Community Drugs Schemes are a generally promising first step, but the need remains for further legislation and improved prescriber habits. Future policy debate is likely to be dominated by how to encourage price competition within the drugs market and how to address the rapidly growing costs of novel biologic products. Ireland can afford to maintain one of the best healthcare systems in the world; what we can no longer afford is to run the system inefficiently.

ACKNOWLEDGMENTS

I am grateful for the guidance and enthusiasm of the staff of the National Centre for Pharmacoeconomics, particularly Dr Michael Barry, Senior Lecturer in Pharmacology and Pharmacoeconomics at TCD; and for the financial support of the Haughton Institute which enabled the background research on which this review depended.

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ORIGINAL RESEARCH

Atopy and HIV: Do basophils play a role in both?

Investigating basophil counts and activation marker expression in different disease states

Sara Naimimohasses *(Fourth Year Medicine, TCD)*

Clinical Points

- HIV positive patients had statistically significant lower absolute basophil counts and higher levels of CD63 expression *in vivo* compared to healthy controls.
- Absolute basophil counts in the eczema, asthma and allergy patient groups did not statistically differ from the healthy controls.
- There was no statistically significant variation in basophil CD63 expression in the eczema, allergy and asthma patient groups in comparison with healthy controls.
- This study is one of the first to compare absolute basophil counts alongside *in vivo* CD63 expression. The majority of other studies have focused on CD63 expression following allergen challenge *in vitro*.
- Future research directives may focus on the role of basophils in different stages of HIV infection.

Abstract

Background: Recent experimental evidence has implicated a role for basophils in allergic diseases. Basophils are also believed to be stimulated in HIV-1 infection by the glycoprotein expressed on the surface of the viral envelope, gp120, and directly through viral interaction with the chemokine receptor CCR3.

Objectives: To investigate absolute basophil counts and peripheral blood basophil surface marker expression in healthy individuals, patients with atopic diseases and HIV positive patients.

Methods: Blood was taken from a total of 68 patients: 17 healthy adult volunteers, 18 patients diagnosed with asthma, four patients with eczema, 14 patients with a suggestive history of allergy and 15 HIV positive patients. The samples were stained with anti-CD123, anti-HLA-DR and anti-CD63 antibodies. A double gating strategy was used to isolate the basophil population and analyse CD63 expression.

Results: No significant difference was found between the absolute basophil count in patients with asthma ($p=0.402$) and eczema ($p=0.947$) compared to the healthy volunteers. HIV positive patients ($p=0.007$) and allergic patients ($p=0.022$) had statistically significant lower basophil counts compared to healthy controls. No significant difference was found in the level of CD63 expression in asthma patients ($p=0.521$), eczema patients ($p=0.288$) and patients with allergies ($p=0.346$). HIV positive patients expressed significantly higher levels of CD63 compared to healthy volunteers ($p=0.005$).

Conclusion: There was a significant reduction in absolute basophil counts in patients with HIV, which may be due to the virus directly infecting basophils, reducing their $T_{1/2}$ in circulation. The reduction in basophil count seen in allergic patients could be explained by allergen-induced migration. Basophils from HIV positive individuals expressed significantly higher levels of CD63, possibly owing to the allergen-like function of HIV gp120. There was no evidence to suggest patients with atopic diseases expressed higher levels of CD63.

Introduction

Over the past few decades there has been a progressive increase in the incidence of atopic diseases. More than 20% of the world population is affected by IgE-mediated allergic diseases, with an estimated 300 million people alone suffering from allergic asthma[1,21,31].

The central pathophysiology behind allergic diseases is believed to be an imbalance in the expression of two $CD4^+$ T lymphocyte subsets: Th1 and Th2. Th1 lymphocytes secrete IL-2, IFN-α and TNF-β, which activate macrophages and are involved in stimulating cell-mediated immunity whilst simultaneously inhibiting humoral immunity. Th2 lymphocytes secrete IL-4 and IL-13 and are involved in activating the humoral immune response by promoting B cell proliferation and heavy chain class switching, stimulating allergen-specific IgE production. It has been hypothesised that abnormal polarization of the immune system from an early age leading to an increased Th2:Th1 ratio could result in an atopic phenotype[14,40].

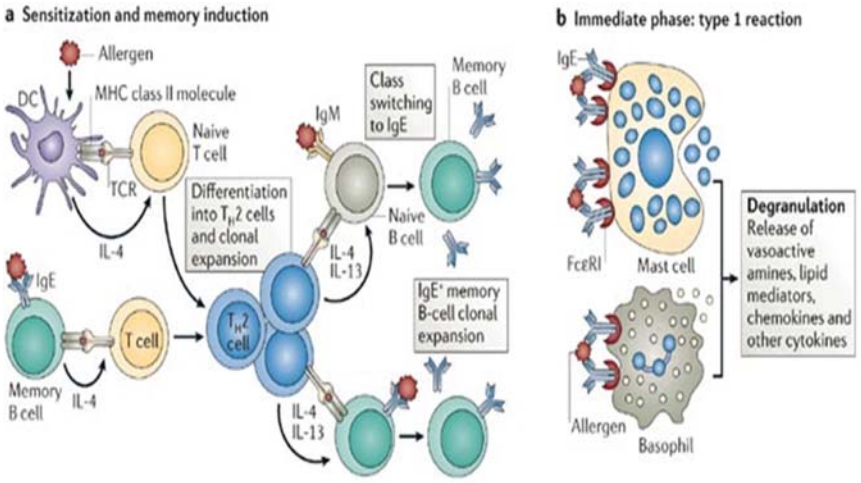
IgE-mediated hypersensitivity is thought to be triggered by a sequence of events following initial allergen exposure. Specialised antigen presenting cells, such as macrophages and dendritic cells, process and present allergens via cell surface MHC class II molecules to allergen-specific Th2 cells. This activates allergen-specific Th2 cells, causing them to release IL-4 and IL-13. The secretion of IL-4 and IL-13, combined with T cell CD40 ligand-CD40 receptor interaction, facilitates B cell proliferation, differentiation and heavy-chain isotype class switching to the IgE subtype. The activated B cells

produce and secrete allergen-specific IgE antibodies, which bind to FCεRI receptors on basophils and mast cells. Subsequent allergen exposure cross-links the IgE molecules and leads to activation, basophil degranulation, the release of vasoactive amines and lipid mediators and the synthesis of cytokines[17, 21, 22, 26](Figure 1). These mediators stimulate vasodilatation, increase vascular permeability, activate the complement cascade and cause migration of neutrophils, mast cells and basophils. This leads to the clinical manifestation of allergic diseases such as urticaria, angioedema and anaphylaxis.

Recent experimental evidence has demonstrated the pathogenic role of basophils in IgE-mediated hypersensitivity[8,10,12,14,17,20]. Basophils have been found in bronchial biopsies from asthmatic patients, in nasal lavage fluids following allergen provocation in patients with allergic rhinitis and in skin biopsies from patients with atopic dermatitis[14,30,37].

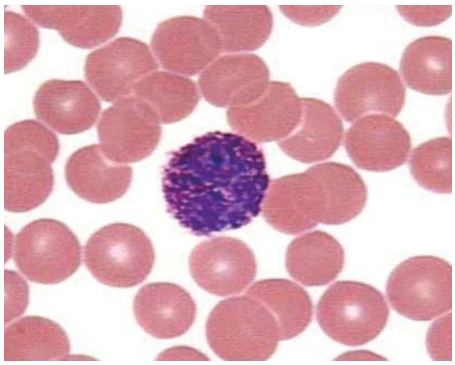
Basophils are small, circulating leukocytes with cytoplasmic granules that stain metachromatically with basic dyes (Figure 2)[32]. They constitute less than 0.2% of peripheral blood leukocytes and are only recruited in peripheral tissue in disease states[3,6]. They are derived from $CD34^+$ haematopoietic progenitor cells, which differentiate and mature in the bone marrow in the presence of IL-3, and have a lifespan of several days[12,13,19].

The cellular source of the early peak in IL-4 responsible for triggering the Th2-type immune response has been the subject of much debate; however, basophils have recently been identified as the main source of the cytokine. IL-4 stimulates the differentiation of naïve $CD4^+$ T cells to the Th2 type; basophils are consequently thought to act



▲ **Figure 1.** A, Allergen induces the humorally-mediated immune response and produces Th2 cells, which in turn encourage B cells to secrete IgE antibodies. B, Allergen activates mast cells and basophils, causing degranulation of substances that cause the clinical features of allergic disorders[47]. Taken from Nature Review Immunology.

as modulators of the immune response. Following activation, they release large quantities of the pro-inflammatory mediators histamine and leukotriene C4 and rapidly synthesise the Th2-type cytokines IL-4 and IL-13[3,6,12,16]. Release of these cytokines combined with T-cell -CD40 ligand interaction promotes B cell proliferation and heavy chain

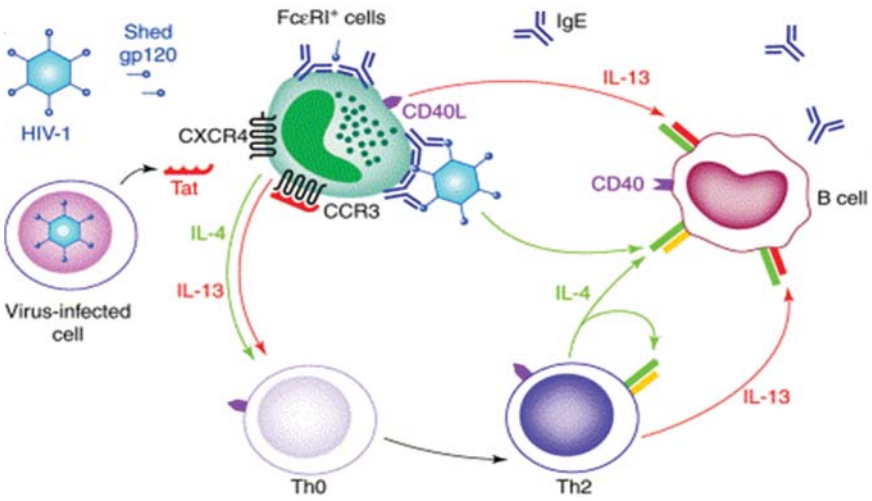


▲ **Figure 2.** Peripheral blood film showing basophil in centre, which stains blue due to the negatively charged cytoplasmic granules[44].

isotype switching to the IgE and IgG4 subtypes. The cytokines also play an important role in leukocyte recruitment to affected tissues by increasing expression of the cell adhesion molecule VCAM-1 in endothelial cells and synthesis of the chemokine eotaxin[3, 6, 15, 27].

What is the link between HIV infection and allergic diseases? Although there is no direct relationship between the two, studies have shown that HIV-1 infection may influence the behaviour of basophils by polarising the host immune response to be humorally-mediated[24,25].This may explain why HIV positive patients demonstrate increased prevalence and severity of allergic reactions[33, 36].

Previous studies on HIV-1 pathogenesis showed a shift to the Th2-type immune response, an increase in serum IgE levels and increased IL-4 and IL-13 in patients' lymph nodes. This indicates a possible allergen-like function executed by HIV-1[24, 25, 33]. The basophil chemokine receptor CCR3 also serves as a co-receptor through which HIV-1 particle can directly infect the basophil[28]. Further investigation has revealed that the HIV-1 glycoprotein gp120 contains a superantigen domain, which binds to the VH3 region of VH3+ IgE molecules bound to the FCεRI on basophils and mast cells. This gp120 - VH3 domain interaction resembles that of an allergen,



▲ **Figure 3. FCεRI positive cells express CCR3 and CXCR4 which act as co-receptors for specific strains of HIV-1 can serve as direct routes for HIV-1 infection. Shed or bound viral gp 120 also binds to the VH3+ domain of surface bound IgE molecules, stimulating the release of IL-4 and IL-13. The viral protein Tat functions as a virokine through its interaction with the chemokine receptor, CCR3 on FCεRI positive cells, stimulating the migration of basophils and mast cells to the site of HIV-1 infection[45].**

stimulating the basophil and leading to degranulation. This is an important mechanism by which the virus modulates the immune response to the Th2-type, inhibiting the host's adaptive cell-mediated immunity vital in killing HIV infected cells, whilst simultaneously increasing the pool of cells susceptible to infection[23,25,28].

Another product of the HIV-1 virus, Tat protein, increases the accessibility of basophils and mast cells by acting as a virokine[33]. Tat protein is released by HIV-1 infected cells and stimulates the migration of basophils and mast cells to the site of HIV-1 infection through its interaction with the chemokine receptor CCR3 expressed on the surface of basophils. In addition, Tat stimulates the up-regulation of CCR3 receptors, further facilitating HIV-1 infection of FCεRI positive cells[33,34](Figure 3).

How can the peripheral basophil population and activation marker expression be analyzed? Basophils can be identified by labelling the cells with antibodies conjugated with fluorochromes. Laser light excites the fluorochromes and this causes them to emit light at a specific wavelength. The cells themselves also scatter light according to their size and cytoplasmic complexity. The light emitted and scattered is then detected by photomultipliers and is processed by the computer enabling specific cell populations to be analyzed through a variety of different parameters.

Basophils constitutively express high levels of the IL-3 receptor α chain, CD123. CD123 is a member of the type 1 cytokine receptor family with a single transmembrane-spanning segment. It is a low affinity IL-3 receptor and its stimulation encourages cell proliferation and differentiation. This receptor is also expressed on CD34+ cells, monocytes, neutrophils and plasmacytoid dendritic cells. The use of monoclonal antibodies against the α chain of the CD123 predominantly stains basophils and dendritic cells. This enables accurate differentiation from neutrophils and monocytes in a side scatter versus CD123 expression graph, otherwise known as a 'dot plot'. Basophils express very low levels of HLA-DR, which can be used to differentiate them from dendritic cells[7,29].

Quantifying the expression of the glycoprotein CD63 on the plasma membrane of basophils can be used as a measure of basophil activation. CD63 is expressed on mast cells, macrophages, eosinophils and platelets. It is usually found within the cell attached to intracytoplasmic granules. Following stimulation, degranulation leads to the fusion of these granules with the plasma membrane and their subsequent expression on the surface of the cell[2,4,5]. It is believed that CD63 mediates signal transduction events involved in cell development, activation and motility, although its precise function in basophils is unknown. Previous studies have shown that CD63 expression mirrors basophil histamine release, which demonstrates that it is a reliable method of evaluating basophil activation[2,4,5,11, 13,20].

Previously, the lack of basophil-specific markers and the difficulties in purifying techniques meant that very little was understood about the function of basophils; however, recent development of specific monoclonal antibodies has enabled basophil enumeration and identification in tissues, shedding further light on their role. To date, CD63 expression has been used to analyse allergen-specific activation of basophils *in vitro*[2,10,12]; however, few studies have compared the resting *in vivo* basophil CD63 expression of individuals with atopic diseases and HIV infection to those of healthy controls[20,37]. This paper aims to explore if there is a difference in basophil number and activation marker expression in atopy and HIV infection compared with healthy controls, helping to further understand their behaviour *in vivo*.

METHODS

In this study, approved by the institutional ethics committee, blood was taken from 17 healthy adult volunteers who were HIV negative and had no history of atopy (7 females, 11 males, mean age=38.8, range 23-58). Samples were taken from 18 patients diagnosed with asthma (13 females, 5 males, mean age=54.9, range 30-80), four patients diagnosed with eczema (3 females, 1 male, mean age=44.3, range 22-73) and 14 patients with a suggestive history of allergy (10 females, 4 males, mean age=43.1, range 20-68). Blood was taken from 15 HIV positive patients and was analysed (1 female, 14 males, mean age=37.7, range 22-45). All participants gave informed consent. Patients had previously been diagnosed and were attending dermatology, respiratory, immunology and infectious diseases outpatient clinics for their conditions. Patients remained on treatment throughout the study. Inclusion criteria for the allergy subgroup consisted of a history of urticaria, angioedema or anaphylaxis. For the asthma and eczema subgroups, we set out to include patients with a history of childhood onset only; however, in practice some of the samples obtained were from patients who suffered from intrinsic asthma. Patients with serological evidence of HIV infection were included in the HIV positive subgroup. No specific exclusion criteria were defined for the study.

100 µL of venous whole blood collected in EDTA-coated tubes was incubated with antibodies (5 µL PE-CD123, 5 µL APC AntiHLA-DR, 5 µL Anti-human CD63) for 15 minutes at room temperature in the dark. 2ml of LysingSolution ® was then added to lyse the erythrocytes. The samples were then centrifuged at room temperature at 1200 rpm for 5 minutes. The supernatant was discarded and the cells were washed in 2mls of FACSflow. The samples were re-centrifuged at 1200 rpm for 5 minutes, the supernatant discarded, and the cells were suspended in 0.5mls of Cell FIX.

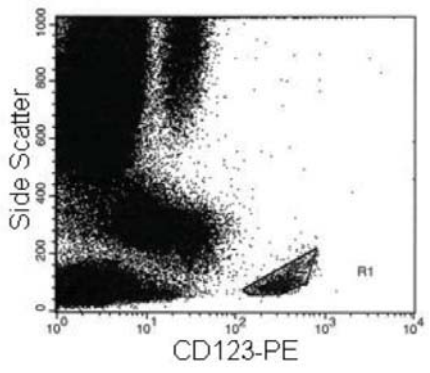
The data was then acquired using a FACSCalibur and analyzed using Cell Quest Pro software® (BD Biosciences). A double gating strategy was employed. Initially, a dot plot of side scatter versus CD123 expression (Figure 4) was drawn up to gate on cell populations with relatively high CD123 expression. The basophil population was then identified as displaying relatively high levels of CD123 expression coupled with low HLA-DR expression (Figure 5). At least 1000 basophils were gated on. Absolute basophil count was calculated using the percentage of total cells acquired that were identified as basophils and the total white cell count.

Absolute basophil count = (Percentage total x White cell count)/100

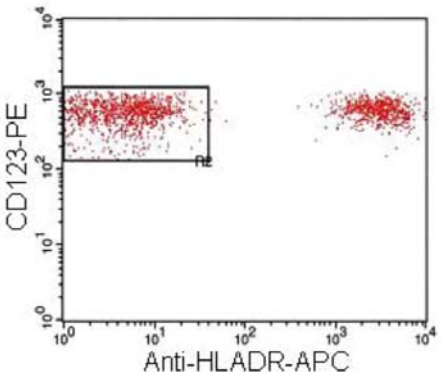
The gated basophil population was then analysed using a biparametric dot plot of CD123 expression against CD63 expression (Figure 6). Basophil population CD63 expression was measured as the geometric mean fluorescence intensity detected for CD63-FITC. A reference range for CD63 expression was established using values from the volunteers: 24.19-13.71 (mean: 18.95, SD: 2.62, Range: 22.90- 14.76).

The protocol employed to identify the basophil population and CD63 expression using flow cytometry was similar to that used by Gyimesi *et al* [9].

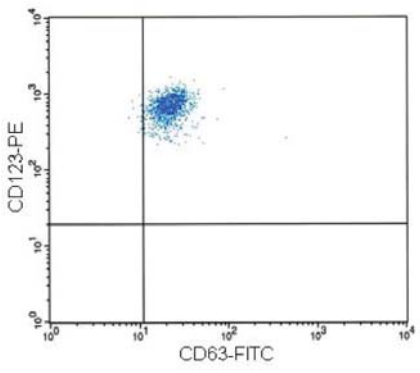
Statistical analysis was performed by Microsoft Excel.



▲ **Figure 4.** Cell populations with high levels of CD123-PE are gated on; region consists of basophils, monocytes and dendritic cells.



▲ **Figure 5.** The basophil population is gated on; high CD123 expression coupled with low HLA-DR expression.



▲ **Figure 6.** Basophils in the upper right quadrant stain positive for CD63.

	Healthy Controls	Asthma Patients	Allergy Patients	Eczema Patients	HIV Patients
Number of Patients:	17	18	11	4	15
Mean absolute basophil no: x10³cells /µL	0.0515	0.0453	0.0321	0.0507	0.0297
SD:	0.0222	0.0214	0.0151	0.0075	0.0203
Range:	0.016-0.099	0.0141-0.0955	0.0137-0.0639	0.0415-0.0584	0.0069-0.0655

▲ **Table 1**: A table displaying the mean, standard deviation (SD) and range of absolute basophil counts in the different patient groups.

	Healthy Controls	Asthma Patients	Allergy Patients	Eczema Patients	HIV Patients
Number of Patients:	17	18	14	4	15
Mean CD63 expression: Mean fluorescence intensity (MFI)	18.95	18.27	20.31	17.42	23.41
SD:	2.62	3.52	5.09	2.01	5.41
Range:	22.90-14.76	26.38-12.78	29.77-13.39	20.33-15.79	30.29-15.51

▲ **Table 2**: A table displaying the mean, standard deviation (SD) and range of basophil CD63 expression measured as mean fluorescence intensity in the different patient groups.

RESULTS

Table 1 compares the absolute basophil count between the different patient groups. Full blood counts for three of the allergy patients were unavailable; consequently, only the results of 11 allergic patients were available for comparison.

HIV positive patients ($p=0.007$) and allergic patients ($p=0.022$) had statistically significant lower basophil counts compared to the healthy controls. No significant difference was found between the absolute basophil count in patients with asthma ($p=0.402$) or eczema ($p=0.947$) compared to healthy controls (Figure 7).

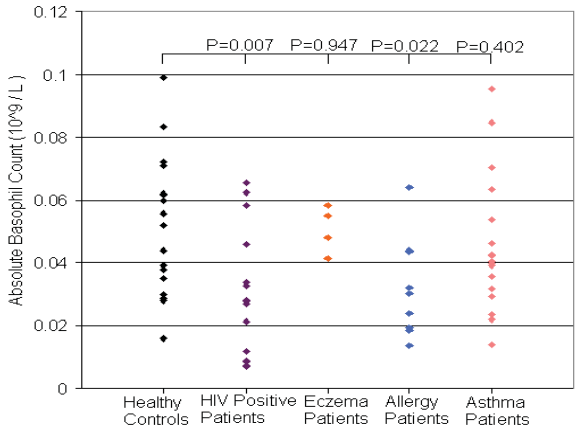
On analysing the results from the healthy volunteers, a large proportion of basophils (mean: 93.81%, range: 100.00-76.26%, SD: 5.85) were present in the positive quadrant, which indicates that the majority weakly expressed CD63. No significant difference was found between the percentages of basophils present in the positive quadrant in healthy controls compared to asthma patients ($p=0.489$), allergy patients ($p=0.254$), eczema patients ($p=0.251$) or HIV patients ($p=0.471$) (Table 2).

HIV positive patients expressed significantly higher levels of CD63 compared to the healthy controls ($p=0.005$). No significant difference was found in the level of CD63 expression in asthma patients ($p=0.521$), eczema patients ($p=0.288$) or patients with allergies ($p=0.346$) compared to healthy controls (Figure 8).

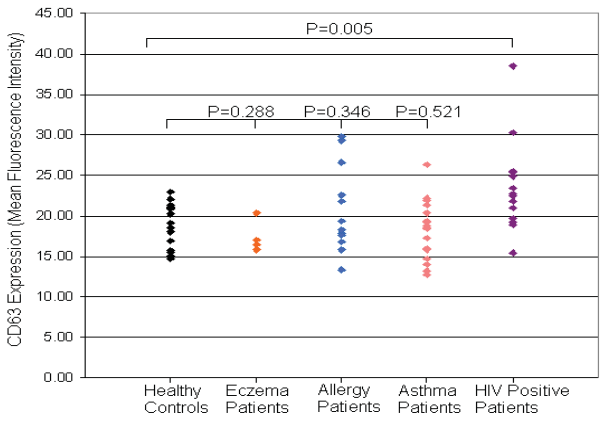
There was no significant difference in the level of CD63 expression in atopic individuals (serum IgE levels >120 kU/L) in comparison to non-atopic individuals ($p=0.919$) (Figure 9).

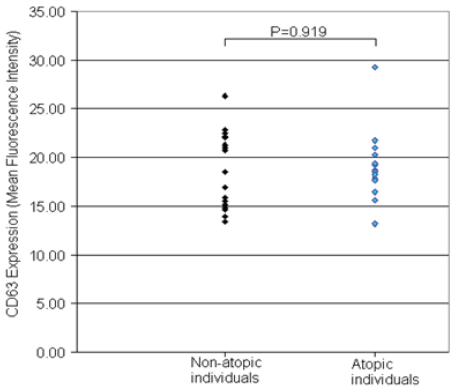
The results also showed no significant difference in the level of CD63 expression between males and females in the control group ($p=0.593$).

▼ **Figure 7.** A graph comparing absolute basophil counts in the different patient groups. There was no significant difference between CD63 expression in patients with eczema, asthma compared to the healthy volunteers. There was a significant decrease in the basophil counts of HIV patients and patients with allergies.



▼ **Figure 8.** A graph comparing the level of CD63 expression in the different patient groups. There was no significant difference between CD63 expression in patients with eczema, asthma and allergies compared to the healthy volunteers. There was a significant increase in CD63 expression in HIV patients





▲ **Figure 9.** **This graph compares the level of CD63 expression in non-atopic individuals and atopic individuals.**

Discussion

Basophil counts were reduced in allergic patients. This may be due to allergen-induced basophil migration into the affected tissues uncompensated by release from the bone marrow, reducing the numbers in circulation. Since a relatively small patient sample was used, it is necessary to repeat the investigation with larger patient groups to determine the significance of this apparent reduction. It would be valuable to elucidate the relationship, if any, between different allergic reactions, such as urticaria, angioedema and anaphylaxis, and absolute basophil counts.

There was a statistically significant reduction in absolute basophil counts in patients with HIV. Basophils express CCR3, which binds to the chemokines eotaxin and RANTES, mediating signal transduction events necessary for migration. CCR3 also functions as a co-receptor for HIV infection. Consequently, a fraction of basophils in HIV positive patients are directly infected by the virus, significantly reducing their half-life in circulation. Basophil maturation and release may be unable to compensate for the decreased half-life of HIV-infected basophils. Another suggestion for the observed decrease in basophil counts may be due to Tat-mediated basophil migration to HIV-1 infected tissue, thereby decreasing basophils in systemic circulation. All HIV positive individuals who took part in this study were on anti-retroviral therapy, it would be interesting to investigate whether antiretroviral drugs have any effect on peripheral blood basophil counts and activation marker expression.

No significant difference was found in the absolute basophil counts in patients with asthma or eczema as compared to healthy volunteers. This could suggest that basophil migration from systemic circulation to the affected tissues in these conditions is balanced by basophil maturation and release into peripheral blood.

The results obtained from this experiment revealed no significant difference in the level of basophil CD63 expression in asthmatic patients. This could be explained by the fact that most of the patients who took part in the study were on treatment with steroids. Steroids have been shown to cause a reduction in absolute basophil count and inhibit mediator release[38]. It would, therefore, be recommended to exclude patients on regular systemic steroid therapy from future investigations.

No significant difference was found in the level of CD63 expression in allergic patients. It is important to note that a heterogeneous patient group was selected. Some individuals who reported allergic reactions to unspecified allergens may have suffered from idiopathic urticaria or angioedema. The underlying mechanism may be autoimmune in nature, mediated by auto-antibodies directed against the FCεRI receptors.

The eczema patient group was too small to allow for effective analysis and comparison. Nevertheless, statistical analysis showed no significant difference in CD63 expression. Two of the patients were on oral steroids and one was on immunosuppressant therapy, which might explain the results obtained.

The site of allergen exposure determines the organ systems affected. In patients with asthma, eczema and allergies, the allergens remain localised to the tissues affected. Basophils have been shown to migrate to those tissues in those conditions[14,18,37]. Consequently, the results could demonstrate that basophils in peripheral blood are not an accurate representation of those directly involved in the pathogenesis of the conditions. Basophils that have migrated to the affected regions are exposed to the allergen and are more likely to be stimulated and may consequently express higher levels of CD63 than those present in circulation.

This study demonstrated a significant increase in basophil CD63 expression in HIV patients despite a significant reduction in absolute basophil counts compared to the healthy controls. This could suggest that a greater proportion of basophils present in peripheral blood were stimulated in HIV in comparison to healthy controls. The HIV glycoprotein, gp120, is a viral envelope protein. It is present in systemic circulation as either virus-bound or in its shed form and its concentration in circulation increases as the virus replicates. In the early stages of HIV infection associated with viraemia, a rise in serum IgE and IL-4 has been clinically observed[23,24,25,33]. Since the glycoprotein is not localised to specific tissues, peripheral blood basophils are exposed to the superantigen and are stimulated via

its interaction with the VH3 domain of the VH3+ IgE molecules[23,24,25]. This may lead to the production of the Th2 type cytokines IL-4 and IL-13 and the up-regulation of CD63 on the cell surface. HIV preferentially replicates in Th2 cells. Hence, HIV-1 induced basophil activation can be considered a method by which the virus optimises conditions for replication. Early studies have shown that peripheral IgE levels may serve as a marker for poor prognosis in HIV positive individuals[39]. It would be interesting to see if there is a relationship between a history of atopy and disease severity following infection. It is also a potentially exciting avenue to explore with regards to novel medical interventions. Could inhibition of HIV-induced modulation of the immune response in early stage HIV infection serve as a viable therapeutic option?

Conclusion

The results of this study showed no difference in absolute basophil counts in patients with asthma or eczema compared to healthy controls. There was a significant reduction in the basophil counts in patients with allergies and HIV positive patients. There was no evidence to suggest that peripheral blood basophils from patients with atopic diseases expressed higher levels of the basophil activation marker CD63 compared to healthy individuals. Basophils from HIV positive individuals expressed significantly higher levels of CD63, possibly owing to the allergen-like function of the viral envelop protein, gp120. Further studies should investigate basophil CD63 expression in HIV positive patients at different stages in disease progression and assess absolute basophil numbers in better characterised allergic patient groups.

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Tako-tsubo cardiomyopathy: The "broken heart syndrome"

James Nolan and Alexey Gunko *(Fourth Year Medicine, TCD)*

Clinical Points

- Tako-tsubo cardiomyopathy (TCM) is a clinical mimic of acute myocardial infarction (MI) and usually presents with chest pain and dyspnoea. Studies estimate that TCM accounts for 1-2% of acute MI hospital admissions.
- The condition is most common in postmenopausal women, and two-thirds of cases are preceded by an identifiable physically or psychologically stressful event.
- Non-specific findings on electrocardiogram and cardiac enzyme assays similar to MI are associated with TCM. "Ballooning" of the left ventricle on systolic ventriculogram is pathognomonic of the condition.
- Management is usually supportive, although complications are managed as they arise. There is a potential role for chronic beta-blockade and ACE-inhibition on discharge.
- TCM usually resolves spontaneously, has a low mortality rate and recurs in less than 10% of individuals.

Abstract

Tako-tsubo cardiomyopathy is a recently described clinical entity which classically presents as an acute coronary syndrome. Key features include "ballooning" of the left ventricle, patent coronary arteries, non-specific electrocardiogram changes and elevated cardiac enzymes. This condition clinically mimics acute myocardial infarction and is believed to account for at least 1-2% of patients admitted to hospital with this diagnosis. The typical patient with tako-tsubo cardiomyopathy is a postmenopausal woman presenting with acute onset of chest pain and dyspnoea, who has recently experienced a profoundly stressful physiological or psychological event. Catecholamines are implicated in the pathophysiology of this condition, although their precise role is the subject of much debate. Currently, routine investigations are not specific for tako-tsubo cardiomyopathy and it should be considered as a diagnosis of exclusion. Relative to myocardial infarction, the prognosis of tako-tsubo cardiomyopathy is excellent; the mortality rate is low, fewer than 10% of patients experience a recurrence of the condition and recovery is generally spontaneous with minimal intervention. Herein, the aim of this review is to provide an overview of tako-tsubo cardiomyopathy by examining its pathophysiology and clinical characteristics.

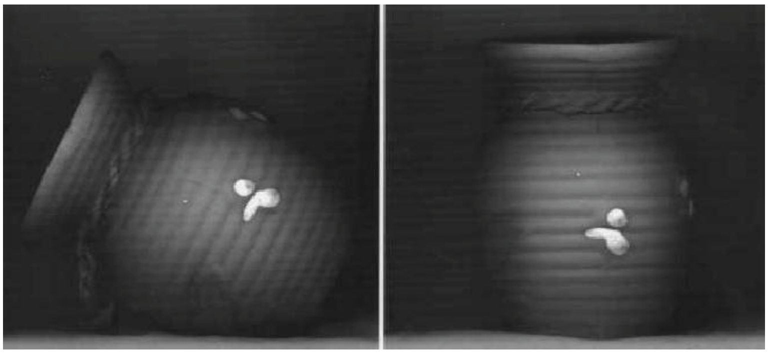


Figure 1: A tako-tsubo. This is a device used by Japanese fishermen to capture octopuses. Reproduced with permission[29].

Introduction

First described in 1991[1], tako-tsubo cardiomyopathy (TCM) is a discrete, transient cardiomyopathy which clinically mimics acute myocardial infarction (MI). The syndrome is defined by its clinical characteristics: dyskinesia of the mid and apical segments of the left ventricle, normal or non-significantly stenotic coronary arteries, abnormal electrocardiogram (ECG) findings and moderately elevated cardiac enzymes. A patient with TCM typically presents with acute chest pain and dyspnoea, temporally associated with an acute psychologically or physically stressful event. The precise nomenclature of TCM remains controversial; the condition is also referred to as transient left ventricular apical ballooning syndrome, stress cardiomyopathy and "broken heart syndrome". A "tako-tsubo" is a pot used by Japanese fishermen to capture octopuses and resembles the "ballooned" appearance of the left ventricle observed in TCM (Figure 1).

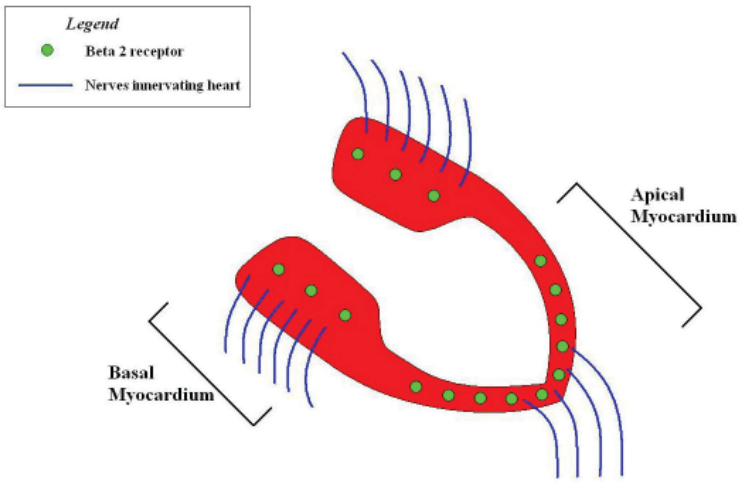
Current studies estimate that TCM is responsible for 1-2% of admissions for acute MI[2,3,4]. American Heart Association data reports that approximately 732,000 Americans are discharged

with a primary diagnosis of acute MI each year[5]. Therefore, it may be surmised that TCM accounts for at least 7,000-14,000 hospital discharges per year in the United States. Similarly, ESRI (HIPE) data suggests that TCM is responsible for 60-121 hospital discharges from Irish hospitals per year[6].

TCM shows a marked preponderance for females[7], with women accounting for 89% of patients. The mean age ranges from 58-75 years and <3% of patients are under the age of 50 years[7,8,9]. A stressful triggering event is readily identifiable in two-thirds of cases[9,10]. Classical emotional triggering events include major medical diagnoses[11], confrontational arguments[12], unexpected death of a friend or relative, gambling losses and domestic abuse[7]. Examples of reported physical stressors include demanding work or exercise[13], administration of EpiPen[14] and non-cardiac surgery[9,15]. One interesting study[16] reported a rise in incidence of TCM following the Central Niigita Prefecture earthquake in Japan in 2004. In the four weeks preceding the earthquake, only one case of TCM was reported, whereas 25 cases of TCM were confirmed in the four weeks following the incident.

By considering TCM as a differential diagnosis of acute MI, patients may be rendered a diagnosis with an extremely good prognosis and less significant emotional burden. Indeed, both the recurrence and mortality rates for TCM are extremely low relative to MI and it generally resolves spontaneously with minimal or supportive therapy. There is conflicting evidence regarding how to differentiate TCM from acute MI using routing investigations in the acute setting. Emerging research is focused on identifying findings on routine investigations which are specific for TCM and elucidating the underlying pathophysiological mechanisms. An increased understanding and awareness of this unique condition is necessary to improve diagnostics and optimize management. The aim of this introductory review, therefore, is to present the pathophysiology of TCM as it is currently understood and to provide an overview of the clinical aspects of this increasingly recognised clinical entity.

Figure 2: Illustration of the densities of Beta-2 receptors and sympathetic nerve fibres in the apical and basal myocardium. A comparable dilation is seen at the apex relative to basal contraction ("ballooning"). This is due to the greater density of beta-2 receptors at the apex and the greater density of sympathetic fibres at the basal myocardium. Thus, serum catecholamines have a more pronounced effect at the apex, causing a localised relative negative inotropic effect.



PATHOPHYSIOLOGY

The precise pathological mechanism of TCM has yet to be identified[5]. Although several hypotheses have been proposed, the Catecholamine Hypothesis is the most widely accepted. Therefore, a detailed overview of this theory will be provided, in addition to a synopsis of the salient points of alternative theories underlying TCM.

CATECHOLAMINE (NEUROHUMORAL) HYPOTHESIS

Catecholamines are released from the adrenal glands and some presynaptic neurons during episodes of stress, exercise or other "fight or flight" reactions.

Raised serum total catecholamine levels of up to 3600 pg/L have been reported in TCM[17] (normal level <250 pg/L[18]). This catecholamine excess has been implicated in the pathogenesis of so-called myocardial "stunning"[17], proposed as the cause of apical ballooning of the left ventricle which is pathognomonic of the syndrome. The neurohumoral hypothesis postulates that a complex interplay between neural (related to nervous system) and humoral (pertaining to elements in blood) factors is responsible for the manifest features of TCM[19].

Norepinephrine and epinephrine exert their effects on the heart primarily through β_1 and β_2 adrenergic receptors (the ratio of β_1:β_2 in the heart is approximately 4:1[20]). Binding at these receptors normally results in activation of a cascade of signalling molecules beginning with G_s, which results in a positive inotropic effect (more forceful contraction of heart muscle)[21]. While this normal pathway is preserved at the β_1 receptor, extremely raised catecholamine concentrations result in a switch at the β_2 receptor from a G_s to a G_i pathway

(probably via phosphorylation of the β_2 receptor[22]). The G_i pathway results in negative inotropy and is believed to act as a protective mechanism against myocyte apoptosis. It is proposed that as serum catecholamine levels rise, a greater proportion of β_2 receptors transduce signals through the G_i pathway causing an increasingly negative inotropic effect. Meanwhile, the stress response in the central nervous system (sympathetic response) results in both positive chronotropy (increased rate of contraction) and positive inotropy.

In the human heart, the density of sympathetic nerve fibers is approximately 40% higher in the basal myocardium than in the apical myocardium[23] (Figure 2). Conversely (extrapolated from a canine model), the apical myocardium has a greater concentration of β receptors than the basal myocardium[24]. Thus, neural input has a greater effect in the basal myocardium and receptor-mediated effects are greater in the apical myocardium. Functionally, this suggests that the negative inotropic effect produced by transduction from the β_2 receptor in the presence of raised cathecholamines is relatively larger in the myocardium at the apex of the heart. This mildly counteracts the sympathetic overdrive, leading to relatively weaker contractions in the apical than in the basal myocardium – a local humoral response at the apex resisting the generalized positive inotropy. This provides a possible explanation for the characteristic takotsubo-like ventricular changes of basal contraction and apical ballooning.

In the presence of raised serum catecholamines, cardiac myocytes undergo oxidative stress and some may apoptose (though less than encountered in MI). Since both TCM and MI share the feature of myocyte apoptosis, this may explain their similar ECG and biochemical findings. Moreover, as this apoptotic phenomenon is present to a lesser degree in TCM, this may explain why these abnormalities are less marked and observed for a shorter period of time.

Additional support for catecholamine involvement in TCM includes the finding that β blockers such as propranalol have also been effective in preventing certain stress-induced cardiac pathology[25]. Furthermore, in some cases of phaeochromocytoma (a catecholamine-secreting adrenal gland tumour), a similar pattern of apical ballooning has been observed[26].

Inflammatory Hypothesis

This hypothesis postulates that catecholamine excess directly causes cardiac inflammation and apoptosis, which in turn gives a picture of heart failure[27]. This arose from the detection of elevated non-specific inflammatory markers such as C-reactive protein (CRP)[28], as well as the observed infiltration of inflammatory cells into the myocardium in TCM[29]. Catecholamines can cause apoptosis via cyclic AMP-mediated calcium overload[30], serving also as a potential source of oxygen-derived free radicals[31]. The significance of raised inflammatory markers has been disputed and is currently believed to be an epiphenomenon as CRP levels reach a peak several days after presentation.

Coronary Flow Impairment Hypothesis

Coronary flow impairment was one of the earliest pathophysiological hypotheses of TCM. This theory postulates that increased sympathetic activity from stress induces coronary artery spasm and vasoconstriction[32], resulting in transient ischaemic myocyte apoptosis. Recently, many studies using acetylcholine or ergonovine to induce coronary artery vasospasm during angiography have yielded inconclusive results[7]. However, further research has indicated that microvascular spasm may result in impaired blood supply to discrete areas of the myocardium and reversible myocardial dysfunction[33].

Myocyte Metabolism Hypothesis

Having observed that coronary microcirculation may be markedly impaired in the early stages of TCM[33], researchers sought to elucidate whether abnormalities of myocyte metabolism similar to those seen in acute MI are also present. Under aer-

Mayo Clinic Diagnostic Criteria for TCM
Each of the following criteria must be satisfied for the diagnosis of TCM:
1) Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3) New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4) Absence of phaeochromocytoma and myocarditis.

▲ **Table 1:** Mayo Clinic Diagnostic Criteria for Tako-tsubo Cardiomyopathy (TCM)[8]

obic conditions, the normal myocardium utilises fatty acids (via β oxidation) as 70-80% of its energy source. In TCM, fatty acid oxidation is significantly impaired with only a slight decrease in perfusion[34]. This disproportionate impairment was confirmed in multiple studies, usually involving reduced uptake of iodine-123-BMIPP radioisotope tracer into myocytes and is thought to be consistent with a mildly ischaemic picture[34].

Clinical Presentation and Diagnostic Criteria

Clinically, TCM is essentially indistinguishable from acute MI with reversible left ventricular dysfunction. In a systematic review by Gianni et al[7], cardiac-type chest pain and dyspnoea were reported as cardinal symptoms in 67.8% and 17.8% of TCM patients, respectively. Nevertheless, patients may present with more serious complications, such as cardiogenic shock (4.2%) and/or ventricular fibrillation (1.5%)[5]. Mild to moderate congestive cardiac failure is frequent and due to the reduction in stroke volume, hypotension may occur, though syncope is uncommon[8]. Rarely, patients may present with sudden cardiac death syndrome[35].

To assess a patient with the above clinical picture for the presence of TCM, the Mayo Clinic has proposed several diagnostic criteria[36] (Table 1).

Investigations

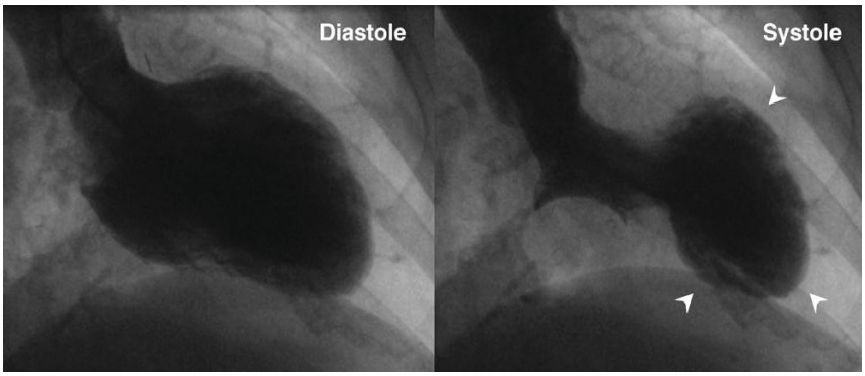
Electrocardiogram Findings

The most commonly observed abnormality on the electrocardiogram (ECG) is ST-segment elevation which mimics ST-elevation MI (STEMI)[15]. Few identified features distinguish STEMI from TCM on ECG, with some papers denying that discriminatory features exist[37]. However, a growing evidence base suggests that certain fine characteristic features may be useful. In a cross-sectional retrospective record review of low power (n=26) by Ogura et al[38], ST-elevation was quantitatively measured in patients with TCM and acute anterior MI. There was a statistically significant (p=0.008) difference in the level of ST-elevation in leads V_{1-3} in patients with acute anterior MI (11.04+/-7.35millimetres) than with TCM (4.33+/-3.10mm). In leads V_{4-6} the ST-segment elevation was also marked but similar in both conditions (p=0.56): MI (7.73+/-6.10mm) versus TCM (6.44+/-4.69mm). Most notable, however, was the difference noted in the ratio of ST-segment elevation in leads V_{4-6} to leads V_{1-3} ($STeV_{4-6}$:$STeV_{1-3}$): MI (0.56+/-0.57mm) versus TCM (1.55+/-0.53mm), which is statistically significant (p=0.0004). Thus, while ST-elevation is present in both conditions, it was found in this study to be quantitatively greater in MI. In practical terms, the ratio of elevation in V_{4-6}:V_{1-3} has the potential to be a specific marker for TCM and requires further investigation in a study of higher power.

Other changes which may prove useful in distinguishing TCM from acute anterior MI include the absence of ST-segment depression in inferior leads[39] and resolution of QT-interval prolongation and T-wave inversion over 4-6 months[40,41]. Pathological Q waves may be less common in patients with TCM than in patients with acute MI[38].

Cardiac Imaging

Transthoracic echocardiography and ventriculography are useful tools in detecting wall motion abnormalities typically seen in TCM, specifically hypokinesis or dyskinesis of the mid or apical portions of the left ventricle. Subsequent "ballooning" of the left ventricle may be observed and is considered to be pathognomonic of the syndrome (Figure 3). Similar regional wall motion abnormalities are seen in the right ventricle in approximately 30% of patients who tend to be sicker and are more likely to develop congestive cardiac failure[42,43]. However, visualisation of the true anatomical apex can be difficult in acutely ill patients[8]. It is worth noting that the characteristic wall motion abnormalities involve myocardium supplied by branches of both the left and right coronary arteries[44]. In studies by Wittstein et al[17], Bybee et al[45] and Tsuchihashi et al[15], left ventricular ejection fraction (LVEF) at presentation of TCM was markedly reduced (to an average of 20%, 39% and 41%, respectively). Full recovery was the trend in each of these trials; follow-up LVEF values were measured at



▲ **Figure 3:** **The characteristic appearance of TCM on ventriculogram. Diastolic and systolic freeze frames from a left ventriculogram of a patient with classic TCM. This illustrates hyperdynamic basal contraction but akinesis of the mid and apical segments of the left ventricle. Reproduced with permission[8].**

an average of 60%, 60% and 64%, respectively (within the normal healthy range of 62.3+/-6.1%)[46].

Unlike typical patients with acute coronary syndromes, angiographically normal or mildly atherosclerotic coronary arteries are usually seen on emergency coronary angiography in patients with TCM[7,9].

Laboratory Studies

In TCM, cardiac biomarkers tend to be modestly raised relative to the levels observed in MI. Sharkey et al[47] found the mean peak Troponin T titre to be elevated in 95% of TCM patients at 0.64+/-0.86 ng/ml, but lower than in those with left anterior descending coronary artery occlusions (3.88+/-4.9 ng/ml). As would be expected, patients demonstrating left heart failure were noted to have elevated serum brain natriuretic peptide (BNP) levels. Further, serum catecholamines have been noted to be two to three times higher than in patients with acute MI[17].

Management and Prognosis

Optimal management of TCM has yet to be established. The initial management should therefore be that of myocardial ischaemia until a diagnosis of TCM is made. Management would include continuous ECG monitoring, administration of aspirin and IV heparin and β-blockade are indicated. Discontinuation of all medications except for β-blockade and supportive fluids is recommended once the diagnosis of TCM is established[8]. Complications should be treated as they arise. Congestive cardiac failure complicates 20% of TCM cases[7] and as with acute MI, mechanical (e.g. free wall rupture and mitral regurgitation) and arrhythmic complications (both atrial and ventricular) may occur. Given the excess of catecholamines, it is sensible to avoid catecholamine vasopressors in treating hypotension[9,48]. Anticoagulation is advisable in the presence of severe left ventricular systolic dysfunction, with warfarin maintenance until function recovers. Mayo Clinic guidelines suggest a role for chronic β-blockade in reducing the likelihood of recurrences and for ACE-inhibitors on discharge[8].

Complete recovery is seen in virtually all patients within 4-8 weeks[8,15,17,48] and recurs in less than 10% of patients[10]. In a four-year follow-up study of 70 TCM patients in Rhode Island, among three deaths in the cohort, only one was reported to be due to cardiovascular morbidity[49]. This further reinforces the low mortality rate reported by other studies[8,48]. Overall, long-term survival is similar to that of the general age-matched population[10].

Conclusion

As evidenced by phrases such as "scared to death" and "dying of a broken heart", TCM seeped into popular culture long before it was recognised and afforded a name. As TCM is further unmasked, its implications are becoming better understood. Improving diagnostics is incentivised not only by the opportunity to offer patients a diagnosis with an excellent prognosis and more tolerable treatment, but also to reduce unnecessary expenditure by shortening inpatient stays and avoiding costly interventions. This unique syndrome should be included in the differential diagnosis of any patient presenting with suspected acute MI. Currently, there is significant international interest in TCM, as reflected by the exponential growth in the number of publications in recent years. As the evidence evolves, enthusiasm for research into this disease has reached new heights and the prognosis will continue to improve.

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Eoin Kelleher *(First Year Medicine, RCSI)*

GP house calls: An entity worth protecting

Rory Stewart *(Third Year Medicine, TCD)*

It was twelve noon on a typical wet and windy Saturday in the west of Ireland. My GP, having finished his breakfast and perused the Irish Times, calls to say that he will shortly be making a routine house call to change the catheter of an elderly man confined to his bed for the past few months. As a medical student with a strong interest in family medicine, I ask if I can tag along. Dr S, a veteran with 25 years of GP experience, duly obliges. Rather than seeming inconvenienced, he appears excited to impart some of his knowledge to a student eager to gain insight into how the front line of primary care actually works.

On the 10 minute journey through meandering roads to the small farmhouse, Dr S briefs me on the patient's history: 'An 80 year-old-man with atrial fibrillation, benign prostatic hyperplasia and early onset dementia; a real classic', he says. He explains how the patient's wife has been caring for him over the previous months, and how this particular case is a perfect example of the kind of house call one could expect when working in rural Ireland. He stresses the importance of providing support for the man's carers, which he tells me is one of the most salient priorities when dealing with a case of this nature. While both the patient's history and the thought of witnessing a new clinical procedure interest me, it's the dynamic between the doctor and the family in this, the most private of places, I find most intriguing.

Contemporary family practice can act as a microcosm of hospital medicine. Under the guise of mini hospitals, primary care facilities are now expanding to include an ever-enlarging multidisciplinary team, with doctors, nurses, physiotherapists, pharmacists and social workers attempting to provide complementary care — often all under one roof. Many of these modern health care practices are further diversifying to incorporate X-ray facilities, DEXA scanners and minor ops clinics. Now, the once small and personalized GP surgeries are increasingly becoming expansive, sanitized clinical limbs of hospital medicine. Or are they? This got me thinking. What is it that sets general practice apart from hospital medicine?

Let's take shopping as a crude analogy. I personally despise even the thought of finding myself at 5 o'clock on a mundane Friday afternoon, in a faceless, soulless, multinational superstore. To me, the prospect of trying to shout and push my way through a hot and overcrowded supermarket is far from desirable. I would be far

more comfortable visiting my local village shop, where I will be greeted by name and asked how I'm doing. I would rather a pleasant ten minutes in a shop that is as sparsely populated as the countryside in which it finds itself. A place where queuing is as obsolete as mobile phones that can change the channel on your TV or running shoes with a built-in GPS tracking device.

Here in lies the beauty of the family practice. It's local and it's personal. It's about family, it's welcoming, it's relatively quiet, it's on your doorstep, and in the case of house calls, it will even come directly to your home. Sure, there are times when I need to source a dozen duck breasts from a small farm in the Dordogne to show off at a dinner party. On the odd occasion when this occurs, I will head to the nearest Hypermarket to brave the crowds and queues. Equally occasionally, I may need to make the trek, like many others in rural Ireland, to get my gallstones removed by Endoscopic Retrograde Cholangiopancreatography (ERCP). When this happens, I take a deep breath, bless myself and launch into the lion's den, ready to become a number on a form, a faceless statistic on someone's report. However until then, where possible, give me local, personalized GP care.

So why general practice? Why local? Why somewhere with a personal touch? Why a partnership rather than a totalitarian regime, where a consultant tells me how it's going to be, or an advertising executive tells me why I need to buy overpriced ham from Iberia? Well it's obvious! It's the same reason people spend six times as much to fly first class to New York and stay in The Waldorf, rather than flying economy and bunking at the nearest Travel Lodge. It's about service. It's about the welcome you receive from staff who care about how your day is going. In short, it's the idea that when you need someone or something, day or night, it will be there, just like your humble GP service.

So here in lies the beauty of the house call. On demand, personal service in the privacy and comfort of your own home. With the exception of the local Parish Priest coming to administer the last rights, there is no other service where you can ring up and within the hour have a skilled professional kneeling by your bedside. I find it somewhat humorous to toy with the idea of ringing my bank manager, accountant or solicitor at 10 o'clock on a Saturday night to ask them to come round for a chat about my finances.

It is easy to argue that GP home visits are reserved for emergency cases only, or for people who are very ill. The reality, however, is that the majority of home visits are more about psychosocial and palliative care. Often visits are more to provide support and counsel than to explore clinical issues. Often these visits are simply to let carers know that they haven't been forgotten, that there is support for them and that they're not alone.

A recent survey of GP home visits in Donegal (yet to be published), which I have been involved in collating, has revealed some pertinent findings. Our study calculated a home visiting rate of 158/1000/year with a 9-fold variation between practices. The gender spread was approximately even, with 54% of calls made to female patients, while the average patient age was 79 years. The mean time taken for a house call was found to be about 30 minutes and the majority of calls were initiated by the patient or a relative (63%). Only 14% were found to be initiated by the GP. Interestingly, of the 651 home visits surveyed, 257 (39.5%) were classified as routine calls, which could have waited at least another 24 hours. Only 59 (9%) resulted in a hospital admission.

So what does this tell us? What is the role of the house call in the current climate of the increasingly depersonalized healthcare system? The results from this study highlight that house calls still comprise a substantial part of the workload for many rural GP's. Further, these home visits tend to be weighted towards elderly patients who often only require routine support, and not for medical emergencies as the service is often sold. Perhaps then, the greatest strength of the house call is that it provides a means of protecting older, more dependent and vulnerable patients; those who cannot protect themselves.

Aside from Ireland, Great Britain and the Netherlands are two of the few countries that still provide GP house calls. This leads one to ask, is this the mark of a society that is grasping onto an archaic way of life and lagging behind the remainder of the developed world? Or are we pioneers for sticking to our traditions and providing a more personal form of health care that greatly fosters community cohesion? To paraphrase Fyodor Dostoevsky, 'the degree of civilization within our society can be judged by the way we treat our outcasts.' We live in a society intent on destroying the local grocer and losing the personal touch, a society accelerating away from one focused on family to one obsessed with personal profit and gain. In order to protect our individuality, our elderly, our marginalized, and our weak, we must also protect the house call.

Hyponatraemia: Pathophysiology, treatment and future directions

Anne Marie Liddy *(Fifth Year Medicine, TCD)*

Dean's Gold Medal

CLINICAL POINTS

- The sequelae of hyponatraemia can be varied and devastating, therefore prompt and appropriate correction is vital.
- Hyponatraemia has multiple aetiologies and the cause needs to be determined before the appropriate treatment can be chosen
- Measurement of volume status, serum osmolality, urinary sodium concentration and urinary osmolality are fundamental in order to correctly diagnose the precipitating cause.
- Over-rapid correction of chronic hyponatraemia can have permanent and devastating neurological consequences
- The introduction of new drugs for the treatment of hyponatraemia, the 'Vaptans', which block the vasopressin receptor and cause excretion of free water are an important addition to the options available to the clinician for the treatment of hyponatraemia.

ABSTRACT

Hyponatraemia is the most common electrolyte abnormality in clinical practice. While it may be an incidental discovery or manifest with subtle symptoms such as mild confusion, it can also be associated with severe neurological complications and may even result in death. Mismanagement of hyponatraemia with over-rapid correction of the electrolyte abnormality can cause serious and long-lasting neurological consequences. An understanding of the pathophysiology of hyponatraemia is necessary in order to select the appropriate treatment and avoid the complications associated with this condition and its management. The recent introduction of vasopressin receptor antagonists offers clinicians a new option in the management of this challenging condition.

INTRODUCTION

Hyponatraemia, commonly defined as a serum sodium ≤ 135 mmol/L, is the most frequently encountered electrolyte abnormality in clinical practice[1]. Both the disorder itself and its management can lead to significant morbidity and mortality. Severe hyponatraemia (≤120 mmol/L) developing acutely can result in serious neurological sequelae due to water shift into brain cells, leading to confusion, restlessness, seizures, coma, brainstem herniation, respiratory arrest and even death. These neurological signs and symptoms are usually absent in those in whom hyponatraemia develops gradually due to the ability of brain cells to adapt to the slow change in the tonicity of the extracellular fluid[2].

Patients in whom the development of hyponatraemia is gradual are not always truly asymptomatic, however, and they may have subtle neurological abnormalities that lead to attention deficits and an increased risk of falls[3]. This is crucially important in the elderly, a population at increased risk of both falls and hyponatraemia[4,5]. There is also emerging evidence to suggest that chronic, mild hyponatraemia may result in metabolic bone loss, further increasing the risk of fracture in the elderly patient with chronic hyponatraemia[6]. In hospitalised patients, low serum sodium is an independent risk factor for in-hospital mortality, meaning that regardless of the cause of the hyponatraemia or the co-morbidities present, these patients have a greater mortality risk and this risk increases in proportion with the decrease in their serum sodium concentration[7]. Furthermore, hyponatraemia may be a modifiable risk factor for mortality in congestive heart failure as suggested by the Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist (Tolvaptan) in Congestive Heart Failure (ACTIV in CHF) study in which an increase in serum Na^+ of ≥ 2 mmol/L almost halved the mortality rate sixty days post discharge after an exacerbation of congestive heart failure[8]. More research is needed in this area to evaluate the role of serum sodium as a risk factor for mortality in seriously ill patients.

In addition to appreciating the significance of hyponatraemia as it relates to patient outcomes, a thorough understanding of the treatment of this

Osmolality is the number of osmoles of solute per kilogram of solvent

Tonicity is the total concentration of particles which *cannot* freely cross the membrane and therefore induce transcellular shifts of water

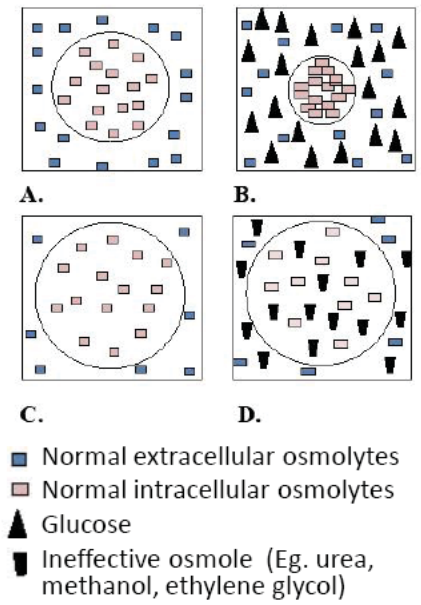
condition is essential to avoid the devastating consequences of mismanagement. Over-rapid correction of long-standing hyponatraemia can result in a demyelination syndrome in the central nervous system (CNS) which destroys CNS structures and leaves the patient with serious, persistent neurological disabilities. Classically, demyelination occurs in the pons resulting in central pontine myelinolysis (CPM) but demyelination due to over-rapid sodium correction can occur anywhere in the CNS[9].

The following paragraphs will explain the pathophysiological mechanism of various types of hyponatraemia and their potential consequences. Moreover, a discussion of the proposed method of correction of each of these conditions will be provided.

PATHOPHYSIOLOGY

Treatment of hyponatraemia in clinical practice firstly involves correctly identifying the cause in order to choose the most appropriate therapy. The causes of hyponatraemia are exceedingly varied and an understanding of the underlying pathophysiology of the condition is of utmost importance. This understanding helps the clinician distinguish a patient who may have hyponatraemia merely from excessive consumption of water from one in whom a subtle electrolyte imbalance is their first presentation of malignancy.

Broadly speaking, hyponatraemia occurs due to an excess of extracellular water relative to extracellular sodium. In order to discuss the causes of this excess in extracellular water, two important terms first need to be defined: osmolality and tonicity. The osmolality of a solution is the number of osmoles of solute per kilogram of solvent. Note that the particles considered in the calculation of the osmolality of a solution may or may not freely cross the cell membrane; that is, this measurement does not confer any information about how the dissolved particles will affect transcellular shifts of water in vivo. The tonicity of a solution, however, is the measure of the total concentration of particles which *cannot* freely cross the membrane and these, therefore, do induce transcellular shifts of water. The causes of the excess in extracellular water that lead to hyponatraemia can be associated with a hypertonic, isotonic or hypotonic



▲ **Figure 1. A. Normal plasma osmolality and tonicity with normal cell size. B. Hypertonic hyponatraemia with cell shrinkage due to hyperglycaemia. C. Hypotonic hyponatraemia with low plasma osmolality. D. Hypotonic hyponatraemia with normal/high osmolality due to th abnormal presence of a substance that can cross the cell membrane.**

extracellular fluid and the treatment of these types of hyponatraemia differs. There is also the case of pseudohyponatraemia, which refers to a laboratory artefact that results in a low sodium measurement in the presence of normal serum sodium[10].

NON-HYPOTONIC HYPONATRAEMIA

Consider first the following types of non-hypotonic hyponatraemia, that is those associated with a hypertonic or isotonic extracellular fluid and pseudohyponatraemia resulting from a laboratory artefact.

HYPERTONIC HYPONATRAEMIA

This can be caused by any solute which remains in the extracellular space and cannot cross the membrane, thereby inducing movement of water out of cells and a decrease in the concentration of the extracellular sodium. A common example of this is the dilution of extracellular sodium that occurs due to the osmotic effect of extracellular glucose in diabetic ketoacidosis. In this condition, glucose cannot enter the cell due to lack of insulin and the high extracellular concentration of glucose therefore draws water out of the intracellular compartment and dilutes the serum sodium (See Figure 1, example B)[11].

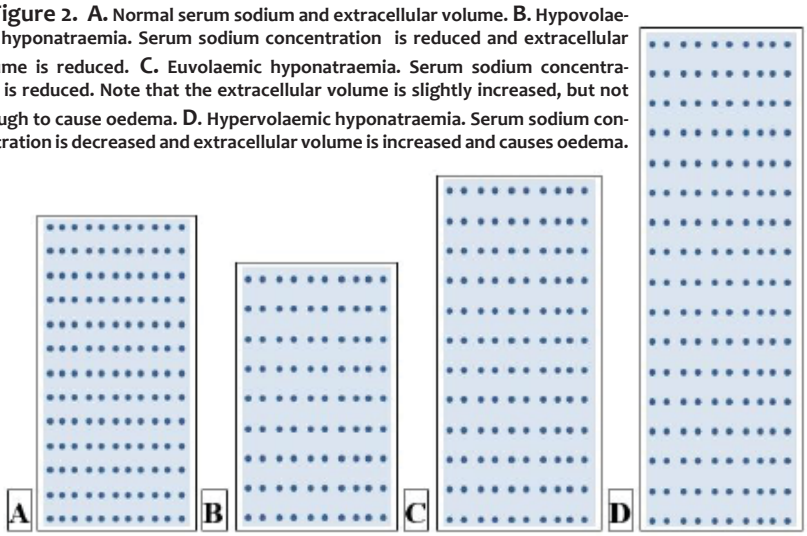
ISOTONIC HYPONATRAEMIA

This situation occurs when there is infusion or absorption of an isotonic solution, such as mannitol, that does not contain sodium. As a result, the measured sodium concentration will be low, but there will be no transcellular shifts in water. Isotonic hyponatraemia can arise following trans-urethral resection of the prostate (TURP) and does not require correction unless there is progression to hypotonic hyponatraemia as substances in the irrigating fluid such as glycine are metabolised to CO_2 leaving free water in the serum[11].

PSEUDOHYPONATREMIA

This occurs when the sodium concentration is measured using methods that allow high serum protein or lipid concentrations to interfere with the interpretation of the result, leading to a falsely low sodium measurement. Pure pseudohyponatraemia does not require any correction of the serum sodium. It does, however, alert the clinician to the presence of a serious derangement in a patient's

Figure 2. A. Normal serum sodium and extracellular volume. **B.** Hypovolaemic hyponatraemia. Serum sodium concentration is reduced and extracellular volume is reduced. **C.** Euvolaemic hyponatraemia. Serum sodium concentration is reduced. Note that the extracellular volume is slightly increased, but not enough to cause oedema. **D.** Hypervolaemic hyponatraemia. Serum sodium concentration is decreased and extracellular volume is increased and causes oedema.



blood lipids or protein concentration and could, for example, suggest a diagnosis of familial hypertriglyceridaemia or multiple myeloma[12].

HYPOTONIC HYPONATRAEMIA

This is, by far, the most common type of hyponatraemia in clinical practice and can be associated with low, normal or increased serum osmolality depending on the cause. Again, determining the serum osmolality will give essential clues to the cause of the hyponatraemia and will guide the treatment required.

Hypotonic hyponatraemia with normal or high serum osmolality occurs when there is a large volume of a solute such as urea, ethanol, methanol or ethylene glycol in the extracellular fluid that can freely cross the cell membrane. These substances contribute to the osmolality but have no effect on the tonicity of the extracellular fluid. Consequently, they do not affect transcellular shifts in water (See Figure 1, example D). This is important as these patients are as much at risk for the complications of a hypotonic extracellular fluid as are patients with hypotonic hypo-osmolar hyponatraemia. This means they are equally at risk of suffering from the osmotic demyelination syndrome as a patient with both low osmolality and low tonicity if their serum sodium is corrected too quickly[11].

Finally, hypotonic hyponatraemia may be associated with low osmolality. The extracellular sodium in this case is diluted by either excessive water intake or, more commonly, by some impairment in the ability of the kidney to excrete excess water. Total body stores of sodium in these patients may be decreased, normal or increased and the sodium stores can be clinically estimated by assessing the volume of extracellular fluid, as will be discussed below[11].

HYPOTONIC HYPONATRAEMIA – EXCESS WATER INTAKE

In this situation, water intake exceeds the maximum diluting capacity of the kidney and thus the kidney cannot correct the serum electrolyte concentrations. The kidney can excrete approximately 17 litres of water per day with a minimum urinary osmolality of 50 mmol/kg. Water consumption in excess of 17 litres per day will therefore result in dilution of the extracellular fluid. This occurs most often in psychiatric disease as psychogenic polydipsia and is also seen following endoscopic surgery in which hypotonic irrigation solutions are used[13].

Psychogenic polydipsia occurs most frequently in patients with schizophrenia and hyponatraemia in these patients is more severe than in a healthy subject for an equivalent water intake. This may be attributed to alterations in the secretion of vasopressin (antidiuretic hormone–ADH), atrial natriuretic peptide (ANP) or both. Vasopressin acts in the collecting duct of the kidney and results in retention of free water. In the presence of a hypotonic extracellular fluid the secretion of vasopressin should be suppressed. ANP also acts on the kidney through multiple mechanisms causing excretion of sodium. In patients with schizophrenia, vasopressin often fails to suppress completely in the presence of hypotonic extracellular fluid and ANP release is stimulated resulting in retention of free water and loss of sodium, respectively, thus exacerbating the effects of excessive intake of free water[14].

TURP and trans-cervical resection of the endometrium (TCRE) are endoscopic surgeries for treatment of benign prostatic hyperplasia and menorrhagia, respectively. Both procedures can require the use of hypotonic irrigating fluid. These hypotonic solutions may be absorbed into the circulation and cause dilution of the extracellular fluid thereby causing a hypotonic hyponatraemia[15]. While excess water absorption in both TURP and TCRE can have serious, even fatal, consequences, the case of TCRE-induced hyponatraemia is especially alarming as menstruating females, for reasons that are as yet unclear, are 25 times more susceptible to permanent brain damage and death than men once cerebral oedema from a sudden fall in serum sodium occurs[16,17].

HYPOTONIC HYPONATRAEMIA – IMPAIRED WATER EXCRETION

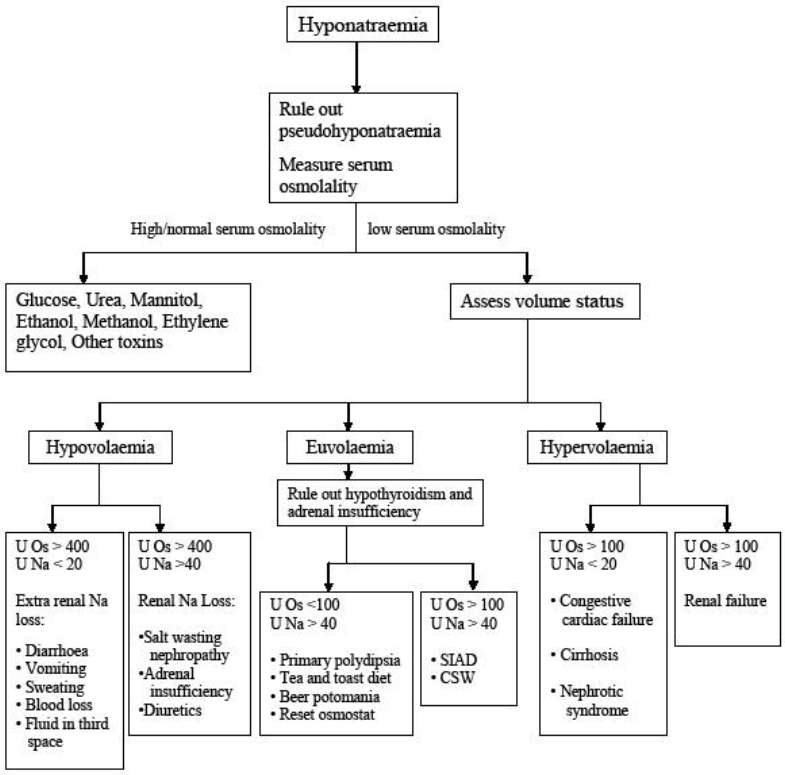
Hypotonic hyponatraemia associated with an impaired ability of the kidney to excrete excess water can be subdivided into hyponatraemia with a hypovolaemic, euvolaemic or hypervolaemic state. In hypovolaemic hypotonic hyponatraemia, total body sodium as well as total body water is low but there is a relative excess of body water leading to dilutional hyponatraemia (See Figure 2, example B). The total body sodium can be reduced by renal sodium loss (for example in adrenal insufficiency, salt wasting nephropathy and diuretic use), extra-renal sodium loss (for example diarrhoea, vomiting, blood loss and excessive sweating) or by sequestration of fluid in a third space (for example burns or peritonitis)[11].

HYPERVOLAEMIC HYPONATRAEMIA

Characterised by high total body sodium and a relative excess of body water leading to dilutional hyponatraemia. This occurs in conditions where the effective circulating volume is reduced and there is secretion of aldosterone and vasopressin in order to stimulate the kidney to retain sodium and water to restore the circulating volume. Such conditions include congestive heart failure (CHF), cirrhosis and nephrotic syndrome. Hypervolaemic hyponatraemia also occurs in renal failure where the kidney loses the ability to excrete excess water (See Figure 2, example D)[11].

EUVOLAEMIC HYPONATRAEMIA

It can be associated with decreased intake of solutes. This often occurs in individuals who are malnourished such as elderly persons who consume a tea-and-toast diet or in beer potomania in which there is regular intake of large amounts of beer with little food consumption. The low intake of solutes impairs the ability of the kidney to excrete water.



▲ **Figure 3** U Os - Urinary osmolality; U Na - Urinary sodium concentration. Adapted from 2,11,23,25.

Hypothyroidism, through multiple mechanisms which are incompletely understood, as well as adrenal insufficiency, through loss of sodium from the kidney due to deficiencies in aldosterone and cortisol, can also cause euvolaemic dilutional hyponatraemia[2]. The syndrome of inappropriate antidiuresis (SIAD), which is caused by inappropriate vasopressin release in the presence of hypotonic extracellular fluid leading to retention of free water by the kidney, is another commonly diagnosed cause of hypotonic euvolaemic hyponatraemia. SIAD has many varied causes ranging from cancers, CNS disorders, drugs, pulmonary conditions, human immunodeficiency virus, pain, nausea and the post-operative state (See Figure 2, example C)[18].

DIAGNOSIS

The symptoms of hyponatraemia depend on the degree of the hyponatraemia and the speed with which it develops. The most serious manifestations of hyponatraemia occur when serum sodium is rapidly (within 48 hours) and severely reduced (<120mmol/L). Symptoms include confusion, hallucinations, seizures, coma, and death. Conversely, chronic mild hyponatraemia may be asymptomatic, or may have subtle symptoms such as poor concentration[3,11].

Patients presenting with symptoms that could result from hyponatraemia should be questioned about conditions that lead to derangements of serum sodium concentration in their medical history. It is evident from the extensive range of types and causes of hyponatraemia that all elements

of the medical history are of utmost importance since long-standing or recent illness, psychiatric illness, medications, recent surgery and poor social circumstances may either cause or exacerbate the condition.

Once a diagnosis of hyponatraemia has been confirmed by a serum sodium level, the aetiology needs to be confirmed. The cornerstone tests used in the differential diagnosis of hyponatraemia are serum osmolality, urine sodium and urine osmolality. These simple tests help classify the hyponatraemia as discussed above and allow the clinician to identify the cause of the hyponatraemia and thereby choose the appropriate treatment[2].

A step-by-step approach to elucidating the cause of hyponatraemia first begins with ruling out pseudohyponatraemia by checking total serum protein and a lipid profile (See Figure 3). Serum osmolality should then be considered. If it is normal or high, substances such as glucose and urea in the serum that can increase the osmolality, should be sought (use of the osmolal gap at this point has been shown to be unhelpful; for further discussion see references 19-21). It is useful to remember that if the osmolality is normal or high the tonicity may be low, normal or high depending on the nature of the substance that is causing the increase in the osmolality of the extracellular fluid. A low osmolality, however, always implies a low tonicity[2].

If serum osmolality is low, the volume status, which is an indication of total body sodium stores, should be established. Many of the traditional clinical signs of hypovolaemia such as sunken eyes and dry mucous membranes, have very poor sensitivity and specificity, but the presence of dry axillae is a good clinical indication of hypovolaemia and low total body sodium. Hypervolaemia is most reliably indicated by measurement of the jugular venous pressure[22]. To increase accuracy, these clinical parameters can be combined with measurements of serum urea (low in hypervolaemia and SIAD, high in hypovolaemia) and serum uric acid (normal or high in hypovolaemia except in renal salt wasting where levels are surprisingly low; low in SIAD)[23]. If the patient is found to be hypovolaemic, the urine sodium concentration can help reveal the underlying cause. In all cases of hypovolaemia, with the exception of renal salt wasting, the kidney will avidly retain sodium and the urinary sodium will be less than 20 mmol/L (urine sodium <20mmol/L is a sensitive indicator of decreased circulating volume)[2].

The presence of a euvolaemic state can be confirmed by a urinary sodium measurement of > 40 mmol/L, assuming sufficient dietary salt intake. The causes of euvolaemic hyponatraemia can be further differentiated by measuring the urinary osmolality. The urinary osmolality will be low, that is the urine will be maximally dilute, in conditions where there is appropriate suppression of vasopressin such as in primary polydipsia. Conversely, urine will be less than maximally dilute in SIAD and cerebral salt wasting (remember that urinary osmolality is made up of many osmolytes other than sodium so there is no direct relationship between urinary sodium and urinary osmolality)[2,24].

In hypervolaemic patients, the urinary sodium again helps to differentiate the cause. Renal failure in hypervolaemic patients is suggested by a urinary sodium of >40 mmol/L. Other causes of hypervolaemia (CHF, cirrhosis, nephrotic syndrome) will result in a decreased effective circulating volume and avid retention of sodium by the kidney through the renin-angiotensin-aldosterone system[2,25].

TREATMENT

There is not a single, proven strategy for the treatment of hyponatraemia[11]. However, irrespective of the treatment modality chosen, in the case of symptomatic hyponatraemia in which correction is critical to avoid neurological damage, it must increase serum sodium with sufficient speed in order to prevent serious neurological sequelae while avoiding the devastating effects of osmotic demyelination. When hyponatraemia presents with less severe symptoms, correction is still necessary but it can be achieved over a longer time period as the immediate risks of severe neurological damage due to the hyponatraemia are not present.

Osmotic demyelination occurs with the over-rapid correction of long-standing hyponatraemia (>48 hours). The significance of the risk of osmotic demyelination cannot be overestimated. Sodium correction of >12mmol/L/24 hours, or in some reported cases as little as 10 mmol/L/24 hours[26], can result in central pontine demyelination. This condition leads to multiple neurological deficits including

$$\text{Change in serum sodium} = \frac{\text{infusate}^{*}\ Na^{+} - \text{serum } Na^{+}}{\text{Total body water}^{\dagger} + 1}$$

*Normal saline infusate Na^{+} = 154 mmol/L
Hypertonic saline (3%) infusate Na^{+} = 513 mmol/L

† Total body water in non-elderly women = body weight in kilograms x 0.5
Total body water in non-elderly men = body weight in kilograms x 0.6
Total body water in elderly women = body weight in kilograms x 0.45
Total body water in elderly men = body weight in kilograms x 0.5

Figure 4. Calculating infusion rate in symptomatic hyponatraemia. Adapted from 11,29.

dysarthria, dysphagia, quadriparesis, pupillary and occulomotor abnormalities. Osmotic demyelination can also occur outside the pons resulting in a huge variety of lesions in structures such as the cerebellum, external capsule, hippocampus, putamen, cerebral cortex, thalamus and caudate nucleus[27].

Certain populations are more at risk for osmotic demyelination syndromes. These include alcoholics, malnourished populations, those with prolonged use of diuretics as well as patients post-liver transplant. It should be emphasized, however, that regardless of the aetiology of the chronic hyponatraemia and the method used to correct it, there is always a risk of osmotic demyelination with rapid correction of hyponatraemia[27]. This review focuses on the treatment of the most common type of hyponatraemia encountered – hypotonic hyponatraemia.

Symptomatic hypotonic hyponatraemia with euvolaemia or hypervolaemia and *concentrated* urine should be treated with hypertonic saline until such time that either i) the symptoms have resolved ii) the serum sodium is >130mmol/L or iii) the serum sodium has been increased by a total of 18mmol/L. Associated hypothyroidism and cortisol deficiency should be treated concurrently as appropriate. (Note that autocorrection of hyponatraemia can result from treatment of these conditions without the addition of saline or water restriction so these patients are at particular risk for inadvertent rapid correction of the serum sodium and osmotic demyelination). The serum sodium may be increased by 1-2 mmol/L for several hours in patients with severe symptoms, but total correction in 24 hours should ideally be kept below 8 mmol/L. This should be feasible, as small increases in serum sodium substantially decrease cerebral oedema and alleviate symptoms[28]. There are several formulae available to calculate the speed and concentration of the infusion necessary to achieve a controlled increase in serum sodium and one example is given in Figure 4. This formula calculates the magnitude of the change in serum sodium with infusion of 1 full litre of infusate. The litre of fluid should be given over a sufficient amount of time so that the hourly increment in sodium concentration does not exceed 1–2mmol/L/hour[29]. Furosemide – a loop diuretic – may be administered along with hypertonic saline to avoid excessive volume expansion[28].

Patients with hypervolaemia and *concentrated* urine with less severe or no symptoms and patients with hypotonic euvolaemic hyponatraemia with dilute urine can be treated with water restriction (usually < 800mL/day) and close observation. Severe symptoms (for example seizures or coma) may call for the use of hypertonic saline in those with dilute urine. Water restriction in these cases needs to be closely monitored as water restriction carries the same risk of osmotic demyelination as the use of hypertonic saline[28].

Hypovolaemic hypotonic hyponatraemia can almost always be managed with isotonic saline[2]. Patients with hypovolaemic hypotonic hyponatraemia associated with the use of thiazide diuretics use should stop the drug and it should not be reintroduced as the hyponatraemia is likely to return with reintroduction of the drug[30].

Details of the long-term management of hypotonic hyponatraemia is beyond the scope of this article but broadly speaking SIAD is traditionally managed by removing any inciting cause as well as restricting water intake. Hypervolaemic hypotonic hyponatraemia is more effectively managed with salt restriction and diuretics (with the exception of renal failure where fluid restriction is necessary)[28].

VAPTANS

The recent introduction of vasopressin antagonists, the 'vaptans', offers clinicians new options for the management of hyponatraemia. These drugs work by antagonising the vasopressin receptor in the medullary collecting duct (V_2R) of the kidney. This halts insertion of water channels and leads to increased excretion of free water. The first of these drugs, conivaptan, approved by the FDA in 2005, has been approved for short-term in-patient intravenous use. It is restricted to inpatient use due to its potent inhibition of the cytochrome P450 isozyme CYP 3A4 and subsequent potential for serious drug interactions. Its action is not confined to the V_2R as it antagonises vasopressin receptors on blood vessels, platelets and the myocardium, increasing the potential for adverse effects[28,31-2]. This drug's ability to antagonise such a wide range of receptors may have advantages, however, and current research is exploring the potential use of conivaptan in congestive heart failure where antagonism of vasoconstriction and increased platelet adherence mediated by vasopressin may be advantageous[33-4].

In contrast to conivaptan, the newly approved tolvaptan is V_2R selective. It is available as an oral preparation and exhibits fewer CYP 3A4 interactions. It is indicated for the treatment of hypervolaemic and euvolaemic hyponatraemia with inappropriately concentrated urine where the serum sodium concentration is <125 mmol/L or where the patient is symptomatic and has resisted correction with fluid restriction[35-6]. As it is an oral preparation with fewer drug interactions it is suitable for outpatient use. However, as with all methods of correcting hyponatraemia, initial correction must

be closely monitored and the patient should be admitted to hospital for this[28].

An understanding of the pathophysiology of hyponatraemia makes the indications for the use of the vaptans clear. In situations where there is *inappropriate* concentration of urine, that is where the total body water is normal or increased, the vaptans can be used to encourage the excretion of free water by the kidney in order to increase the sodium concentration. There is no role for the vaptans in conditions where urine is appropriately concentrated, such as in dehydration, or where the sodium is low due to increased water or decreased solute intake. Finally, the role of vaptans in the treatment of acute severe hyponatraemia that is unsuitable for a trial of water-restriction has yet to be defined.

CONCLUSION

Hyponatraemia is a common electrolyte imbalance with an aetiology that is still imperfectly understood. It can be associated with a large spectrum of neurological complications ranging from mild, reversible cognitive deficits to permanent and devastating neurological disability. The cause of the drop in serum sodium must be accurately determined in order to choose an appropriate and safe treatment. Once the diagnosis is made, striking the balance between adequate and dangerous correction still poses a significant challenge. The introduction of vasopressin antagonists has been a significant advancement in the management of the condition. This treatment option, along with ever-expanding knowledge of the complex physiology underlying sodium homeostasis, promises to improve the outlook for patients with hyponatraemia in future years.

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A 25-year-old woman with dysphagia and food impaction: A case of asthma of the oesophagus?

Aoife Sweeney *(Fourth Year Medicine, TCD)*

Clinical Points

- Eosinophilic oesophagitis (EO) is a relatively novel inflammatory disease characterized by eosinophilic infiltration of the oesophageal mucosa.
- Symptoms of EO include dysphagia, food impaction, chest pain, heartburn, early satiety and abdominal pain.
- Diagnosis of EO is made histologically by taking a biopsy of oesophageal tissue on endoscopy.
- Various food, environmental and drug allergens are thought to play a role in the pathogenicity of EO.
- The mainstay of treatment of EO includes ingested corticosteroids and identification and avoidance of dietary allergens. Mechanical dilatation of the oesophagus may be carried out in severe cases.

Presentation of Case

RD, a twenty-five year old Irish female, presented to her general practitioner (GP) following a recent episode of food impaction in her oesophagus and associated chest tightening after a meal. Although she admitted to having suffered from swallowing difficulties over the past five years, RD had never sought previous medical attention as she found it difficult to describe her symptoms and felt they would not be recognized as a medical problem.

RD reported that whenever she swallowed food, it 'did not clear properly from her throat.' She also reported feeling 'bloated' and 'over-full' after small meals; however, she did not experience symptoms of heartburn (a burning sensation in the chest or throat) or gastro-oesophageal reflux (regurgitation of gastric acid into the oesophagus). RD further denied any abdominal pain, haematemesis (vomiting of blood) or changes in her appetite or bowel habit. She did, however, admit to eating less at mealtimes to ease the bloating she experienced but denied any weight loss as a result. Moreover, she was unable to identify any other factors that aggravated or relieved her dysphagia (difficulty in swallowing) and bloating.

Aside from additionally noting an itchy rash on her left forearm, RD was healthy, with no other relevant medical or surgical history. She was not taking any medications at the time of presentation and denied any drug allergies. When questioned about her family's medical history, she reported that her father had been diagnosed four years previously with hypertension, and that both her brother and aunt each suffered from asthma and eczema. At the time of consultation, RD was a student living in Dublin. She was a non-smoker, had never taken illicit drugs and consumed approximately eight units of alcohol per week. Review of systems was non-contributing.

On examination, RD was apyrexial with a blood pressure of 115/75 mmHg and a pulse rate of 68 beats per minute. Her abdomen was found to be soft and non-tender. On the anterior surface of her left forearm, her GP noted an erythematous, macular rash. There were no positive findings on physical examination of cardiovascular, respiratory, genitourinary and neurological systems.

Investigations and Diagnosis

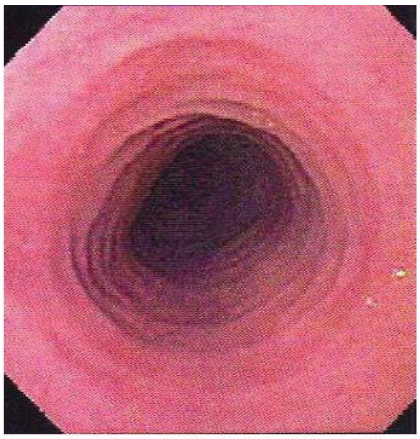
The differential diagnosis for RD's symptoms included both oesophageal and gastric pathologies. Potential oesophageal aetiologies included oesophagitis (inflammation of the oesophagus), oesophageal web (a thin, smooth extension of normal oesophageal tissue into the lumen of the oesophagus causing dysphagia), achalasia (inability of the lower oesophageal sphincter to relax) and oesophageal cancer. Gastric diagnoses considered included gastro-oesophageal reflux disease (GORD), gastritis (inflammation of the gastric mucosa) and infection with Helicobacter pylori (a flagellate organism that causes excess gastric acid secretion and potential ulcer formation). Coeliac disease was also considered as a differential as it is known to cause vague abdominal bloating and indigestion, as well as an itchy, blistering skin rash (dermatitis herpetiformis), and in addition, is a very common condition in Ireland.

Initially, RD's GP ordered a full blood count, as well as ferritin, folate and B12 levels to rule out anaemia since RD was only eating small meals (potentially causing a reduced nutrient intake), in addition to this being a sign of malabsorption. Her GP also

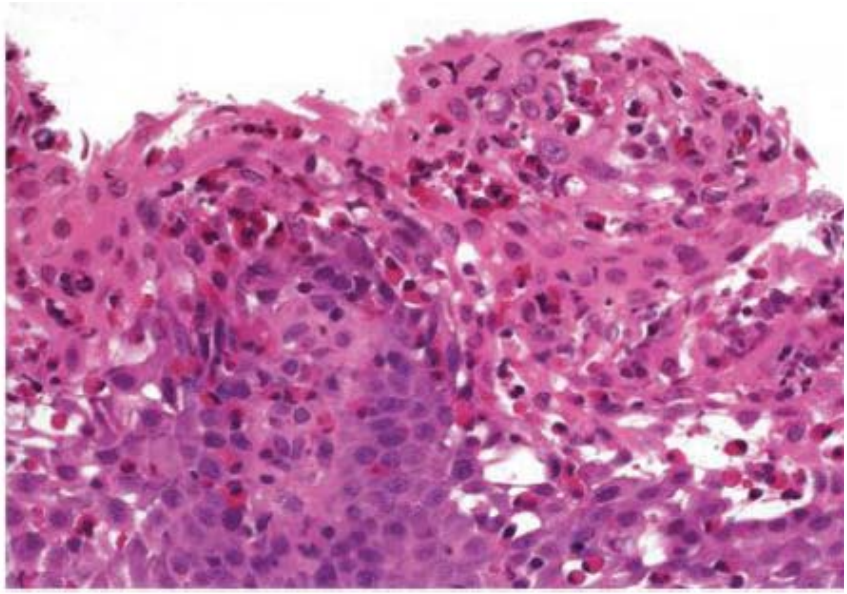
measured her tissue transglutaminase (tTG) autoantibody level, as tTG is a marker for coeliac disease. All were found to be normal. The rash on RD's left forearm was diagnosed by her GP as eczema.

RD was then referred by her GP to a consultant gastroenterologist for an oesophago-gastro-duodenoscopy (OGD), which involves visualizing the oesophagus, stomach and duodenum with a gastroscope, and permits biopsy of the gastrointestinal mucosa. On OGD, inflammatory changes consistent with gastritis were seen in the antrum of RD's stomach. Furthermore, an oesophageal tissue biopsy revealed 'moderate eosinophilic infiltration' which is consistent with current guidelines published by the First International Gastrointestinal Eosinophilic Research Symposium (FIGERS) for a diagnosis of eosinophilic oesophagitis (EO). Refer to Figures 1 and 2 for gross and histological examples, respectively, of EO.

Of note, testing for Helicobacter pylori was undertaken by performing a rapid urease test on a tissue biopsy sample taken during her OGD; this was found to be negative. In addition, RD had also been referred for a barium swallow test. This test involves the oral consumption of a barium sulphate solution that permits the visualization of oesophageal narrowing, hiatal hernias (a defect of the lower oesophageal sphincter causing parts of the stomach to slide into the oesophagus), ulcers and oesophageal tumors on x-ray. No abnormality was detected.



▲ **Figure 1: View of eosinophilic oesophagitis on endoscopy.**



▲ **Figure 2: Histological appearance of eosinophilic oesophagitis. Many eosinophils are present at the luminal surface in this biopsy. Notice the eosinophilic microabscesses and 'moth-eaten' appearance due to intercellular oedema (haematoxylin-eosin, original magnification x400).**

MANAGEMENT

A dual diagnosis of EO and gastritis was established in RD and thus management required targeted treatment of both conditions. To treat her EO, RD was prescribed Fluticasone in inhaler form (200mcg, four puffs twice daily) by her consultant gastroenterologist. In order to target the proximal oesophagus, RD was advised to 'ingest' the Fluticasone, which involved spraying the inhaler into the back of her throat while holding her breath and then swallowing. This technique differs from the inhaler technique used in the treatment of asthma whereby the patient is instructed to 'inhale' deeply after spraying the corticosteroid inhaler.

Fluticasone is a corticosteroid that acts to decrease inflammation of the oesophageal mucosa by reducing the synthesis of the inflammatory mediators IL-5 and eotaxin-3, both of which play a significant role in eosinophil activation and have been shown to be upregulated in EO. A reduction in these inflammatory mediators has been proven to decrease oesophageal mucosal inflammation, thereby alleviating symptoms of dysphagia and food impaction[1].

In addition, RD was prescribed 30 mg of Lansoprazole twice daily, and 10 mls of Gaviscon three times daily for her gastritis. Lansoprazole is a proton pump inhibitor, which reduces the secretion of gastric acid by blocking the hydrogen/potassium ATPase enzyme system of gastric parietal cells. Reduced acid secretion helps to alleviate symptoms of bloating and early satiety. Like Lansoprazole, Gaviscon also has an antacid effect. The combination of calcium carbonate, sodium bicarbonate and magnesium carbonate permits neutralization of gastric acid, and thus provides similar relief of the symptoms of gastritis.

RD was advised to use an over-the-counter hydrocortisone cream for her eczematous rash.

Outcome and Follow Up

RD was followed up one month later with her consultant gastroenterologist at which time she reported a dramatic reduction in her symptoms of dysphagia and bloating. Consequently, the consultant reduced both her Fluticasone and Lansoprazole to maintenance doses of 200mcg two puffs, twice daily and 15mg twice daily, respectively. RD is due to meet her consultant again in six months time for further review of her symptoms and medications. In the long term, RD is likely to be on a maintenance dose of 15mg Lansoprazole twice daily and Fluticasone 200mcg one puff, once daily as symptoms of EO have been found to recur on cessation of corticosteroid therapy[2].

Discussion

Eosinophilic oesophagitis (EO) is defined as an inflammatory disease of the oesophagus and is characterized by eosinophilic infiltration of the oesophageal mucosa[3]. An American gastroenterologist, Robert Landres, first described the condition in 1978[4]; but it was not until the late 1990s that EO was established as a clinical condition[5]. Until approximately ten years ago, EO was considered to be a rare disease and patients were often misdiagnosed as having GORD[5]. Its prevalence, however, is now on the rise as it becomes more widely recognized among physicians. A study carried out in Ohio in 2003 described a prevalence rate of four in ten thousand children in the United States[6]. Exact figures for the Republic of Ireland are currently unknown.

As EO is a relatively new condition, its exact pathophysiology is not well understood. Currently, however, the eosinophilic inflammation seen in patients with EO is thought to represent an allergic process and many food (wheat, eggs, milk, soy)[7] and drug (carbamazepine)[8] allergens have been implicated. These allergens are believed to induce T helper cells to produce inflammatory mediators IL-5 and IL-13, which are thought to play a key role in eosinophil activation. IL-13 appears to cause epithelial cells of the oesophagus to overexpress eotaxin-3 (an eosinophil chemoattractant), while IL-5 appears to regulate eosinophil numbers and their response to eotaxin-3[5]. This eosinophilic allergic response results in impaired smooth muscle function of the oesophagus giving rise to the typical clinical symptoms of EO such as dysphagia, food impaction and chest tightening[5], all of which were experienced by the patient in this particular case. Other common symptoms of EO not experienced by RD include reflux and heartburn[9]. It is this hypersensitivity response to various allergens in association with eosinophilic infiltration of the oesophageal mucosa by which EO receives the title 'asthma of the oesophagus'[10].

Given that EO is an atopic condition, patients commonly present with co-morbid eosinophil-mediated allergic diseases such as eczema, allergic rhinitis, asthma or various food allergies[9]. If food allergens are implicated, dietary alterations in conjunction with corticosteroids may provide maximal symptom relief[9]. Interestingly, after a diagnosis of EO was established, RD underwent skin prick testing and was found to have a wheat allergy, a common allergen associated with EO[11]. RD has thus since been observing a wheat-free diet which, in combination with the use of Fluticasone, has alleviated her symptoms of dysphagia, chest tightening and food impaction.

It is important to distinguish between coeliac disease and wheat allergies, as either condition can co-exist with EO[11,12]. Although these diseases share some similar symptomatic features (such as abdominal pain, cramping and bloating), they differ in their underlying pathophysiology. A wheat allergy is an allergy to the albumin protein of wheat, and involves an IgE-mediated inflammatory response[12]. Coeliac disease, on the other hand, is a T cell-mediated inflammatory disorder that results from hypersensitivity to the gluten protein of wheat[12]. In this particular case, the patient was found to have a wheat allergy and not coeliac disease. Nevertheless, physicians should be acutely aware of the link between EO and coeliac disease given that approximately 1% of the Irish population suffers from coeliac disease[13]. Moreover, a study of an Australian paediatric population undergoing endoscopy for coeliac disease found that approximately 4% of the study group had co-existing EO[14]. Therefore, in light of the high prevalence of coeliac disease in Ireland and it's co-existence with EO, it would be prudent for doctors to bear this in mind in the clinical setting.

A final point of clinical interest is that patients suffering with EO commonly present with dysphagia, which is also a prominent symptom of oesophageal cancer[15]. Although there are no known links between EO and oesophageal cancer at this time, it is of utmost importance that any patient with symptoms of dysphagia and food impaction seek immediate medical attention to rule out the possibility of an underlying malignancy. What is alarming about this particular case is that the patient experienced symptoms of dysphagia for five years before seeking medical attention. This highlights the importance of patient education and the current need for health promotion campaigns to avoid such a lengthy delay in the presentation of patients with dysphagia in the future.

CONCLUSION

EO is a relatively new condition that is currently under-diagnosed in the medical community. Its prevalence, however, is on the rise as more cases are reported from various parts of the world due to an increasing awareness of the condition among clinicians. Since the clinical presentation mimics other gastrointestinal diseases, especially GORD, patients may be misdiagnosed, making endoscopic examination and histological evaluation of oesophageal mucosal biopsies crucial for accurate diagnosis of the disease. In addition, awareness and treatment of co-morbid allergic conditions may permit optimal management of affected individuals. In RD's case, diligent and prudent medical practitioners resulted in a prompt and accurate diagnosis of her condition, thereby permitting the development of an appropriate and effective management plan and an overall improvement in her quality of life.

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New neurons in the adult hippocampus: Hope or hype?

André Mendonça Madaleno (*Third Year Medicine, TCD*)

CLINICAL POINTS

- Adult neurogenesis is the generation of functional neurons from neural stem cells present in the adult.
- Adult hippocampal neurogenesis occurs in the subgranular zone of the dentate gyrus, a central component of the hippocampal neural network.
- Adult neurogenesis is stimulated by specific types of learning, exercise and neurotrophic factors such as BDNF and Shh. It is downregulated by corticosteroids, inflammation and some drugs.
- Recently, several epigenetic mechanisms have been found to regulate neurogenesis and the maturation of new neurons.
- Upregulation of neurogenesis has been implicated in the molecular mechanism of action of treatments for depression (e.g. antidepressant drugs and ECT); possible future applications include treatment of stroke and traumatic brain injury.

ABSTRACT

Stem-cell research has caused a paradigm shift in our understanding of brain function and regeneration. Discovery of the production of functional neurons in the adult hippocampus, a neurogenic niche of the central nervous system (CNS), has refuted the long held theory proposed by Ramon y Cajal that in the CNS "everything may die, nothing may be regenerated". Neurotrophic factors, activity-dependent neurogenesis, downregulation factors and post-translational regulatory mechanisms seem to interact in a complex and still ill-explored fashion to control this endogenous regenerative process. Moreover, in animal models, upregulation of neurogenesis is achieved with fluoxetine and other antidepressant therapies such as electroconvulsive therapy (ECT), demonstrating the clinical relevance of this mechanism. In fact, recent studies suggest that the upregulation of neurogenesis might also provide treatments for conditions such as traumatic brain injury (TBI) and stroke.

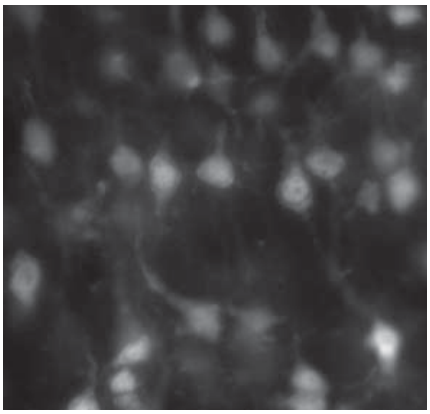


Figure 1:

Immunofluorescent microscopy from rat hippocampus tissue where NeuN was used as a marker and mature neurons can be clearly visualized. This technique and double or triple marker techniques provide an easy and reliable protocol to count different types of cells in hippocampal tissue. Image collected by the author in the Institute of Neuroscience, Trinity College, Dublin.

INTRODUCTION

Stem cells are distinct from most other cells in the body due to their ability to both proliferate indefinitely and to generate a variety of differentiated cell types. In a similar manner to haematopoietic stem cells that produce red blood cells, white blood cells and platelets, neural stem cells can differentiate into the main cells of the CNS: neurons, astrocytes and oligodendrocytes[1-2]. Neurogenesis is the production of mature neurons from neural stem cells. This process was detected in adult humans only a decade ago[3-5], but has since been confirmed in two distinct regions of the brain: the subventricular zone and the dentate gyrus of the hippocampus[6]. The newly formed immature neurons begin expressing a series of transient markers, such as doublecortin, followed by later markers like neuronal nuclear protein (NeuN), present in fully differentiated neurons (see Figure 1). During the differentiation process, dendrites develop within the hippocampal network by initially forming synapses at dendritic shafts and later forming more mature synapses with dendritic spines such as thorny excrescences[7-8]. van Praag et al[9] and others have shown that these neurons are functionally relevant in a key area of the brain involved in memory and emotion – the hippocampus[9-11]. This review provides an introduction to the function and neurogenic properties of the hippocampus followed by an analysis of the regulatory mechanisms of neurogenesis and the possible clinical applications of its stimulation in several neurological conditions.

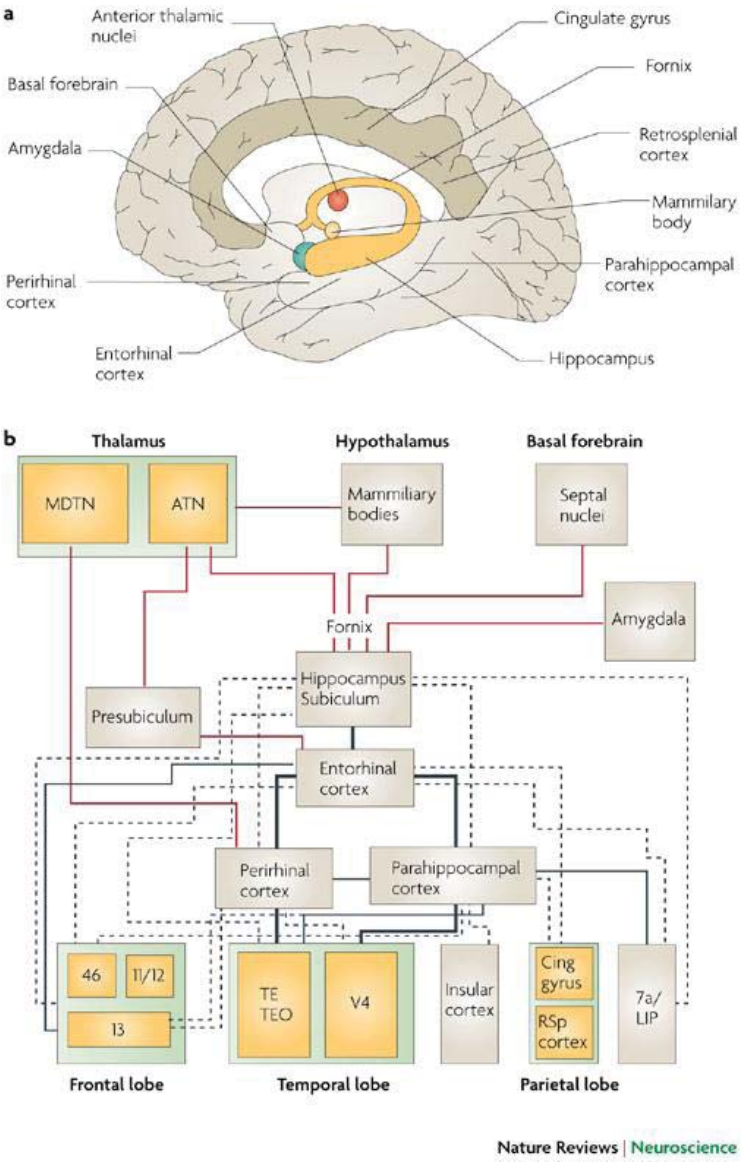


Figure 2: The hippocampus is connected to cortex regions (represented by black lines) and subcortical structures such as anterior thalamic nuclei (ATN), medial dorsal thalamic nuclei (MDTN) and others (represented by red lines). Figure reproduced from Bird C, Burgess N. The hippocampus and memory: insights from spatial processing. Nature Reviews Neuroscience. 2008; 182-94.

STRUCTURE AND FUNCTION OF THE HIPPOCAMPUS

The hippocampus includes the hippocampus proper, the subiculum and the dentate gyrus and maintains an anteroposterior functional specialization pattern. The ventral (anterior) part has been linked to emotionality whilst the dorsal (posterior) part is associated with learning[12-13]. Other studies, using functional magnetic resonance imaging (fMRI), have shown how ventral hippocampal activity is associated with the processing of novel stimuli. This activity gradually shifts to the dorsal hippocampus as these stimuli become more familiar, suggesting that the latter region is associated with long-term memory[14]. Moreover, left-right asymmetry is found in the hippocampus since the anterior left hippocampus is associated with new language material while the right hippocampus is involved in spatial activities such as driving a car[15]. All of these different functions are enabled by the large and diverse set of connections between the hippocampus and other brain regions (see Figure 2).

THE HIPPOCAMPUS: A NEUROGENIC NICHE

Neurogenesis within the hippocampus is supported by its diffuse neuronal connections to other regions of the brain and the characteristics of the hippocampal dentate gyrus, where neurogenesis takes place. The hippocampus receives cholinergic, noradrenergic, serotonergic and dopaminergic connections, most of which pass through the hippocampal fornix. These inputs appear to be important for synaptic plasticity and adult hippocampal neurogenesis[16]. For example, inhibition of serotonin production with the drug parachlorophenylalanine (PCPA) is associated with a reduction in the number of new neurons produced in the dentate gyrus[17].

The dentate gyrus receives connections from the entorhinal cortex and projects efferent connections of unmyelinated granule cell axons (mossy fibers) through the fornix, thereby playing a fundamental role in the hippocampal neuronal network[18]. Its particular properties include the specific functions of astrocytes and capillaries which seem to create a "neurogenic niche". Thus, the dentate gyrus is a microenvironment within the CNS that has unique characteristics allowing for the differentiation of neural progenitors and their integration into the neural circuitry.

Vascular endothelial growth factor (VEGF), a well characterized angiogenic factor, appears to stimulate neurogenesis in the dentate gyrus[19]. This supports the concept of the neurogenic niche as also a "vascular

niche," a dynamic biochemical microenvironment of angiogenesis and vascular remodelling. In fact, Palmer et al[20] found that in vivo areas of high neural stem cell proliferation are in close proximity to dentate gyri capillaries which suggests an overlap between angiogenic and neurogenic mechanisms in the adult brain.

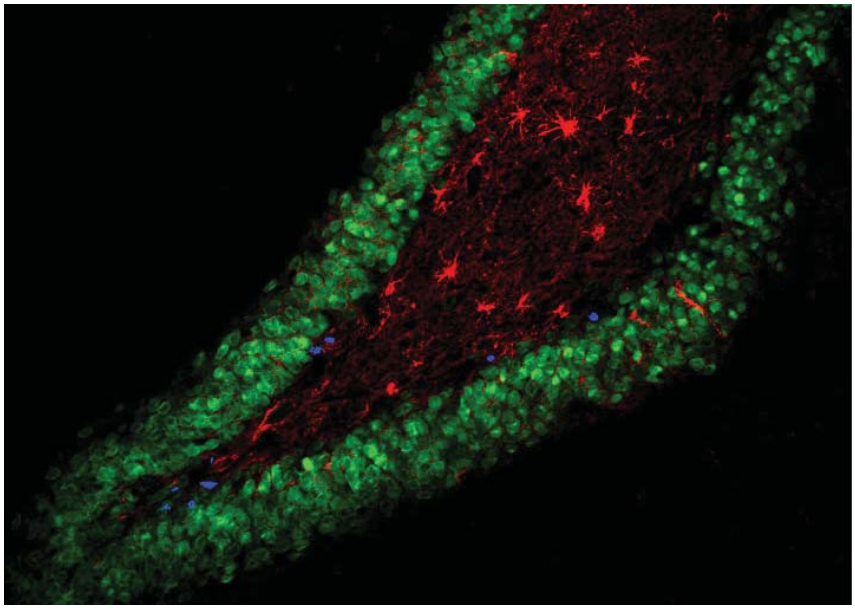
Similarly, astrocytes, now considered the most important non-neural cells involved in regulating neurogenesis, are apposed to the subgranular zone of the dentate gyrus – the zone where neurogenesis takes place (see Figure 3)[21-25]. They promote proliferation and neuronal specification of adult neural stem cells in vitro whereas astrocytes from non-neurogenic areas such as the spinal cord do not. This view is supported by their unique ability to produce neurogenic signals, such as neurogenesin-1, a neuronal cell fate factor that promotes the specialization of neural stem cells into neurons rather than astrocytes[26].

Moreover, certain activities can influence this neurogenic niche. Besides the special properties of astrocytes and angiogenesis in the dentate gyrus which allow for a basal level of neurogenesis, certain types of learning or simple physical exercise have been shown to upregulate hippocampal neurogenesis.

ACTIVITY-DEPENDENT NEUROGENESIS

It is now commonly accepted that adult neurogenesis in the hippocampus is stimulated by local factors such as nearby synaptic activity and systemic factors including some hippocampal-dependent types of learning and physical exercise.

On a synaptic level, there is in vitro evidence for the direct stimulation of neural stem cells through glutamate NMDA receptors and Cav1.2/1.3 channels. Administration of antagonists such as nifedipine to these L-type calcium channels causes a complete block of excitation-induced neurogenesis in rodent models[27]. Moreover, antagonizing NMDA receptors in neural stem cells in vitro blocks both excitation-induced neurogenesis and basal neurogenesis levels[27]. Paradoxically, indiscriminate NMDA glutamate receptor agonist binding seems to reduce neurogenesis in vivo. It is postulated that this effect is mediated by inhibitory GABAergic hippocampal interneurons activated by NMDA glutamate receptors[28-29]. Hence, there is a counterbalance to excitation-induced neurogenesis mediated by GABAergic interneurons.



▲ **Figure 3:** Unlike the remainder of the hippocampal formation, populated by pyramidal cells, the dentate gyrus has granular cells and is composed of the subgranular zone, containing the neural progenitors (blue) responsible for adult neurogenesis, and the outer granular and molecular layers with granular cells (neurons) in green. In this rat brain slice, astrocytes (red) were also marked. This photo was taken in the lab of David Schaffer at the University of California, Berkeley.

The evidence for the stimulation of neural stem cells through NMDA and Cav1.2/1.3 channels demonstrates how neurogenesis is influenced by neuronal activity at a cellular level. Conversely, behavioural data obtained by Shors et al[30] shows that some types of learning are dependent on adult neurogenesis. Hippocampal-dependent types of learning include trace fear conditioning (formation of memories of noxious events) and spatial learning (measured in rodents using a Morris water maze exercise). This study found that only some of these types, such as trace fear conditioning, are dependent on active adult hippocampal neurogenesis suggesting a significant but complex role of adult neurogenesis in hippocampal-dependent learning[30-31].

Similarly, rodent studies looking at the effects of physical exercise on neurogenesis and cognition provide a basis for an exercise-induced neurogenesis hypothesis[32-33]. Through future research, these results might help to explain human cohort data identifying a correlation between cardiovascular fitness and cognition levels[34-35].

Recent studies have also linked the regulation of adult hippocampal neurogenesis with leptin[36], diet[37] and sleep patterns[38]; suggesting that some factors of overall health and lifestyle may influence brain func-

tion by regulating neurogenesis. Although the interplay of all of these factors in the process of neurogenesis is not completely understood, much is known about the mechanisms involved in its control, which include both neurotrophic and downregulation factors.

NEUROTROPHIC FACTORS

A neurotrophic factor is any regulatory factor present in the CNS that upregulates neurogenesis. These include VEGF, fibroblast growth factors 1 and 2 (FGF-1 and FGF-2), oestrogen and endothelial growth factor (EGF). However, two of the most studied and well understood are the brain derived neurotrophic factor (BDNF) and Sonic hedgehog (Shh).

BDNF promotes the differentiation and survival of new neurons in the adult and is essential for the development of the embryonic CNS. A reduction in BDNF is thought to play a role in neurodegeneration, chronic stress and depression[39]. BDNF binds to TrkB, a tyrosine kinase receptor, thereby activating a series of molecular cascades which are fundamental for normal hippocampal structural development. For example, one of these pathways includes mitogen-activated protein kinase kinase (MEK) and extracellular regulated kinase (ERK)[40]. The transcription of BDNF is regulated by calcium/cyclic-AMP responsive-element binding protein (CREB), itself phosphorylated by this MEK-ERK pathway, thus establishing a positive feedback mechanism. Stressful environments, as replicated in animal models, are associated with a down regulation of BDNF mRNA and protein levels[41-43]. Similarly, CREB has been shown to be down regulated in the cerebral cortex of depressed patients and to be reduced in the dentate gyrus following stress. It is thought that most antidepressants achieve their effect through the upregulation of the CREB-BDNF pathway and possibly subsequently through hippocampal neurogenesis[39-44].

Similarly, Shh not only promotes early neural development in the embryo but also promotes survival of stem cell niches in the adult brain. While its role is not yet completely understood, Shh has been shown to elicit a dose-dependent proliferation in neural progenitor cells both in vitro and in vivo. In fact, blocking Shh signalling reduces hippocampal neural stem cell proliferation in vivo[45-46].

DOWNREGULATION

Downregulators of hippocampal neurogenesis such as nicotine, opiates, alcohol, endogenous glucocorticoids and IL-6 have an opposite effect to that of neurotrophic factors[28]. The inflammatory marker IL-6 is particularly interesting since it counteracts a compensatory increase in neurogenesis following neuronal death and inflammation caused by TBI (see Clinical Uses for further discussion). In the rodent model, transgenically induced astroglial production of IL-6 reduced hippocampal neurogenesis by 63% possibly through autocrine and/or paracrine mechanisms[47]. Furthermore, the action of glucocorticoids provides a mechanism that explains how overactivity of the hypothalamo-pituitary-adrenocorticoid axis, present in patients suffering from depression, might be partially responsible for the lower levels of neurogenesis observed in these patients[48].

In addition to these regulators of neurogenesis, there are also mechanisms that control neurogenesis at an upstream level by means of post-translational control of gene expression.

POST-TRANSLATIONAL REGULATORY MECHANISMS

Post-translational regulatory mechanisms, such as epigenetics and microRNA (mi-RNA), influence gene expression without altering the DNA sequence present in all somatic adult cells. As a result, these mechanisms control the production of regulatory factors and the ultimate fate of neural stem cells.

Epigenetic control mechanisms are post-translational modifications of DNA and nuclear proteins that produce permanent changes in chromatin structure and therefore regulate gene expression[49]. Several epigenetic regulatory mechanisms of neurogenesis have been identified in the past decade[50-51] such as DNA methylation[52]. DNA methylation is a well understood post-translational modification that involves the addition of methyl groups to lysine residues of chromatin by DNA methyltransferases. This reduces the transcription of these methylated genes, a process referred to as gene silencing. There are also proteins which demethylate promoter regions thereby allowing for the transcription and expression of the previously methylated genes. Ma et al concluded that the Gadd45b gene, expressed in mature neurons, was required for the demethylation of BDNF and FGF-1 promoters thereby allowing these neurotrophic factors to be transcribed. Gadd45b gene knockout in a rodent model caused a significant reduction in activity-induced neurogenesis and dendritic development[52].

Another post-translational mechanism regulating neurogenesis involves miRNA and was identified by Cheng et al using rodent models. miRNAs are 22-nucleotide-long non-coding RNA sequences that cause the degradation or inhibition of complementary sequences of mRNA

thereby reducing gene expression[53]. This mechanism regulates neurogenesis in the subventricular zone rather than the hippocampus; however, it provides an example of what might underlie neurogenesis control in all neurogenic niches of the CNS. In this study, miRNA miR-124, which causes the downregulation of the transcription factor Sox9, was suggested to be important for adult neurogenesis. Sox9 stimulates glial cell formation from neural stem cells. miR-124 reduces Sox9 expression, thereby promoting an alternative cell fate: neurogenesis. Hence, miR-124 increases the proportion of neurons to glial cells produced from the proliferating neural stem cells and functions as a "neuro-glial cell fate switch" [54-56].

The mechanisms of epigenetic control of neurotrophic factor production and the mi-RNA based "neuro-glial cell fate switch" help us to better understand the process by which cells differentiate and integrate into a complex network such as the CNS. While the clinical potential of these post-translational mechanisms is unknown, other areas of research into adult neurogenesis have already discovered several clinical implications.

CURRENT AND FUTURE CLINICAL IMPLICATIONS

Upregulation of neurogenesis has been inadvertently used as the mainstay of treatment for depression for decades until its role was brought to light by Santarelli et al. Their study showed that selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, did not have an antidepressant effect in animals where neurogenesis was eliminated by selective irradiation of the hippocampus[44]. Hence, the first clinical application of the upregulation of neurogenesis was identified.

In current clinical practice, the treatments that involve upregulation of adult hippocampal neurogenesis are used solely for depression. These include some antidepressants, such as fluoxetine[31], and electroconvulsive therapy (ECT)[57], used in cases of severe depression refractory to conventional pharmacotherapy. The antidepressant effect of ECT seems to be mediated in part by increased VEGF production. This provides a possible explanation for the efficacy of ECT in cases where pharmacological antidepressants do not work because these agents do not increase VEGF production[28,58]. In fact, the clinical use of ECT might be improved in the near future as some small clinical trials, which have focused on fine-tuning the electrical pulse width and electrode placement, have shown increased treatment efficacy and a reduction of its classic side-effects including retrograde amnesia[59].

Another important therapeutic goal for the future is to discover a treatment that would upregulate endogenous neurogenesis after TBI or stroke, hence improving motor and cognitive patient outcomes. It is known that VEGF-induced neurogenesis10 is part of the endogenous repair response to ischaemic stroke in the adult cortex[60] even though it is not clear to what extent cortical neurogenesis is present in adult humans[6]. While adult cortical neurogenesis is significant in vertebrates like fish, amphibians and reptiles, it seems to have been suppressed throughout evolution in birds and mammals[61].

A complete understanding of the necessary conditions for the upregulation of functionally significant neurogenesis after stroke or TBI has not yet been reached. Nevertheless, promising experiments using doublecortin and NeuN markers have shown new hippocampal neurons to migrate to ischaemic striatal areas after induced ischaemic events in rodent models[62-63]. Unfortunately, these new neurons have minimal survival rates in their new location. As a result, the clinical significance of these migratory neurons is limited until the necessary conditions for their integration into functional networks are discovered[62-64].

A caveat for possible future treatments involving the upregulation of neurogenesis is the risk of deregulated neurogenesis. Results from González-Martínez et al[65] suggest that spontaneous neurogenesis is associated with pharmacoresistant human neocortical epilepsy. Nevertheless, it is still unclear whether this is related to its pathogenesis or an endogenous mechanism of repair that fails to function in this condition.

Moreover, it has been shown that it is possible to improve sensorimotor and learning outcomes by upregulating neurogenesis after damage to the mammalian cortex. For example, Shear et al[66] used mammalian models to transplant exogenous neural stem cells after TBI. They reported positive behavioural and motor outcomes, providing a basis for future use of neural stem cells in a wide range of pathologies[66-67]. Another method by which this might be achieved was demonstrated by Xiong et al[68]. This study concluded that administration of erythropoietin six hours post-TBI provided neuroprotection and neurorestoration by enhancing neurogenesis, angiogenesis and synaptic plasticity in the dentate gyrus of a rodent model. More importantly, erythropoietin improved sensorimotor and spatial learning outcomes[68]. The biochemical mechanism of erythropoietin has been studied in the subventricular zone and it appears to upregulate BDNF and VEGF production[69]. Nevertheless, erythropoietin, after an early successful clinical trial[70], was tested in a randomized multicenter trial which has shown that it is not acceptable for use in stroke

due to an increase in mortality at 90 days post stroke[71-72]. Therefore, while we know that it is possible to upregulate neurogenesis with positive clinical outcomes, no drug that will safely do so has yet been discovered.

CONCLUSION

The discovery of adult neurogenesis in key regions of the CNS such as the hippocampus has changed our understanding of brain function and repair[73]. The previous model of a fixed adult neuronal circuitry, similar to a computer circuit board, may be replaced by a model of a more dynamic nature, constantly adapting to exogenous and endogenous signals[74]. Moreover, current knowledge of the regulatory mechanisms involved in neurogenesis allows us to understand the mechanisms of action of some treatments for depression and provides a new framework for research on treatments for many common neuropsychiatric and neurological disorders, including stroke and TBI. Hence, the discovery of adult neurogenesis will probably change the way we treat brain injury as much as it has changed our understanding of how the brain functions.

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ORIGINAL RESEARCH

Best Research

Generic prescribing: A cross-sectional study comparing the prescribing practices of a HSE and a NHS hospital

James Murphy and Sebastian McWilliams *(Fifth Year Medicine, UCC)*

CLINICAL POINTS

- Generic prescribing was found to be significantly lower in a HSE hospital compared to a NHS hospital.
- Generic prescribing has a definite cost benefit and a potential safety benefit to patients.
- Clear handwriting on drug charts may reduce prescription error rates.
- Clinical pharmacist chart review provides the opportunity to both reduce medication errors and to enhance generic prescribing rates.
- Undergraduate medical curriculum should include a dedicated clinical therapeutics module.
- HSE hospitals should consider the introduction of a hospital prescribing formulary.

ABSTRACT

Background: Generic prescribing is currently a politically important topic in Ireland as it is seen as a potential source for easing the healthcare budget.

Objective: To compare prescribing practices at a Health Service Executive (HSE) and a National Health Service (NHS) hospital, with an emphasis on the level of generic prescribing.

Design: A comparative cross-sectional study.

Data Source: Bedside drug charts and medical notes of surgical and medical inpatients.

Methods: Each ward in the respective hospitals was sampled once between July 2009 and September 2009; all patients (over age 17 years) present were included as subjects at the time of assessment. Patient demographics, in addition to the name, dose, frequency, and route of administration of prescribed drugs, were recorded. Clinical pharmacist (CP) review was also noted. A database was constructed for statistical analysis.

Results: HSE hospital patients (n=301) and NHS hospital patients (n=296) received 3640 drug prescriptions (52.5% generic) and 3962 prescriptions (79.7% generic), respectively. A lower level of CP chart monitoring was noted in the HSE hospital (41.5% versus 97%, p<0.001). The rate of drug chart errors was 4.2% in the HSE and 1.5% in the NHS hospital. For all proton pump inhibitors (PPIs) prescribed in the HSE hospital, generic substitution could have saved €23.83/day, according to the Monthly Index of Medical Specialities (MIMS).

Conclusion: Increased generic prescribing in the HSE hospital has potential cost and safety benefits.

Contributor:
Professor Julia Kennedy
Associate Professor in Clinical Pharmacy,
School of Pharmacy, UCC

INTRODUCTION

Prescribing is a central element in the life of contemporary medical practitioners. The adage "the pen is mightier than the sword" has never been more apt; modern medicines can bring about a potential cure to many conditions that previously were only considered treatable via surgery or not at all. However, with this power comes the responsibility of making ethical clinical prescribing decisions in the context of a finite healthcare budget. Central to the theme of responsible prescribing is the issue of generic versus proprietary prescribing. Generic prescribing is widely regarded as best practice medicine[1].

Generic medications, by definition, contain the same active ingredients as their proprietary counterparts. Upon conception, a new drug must navigate its way through clinical trials until both its safety and clinical efficacy are approved by the relevant regulatory bodies; the Irish Medicines Board carries out this task in Ireland. On introduction to the market, this new drug is protected by a patent, giving the parent pharmaceutical company exclusive rights to production and sale of the drug for a specified time period under a proprietary or brand name. When the patent expires, the drug can then be produced by any pharmaceutical company in the form of a generic medication, which contains the same active compound as

the proprietary medication but now under a different name. There may be a slight difference between generic and proprietary drugs in the ultimate composition of the formulation when considering non-active ingredients or excipients. This difference is usually of little clinical consequence, with the exception of some medications that have a narrow therapeutic index or some anti-epileptic drugs[2]. There is a misconception that generic medications are not as safe as their proprietary counterparts. Indeed, generic medications must meet the same standards of clinical safety and efficacy as the proprietary medication in order to enter the market[3].

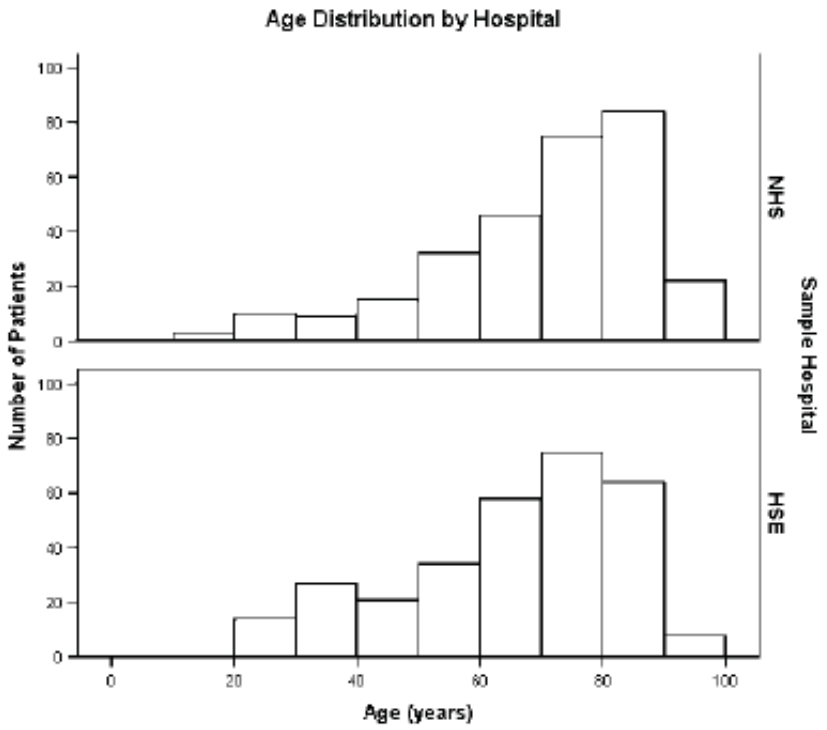
In Ireland, medications account for approximately 13.5% of the healthcare budget[4]. Policy makers believe increased generic prescribing could be a source of potential savings[5,6,7,8]. The Health Service Executive (HSE) of Ireland is regarded as having a relatively low rate of generic prescribing in contrast to the National Health Service (NHS) in the United Kingdom (UK), which promotes high levels of generic prescribing in all areas of healthcare[9]. A literature search using Pubmed, Medline, and Embase revealed that no study exists comparing hospital prescribing practices in the HSE and NHS; this study intends to address this deficit.

OBJECTIVE

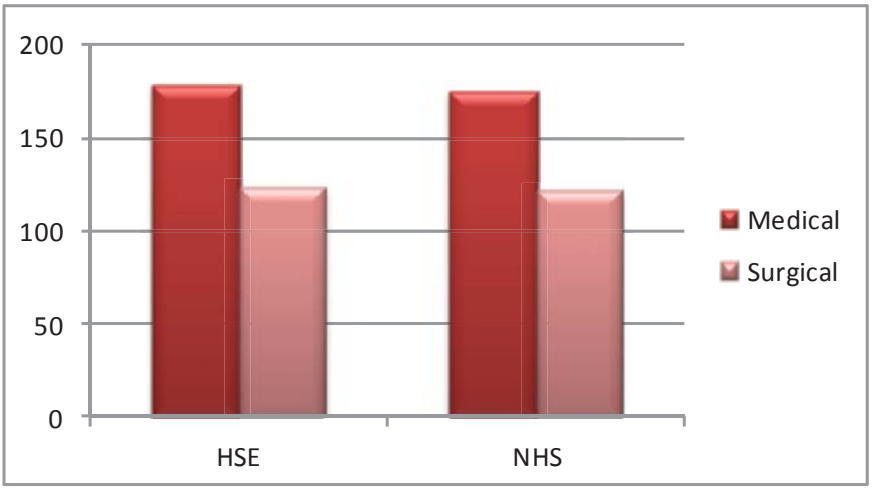
The aim of this study was to compare prescribing practices at a HSE and a NHS hospital, with an emphasis on the level of generic prescribing.

METHODS

A comparative cross-sectional study was designed to elicit any differences in prescribing practices between a HSE and a NHS hospital. The respective HSE and NHS hospitals were chosen as the study centres due to similar bed capacities and service case-mixes. Ethical approval was granted from the ethics committees of each institution. Inclusion criteria specified that subjects should be medical or surgical inpatients over the age of 17 years, and their bedside drug charts and medical notes provided the data source for this study. Data collection was performed by a single researcher and was carried out at the NHS hospital between 23/07/09 – 12/08/09 and from 21/08/09 – 10/09/09 at the HSE hospital. Each relevant ward was sampled once and all patients on the ward at the time of sampling were included as subjects. Approximately 40% of the data collection in each hospital took place over a weekend.



▲ **Figure 1:** Age distribution of subjects by hospital



▲ **Figure 2:** Breakdown of subject numbers under medical or surgical care by hospital

HSE Hospital		NHS Hospital	
Paracetamol	212	Paracetamol	217
Innohep	101	Aspirin	146
Aspirin	88	Enoxaparin	134
Lactulose	79	Cyclizine	118
Movicol	68	Octenisan	112
Tramadol	65	Simvastatin	109
Senna	57	Naseptin	107
Furosemide	51	Senna	92
Atorvastatin	45	Oramorph	90
Stemetil	41	Omeprazole	35

▲ **Table 1:** List of the 10 most commonly prescribed medications by hospital.

	HSE Hospital	NHS Hospital
Generic	52.5%	79.7%
Proprietary	41.7%	10.7%
Appropriate proprietary	5.7%	9.6%

▲ **Table 2:** Percentage of all medications prescribed in generic, proprietary and appropriate proprietary format by hospital.

	HSE Hospital	NHS Hospital
Generic	53.5%	80.4%
Proprietary	42.8%	16%
Appropriate proprietary	3.7%	3.6%

▲ **Table 3:** Percentage of O.O, PRN, and parenterally administered drugs in generic, proprietary, and appropriate proprietary format by hospital.

The data collection was performed such that no patient identifiers were stored to ensure anonymity.

Demographic details of the subjects, in addition to the name, dose, frequency, and route of administration of prescribed drugs, were recorded. Whether a clinical pharmacist (CP) reviewed the drug chart was also noted. Prescribers' handwriting clarity was subjectively assessed as adequate or poor based on the ease of legibility by the researcher carrying out data collection. Medications were classified as generic, proprietary, or appropriate proprietary; drugs considered appropriate proprietary were prescribed as proprietary combinations of two or more drugs in fixed doses (e.g. Sinemet®). Cost evaluations for the HSE and NHS hospitals were based on the prices stated in the Monthly Index of Medical Specialties (MIMS) Ireland August 2009 and the British National Formulary[57], respectively. For the MIMS-based costs, the generic cost was deduced by substituting the cost of the cheapest available bioequivalent generic medication in the correct dose formulation for the prescribed proprietary medication.

All data was input into Microsoft Access® 2007; statistical analysis was performed in SPSS version 14. Chi-squared tests were employed to perform subgroup analysis of categorical variables; Student's t-test was used to compare continuous variables by subgroups.

RESULTS

Patient Characteristics

Data on 301 and 296 subjects were collected in the HSE and NHS hospitals, respectively. An analysis of the population variables revealed NHS subjects to be more elderly [mean ages: HSE 65 years versus NHS 71 years ($p=0.002$) Figure 1]. Males accounted for 56% and 48% of the HSE and NHS subjects, respectively ($p<0.05$). While the absolute numbers of medical and surgical patients were different in each hospital, the difference in proportion between hospitals was not significant (Figure 2). Furthermore, there was no significant difference in the level of generic prescribing between medical and surgical patients in both hospitals.

Prescribing Practices

A total of 3640 and 3962 medications were prescribed to HSE and NHS subjects, respectively. This equated to a mean of 12.1 (SD=5.6) medications per subject in the HSE hospital as opposed to 13.4 (SD=5.6) in the NHS hospital ($p<0.05$). The ten most commonly prescribed medications to study subjects are listed in Table 1.

A clinically significant higher level of generic prescribing was seen in the NHS hospital (79.7% generic) compared to the HSE hospital (52.5% generic) ($p<0.001$, Table 2).

Similar analysis was performed to consider once only (O.O), pro re nata (PRN), intramuscular, intravenous and subcutaneously administered medications, which are drug forms only prescribed in hospital (Table 3). A clinically significant higher level of generic prescribing was seen in the NHS hospital (80.4% generic) compared to the HSE hospital (53.5% generic) ($p<0.001$).

In addition, 41.5% of HSE drug charts had been reviewed by a CP as opposed to 97% in the NHS hospital ($p<0.001$). 34.9% of HSE drug charts contained at least one error compared to 17.2% of NHS drug charts ($p<0.001$). Based on individual prescriptions, an error rate of 4.2% was calculated in the HSE hospital as opposed to 1.5% in the NHS hospital ($p<0.05$). Handwriting was subjectively assessed as "poor" in 14.3% of HSE bedside charts compared to 6.4% in the NHS hospital ($p=0.002$). A breakdown of prescribing errors is displayed in Table 4.

	HSE Hospital	NHS Hospital
Illegible	1	1
Inappropriate decimal point	62	17
No dose	2	0
No route	1	0
No units	19	2
Wrong dose	22	17
Wrong name	4	1
Wrong route	1	4
Wrong units	40	18

▲ **Table 4:** Number of errors by category by hospital

Cost

In the HSE hospital, 74 patients had proton pump inhibitors (PPIs) prescribed in a proprietary format despite the presence of an off-patent generic being available. With reference to these 74 prescriptions, savings of €23.83/day could have been achieved had they been prescribed in the generic format.

DISCUSSION

One of the first prescribing lessons taught to undergraduate medical students is to use generic medication where possible. The reasoning behind this lesson is threefold. Firstly, generic medications are generally cheaper than their proprietary counterparts, therefore minimising cost. The widely used EASE (Effective, Appropriate, Safe, and Economic) model of medication prescribing recognises this concept[10,11]. Increased generic prescribing could have saved €21.8 million in Ireland in 2003 from expenditure on the Drug Payment Scheme and the General Medical Card scheme[12]. Secondly, undergraduate and postgraduate teaching, in addition to medications referenced in the literature, discuss medications using the generic name. It would be logical to extend use of this common language of medications into clinical practice. Thirdly, from a practical view point, using generic naming facilitates pharmacists as the logistical pressure of proprietary prescribing is eased. More importantly than simple logistics, the pharmacist may elect to dispense the cheapest available formulation.

In this study, 41.7% of the HSE hospital prescriptions were in the proprietary format. In contrast, 20.1% of prescriptions were of a proprietary nature in the NHS hospital. The fact that the baseline population demographics were well matched, with the exception of age, adds to the significance of this result. From first principles, a more elderly population in the NHS hospital would not confound the analysis of generic prescribing rates. The similarity of the proportion of medical and surgical subjects in both hospitals is an important finding as it has been reported that prescribing tends to be of a poorer quality in surgical wards[13]. The current study found no statistically significant difference in the proportion of generic prescriptions between the medical and surgical specialities.

These results add to the growing evidence demonstrating that the rate of generic prescribing in Ireland is low[14,15,16]. Bennett et al found generic prescribing to be as low as 4.6%[17]. This contrasts sharply with the situation in the UK where prescribing is predominantly generic in accordance with the British National Formulary (BNF). The percentage of generic prescriptions written in the UK rose from 38% in 1985 to 69% in 1998[18]. Indeed, a recent paper estimated that approximately 80% of prescriptions in the UK are now filled using generic names[19]. The current study findings are in agreement with that estimate.

There are a number of reasons to potentially explain the discrepancy seen in prescribing practices of physi-

cians. Many suspect that prescribing doctors are influenced by pharmaceutical company-sponsored events, and it has been suggested that part of the problem has resulted from a subtle collusion between the two parties[20]. Recently, a six-point plan was published to address the interaction of the pharmaceutical industry with prescribing doctors[21]. Two key recommendations within this plan include that pharmaceutical industry-sponsored continuing medical education should be abolished and that doctors should forgo industry gifts. To many, these are key issues, as they influence doctors' prescribing habits, making the use of proprietary agents more likely.

A potential confounding factor influencing the level of proprietary prescribing seen in the HSE hospital in the current study was that patients may have had certain medications prescribed to them prior to admission to hospital. To account for this, an analysis of the prescribing breakdown of O.O, PRN, and parenterally administered medications was undertaken. With few exceptions, these forms of medications are prescribed on an inpatient basis. There was a similar and equally low level of generic prescribing among the hospital-exclusive subset of medications comparable to the overall level observed in the HSE hospital (See Table 2 and Table 3). This highlights that the level of generic prescribing by medical professionals in the HSE hospital is low. As inpatient drug charts are typically written by a junior doctor, educational interventions in this group have the potential to improve prescribing practices.

CPs are regarded as the guardians of hospital prescribing. There is good evidence confirming the net positive benefit this speciality brings to the healthcare community[22,23,24]. Responsibilities of the CP include review of drug charts and identifying and attending to any prescribing errors. There is a possible association between the lower level of generic prescribing in the HSE hospital and the lower level of CP drug chart review. Increased CP input is seen as a potential method to both reduce the prescription error rate and to possibly alter prescribing habits in the HSE hospital. This may be achieved by allowing the CP to substitute a proprietary prescription for a generic.

The issue of medication errors is currently contentious. Recently, the General Medical Council UK commissioned the EQUIP (Errors—Questioning Undergraduate Impact on Prescribing) study to look at prescribing errors among newly qualified doctors in relation to their medical education[25]. The results showed that newly qualified junior doctors' medication error rate did not differ significantly from their more experienced colleagues. The report strongly encourages the need to increase the emphasis of clinical pharmacology in the undergraduate medical curriculum[26], which many feel is inadequate at present[27,28]. The medical school affiliated with the studied NHS hospital has a 17-week intensive course which combines the core subjects of medicine, surgery, and therapeutics. No dedicated therapeutics course exists in the current undergraduate curriculum of the medical school affiliated with the HSE hospital in this study. It is hypothesised that increased clinical therapeutics teaching would lead to better prescribing habits once qualified[29]. The EQUIP study also recommended the adoption of a standard drug chart throughout the NHS to facilitate a reduction in drug errors.

Poor handwriting of the prescribing physician is often the culprit for medication errors[30]. Despite the subjectivity of the assessment, the higher level of poorly written charts in the HSE hospital poses the opportunity for intervention. A standardised national drug chart may mitigate the effect of poor handwriting as contextual clues on an easily recognised chart would aid understanding.

In Ireland, the proportion that medicines contribute to the overall budget of the General Medical Scheme is significant and is thus a target for cost reductions. Among the methods outlined to achieve such savings are proposals to increase the frequency of generic prescribing. The Department of Health in the UK is hoping to adopt a tactic wherein a pharmacist can substitute a generic drug for certain medications prescribed in the proprietary format. The ultimate aim of such an intervention would be to save money without adversely affecting the quality of care provided. In addition, PPIs have come under scrutiny as many feel they are frequently prescribed without proper indication[31,32,33,34,35]. This group of medications is relatively expensive, however, omeprazole, lansoprazole, and pantoprazole are now off-patent and available generically. As all PPIs have an identical mode of action, it is reasonable to prescribe a cheaper generic alternative to gain the same class-effect benefit[36]. 74 proprietary PPIs were prescribed at the studied HSE hospital despite the availability of an off-patent generic. Had these drugs been prescribed generically, savings of €23.83 per day would have been realised.

This study had several potential weaknesses. Despite analysing several hundred patients from each hospital selected, only one hospital was considered from each healthcare system. A larger sample of hospitals would be needed to generalise conclusions; this study compares the two hospitals as typical examples of their respective system. In addition, cost analysis was done using the MIMS

Ireland. This publication provides medication wholesale costs to retail pharmacies but does not accurately reflect hospital pharmacy costs.

CONCLUSION

Greater levels of generic prescribing in healthcare have a theoretical safety benefit to patients as well as a definite cost benefit. This study highlights that a higher level of generic prescribing could be achieved in the respective HSE hospital if prescribing practices were improved. Enhancing education to prescribing physicians both at an undergraduate and postgraduate level provides the opportunity to promote generic prescribing practices. Other measures such as adopting a generic drug formulary would have a further impact on the proportion of generic prescribing in HSE hospitals. In addition, an increased level of CP drug chart monitoring not only permits the opportunity to ensure generic drug use but may also reduce prescribing errors. This study then, while circumspect to generalise from single institutions, provides evidence of room for systemic improvement in HSE prescribing practices which would be beneficial to the individual patient and the wider population.

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The cervical cancer vaccine in Ireland: Well worth the wait

Eva Mc Larnon and Aimee Murphy *(Fifth And Sixth Year Medicine, TCD)*

CLINICAL POINTS

- Cervical cancer results in approximately 300,000 deaths worldwide per annum and is the third most common cancer in women.
- Over 99% of cervical cancer histological specimens incorporate Human Papilloma Virus (HPV) DNA.
- HPV 16 and 18 are the strains most commonly implicated in the development of cervical cancer.
- Currently, CervicalCheck offers free papanicolaou smears to women in Ireland for the early detection of pre-cancerous lesions and cervical carcinoma; widespread vaccination has the potential to further reduce cervical cancer deaths.
- Two vaccines offer protection against HPV: Gardasil (HPV 6,11,16,18) and Cervarix (HPV 16,18); clinical trials have demonstrated the efficacy of these vaccines for up to 5 years.
- A report in Ireland by the Health Information and Quality Authority (HIQA) indicated that introduction of HPV vaccines into a national immunisation programme, in conjunction with regular papanicolaou smear screening, would be cost effective.

ABSTRACT

Cervical cancer is the third most common cancer in women and results in approximately 300,000 deaths worldwide per annum. Research has uncovered that infection with particular types of the human papilloma virus (HPV) is the strongest independent risk factor for the development of cervical carcinoma. Due to this relationship, vaccines against the foremost carcinogenic strains of the virus were developed in hopes that they would prevent the subsequent development of malignancy. Two vaccines currently exist: the quadrivalent vaccine, Gardasil and the bivalent vaccine, Cervarix. Both vaccines target the two Human Papillomavirus strains that are most commonly associated with the development of cervical cancer, types 16 and 18. The Gardasil vaccine also targets Human Papillomavirus types 6 and 11, which are commonly associated with genital warts. Five-year follow-up studies have shown both vaccines to be over 90% efficacious. There is, however, a lack of long-term data on both vaccines and more research is necessary to further evaluate their long-term outcomes on the prevention of malignancy. Currently, the major protection offered to women in Ireland against cervical cancer is that of secondary prevention via regular screening with the papanicolaou smear. A vaccine campaign is due to commence later this year, with the introduction date currently set as September 2010. It is expected that immunisation against the Human Papillomavirus in combination with regular papanicolaou smear screening will result in a reduction in the incidence of cervical cancer in Ireland. In this review, the link between cervical cancer and the Human Papillomavirus will be discussed in addition to providing support for the introduction of the Human Papillomavirus vaccines into the Irish immunisation schedule.

INTRODUCTION

Cervical carcinoma is the uncontrollable growth of cells in a woman's cervix and is the third most common cancer in women resulting in 300,000 deaths worldwide per annum[1]. In Ireland, there is an average of 180 new cases of cervical cancer diagnosed each year with an incidence of 23.64 per 100,000 women[2]. Furthermore, cancer of the cervix results in 73 deaths annually in Ireland with an average age of mortality of 56 years[2].

Infection with human papilloma virus (HPV) is a critical factor in the development of the majority of cases of cervical cancer. One study found that over 99% of cervical cancer histological specimens had incorporated HPV DNA[3,4]. HPV infects cervical cells via integration of its viral DNA into the host DNA, disrupting key protective proteins of cervical cells and up regulating viral proteins[5]. The result is cells with malignant potential, liable to cause cancer if they are not detected early and treated.

There are many different strains of HPV with some types being more carcinogenic than others. HPV 16 and 18, in particular, are considered high-risk strains and have been implicated in up to 77% of cervical cancers in developed countries[6]. Within Ireland, studies on the prevalence of HPV 16 and 18 found that of those women infected with HPV, 31.5% were infected with HPV 16 and 12% were infected with HPV 18[7,8]. Despite this high prevalence, women in Ireland remain unprotected against these two strains of HPV.

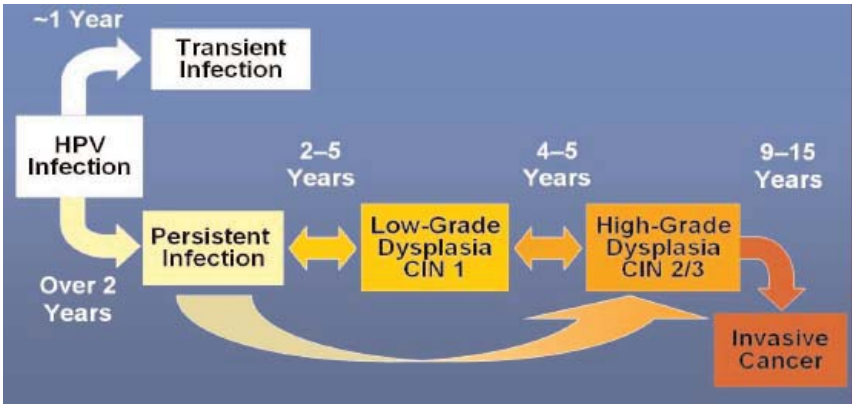
Currently, a screening programme is in place for the early detection of

cervical dysplasia. The National Cervical Screening Programme, 'CervicalCheck', was introduced in Ireland in September 2008. This programme targets 1.1 million eligible women aged 25 to 60 years old and is expected to result in a 91% cumulative risk reduction in the incidence of cervical carcinoma[1]. Under this programme, free cervical screening with a papanicolaou (pap) smear test is offered every three years for women aged 25 to 44 and every five years for women aged 45 to 60[9]. CervicalCheck does not incorporate a vaccine against HPV as part of its programme and therefore, does not prevent HPV infection at its outset.

The long-term outcomes of vaccination against cervical cancer have not been fully elucidated and more research is needed to assess the effectiveness of both commercially available vaccines. However, it is expected that immunisation against HPV in combination with regular pap smears will result in a further reduction in the incidence of cervical cancer. The aim of this article, therefore, is to discuss the potential benefits of introducing a vaccine against HPV in Ireland by reviewing the literature supporting their use with regards to both efficacy and cost effectiveness.

Cervical Cancer

Cervical cancer is primarily a neoplasm of the squamous cells of the cervix, the inferior part of the uterus[5]. The cervix is lined by both columnar and squamous epithelium, which meet at the squamocolumnar junction. During certain times in a woman's life, this junction shifts, under the influence of hormonal factors, exposing some of the columnar cells to the more acidic environment of the vagina[5]. As a result, some of these columnar cells undergo metaplasia or transformation to squamous epithelium. Cervical cells undergoing metaplasia are more susceptible to infection with HPV[5].



▲ **Figure 1:** This schema shows the relationship of a HPV infection and potential outcomes, with the probable timeline dependent on the individual's immune reaction to HPV. Source: Pagliusi[12]

Once infected with HPV, cervical epithelial cells show different characteristics compared to normal cells. Cells infected with HPV are more disorganised, they show enhanced mitotic activity, as well as nuclear pleomorphisms[5]. Cervical intraepithelial neoplasia (CIN) is the term used to describe this dysplastic change, and is considered a pre-cancerous lesion as this dysplasia can progress to malignancy[5]. The location of the dysplasia determines which type of CIN is present[5]. CIN 1 occurs when the abnormal cells are restricted to the lower third of the epithelium of the cervix. CIN 2 occurs when two thirds of the epithelium is involved, while CIN 3 occurs when the abnormal cells make up greater than two thirds of the cervical epithelium[5]. Stage 1 cancer occurs when there is invasion of the stroma of the cervix by these dysplastic cells[5]. For invasive carcinoma to occur from CIN 1, it usually progresses through to CIN 2 and subsequently CIN 3. However, not all cervical cancer progresses in this way, with 20% of CIN 2 and CIN 3 developing de novo[5].

Research has uncovered many other risk factors that are associated with the development of CIN and subsequent cervical cancer. These factors include early age at coitarche, multiple sexual partners, unprotected sexual intercourse and low socioeconomic status[5]. However, infection with HPV has been consistently implicated as the main aetiological agent in the development of cervical intraepithelial dysplasia and ultimately cervical cancer[5]. Factors such as cigarette smoking and immunodeficiency contribute to the development of cervical cancer by impairing immune clearance of HPV[5].

HPV and the Link to Cervical Cancer

HPV is recognised as the main cause of cervical intraepithelial dysplasia. HPV belongs to the Papillomaviridae family and is a non-enveloped icosahedral virus of circular, double-stranded DNA. HPV infects the cells of the cervix via integration of its viral DNA into the host DNA of cervical cells. During integration, viral E2 is disrupted, which is a key protein in the oncogenicity of HPV[10]. E2 is a transcriptional repressor of viral oncogenes E6 and E7 and its degradation thus leads to their up regulation[10]. Protein E6 binds to p53 promoting its proteolysis and thereby preventing virally infected cells from apoptosing. Protein E7 binds to pRb, an inhibitor which prevents growth of the virus within host cells. E7 degrades pRb,

which is no longer able to exert its action, thus promoting DNA synthesis of the virus within the host cells[11].

The integration of viral DNA into the cells of the cervix is a catalyst for the development of cervical cancer as they now have the ability to undergo dysplastic change[5]. The evolution to malignant cells takes approximately 9-15 years with the intermittent stages (CIN) detectable via the pap smear[5]. The typical progression of cell changes with time is illustrated in Figure 1.

The National Cervical Screening Programme: "CervicalCheck"

Free cervical screening under CervicalCheck was introduced in September 2008 and is offered to women in Ireland that satisfy certain criteria. Screening consists of a pap smear in which an endocervical brush is used to collect cells from the outer cervical opening, known as the os. These cells are kept in a liquid medium before being placed on a glass slide and examined microscopically for dyskaryosis. A smear is recommended every 3 years for women aged 25 to 44 and every 5 years for women aged 45 to 60. Screening is not warranted in those over 60, unless the woman has never had a previous smear. If a smear result is abnormal, a follow-up is arranged according to the CervicalCheck protocol. If CIN 1 is suggested cytologically, a repeat smear is advised in 6 months to check for progression. If CIN 2/3 is suggested, referral to colposcopy (cervix viewed more closely under microscope) is recommended[9].

Pap smear screening is the basis of CervicalCheck as it successfully enables detection and treatment of pre-invasive lesions and low-grade cancers, before they progress to invasive cancer[12]. With the advent of cytological screening programmes, the incidence of cervical cancer in the developed world has been significantly reduced. The American Cancer Society has cited that pap smears have reduced the death rate in the United States to one third of its value 50 years ago[13]. Despite the success of pap smear screening, however, there is still a high incidence of cervical cancer. The Irish Cervical Screening Research (CERVIVA) Consortium in 2009 reported a HPV prevalence rate of 18% in a population of 1,300 women screened[2]. The continued high incidence of cervical cancer despite the use of pap smear screening emphasizes the need for the introduction of a vaccination programme.

The HPV Vaccine: Structure, Function and Mechanism of Action

Vaccines against HPV were developed with the hope that, in combination with pap smear screening, they would lead to a significant reduction in the morbidity and mortality of cervical cancer. Currently, two vaccines have been developed and clinically evaluated, the quadrivalent vaccine, Gardasil, and the bivalent vaccine, Cervarix. Both vaccines target the two most common high-risk HPVs, types 16 and 18, while Gardasil also targets HPV 6 and 11 (responsible for >90% of genital warts). Results from clinical trials indicate that the vaccines are safe, well tolerated and highly efficacious in HPV naïve women[6].

Both vaccines are adjuvant non-infectious recombinant vaccines prepared from highly purified Virus-Like Particles (VLPs) of the relevant HPV viruses. VLPs contain the major capsid protein L1 without the viral DNA needed for replication. Thus, they are serologically indistinguishable from natural viral capsids but lack viral nucleic acid and are therefore non-infectious. Gardasil uses an aluminium-based adjuvant, whereas Cervarix uses the proprietary adjuvant ASO4. The difference in the adjuvant base of the two vaccines has been noted to affect immunogenicity. Clinical trials have demonstrated stronger antibody responses against HPV 16 and 18 in ASO4-based vaccines when compared to the aluminium-based vaccines[14]. Furthermore, higher titres of HPV L1–specific B cells were noted in the ASO4 adjuvant group[14]. It is unclear yet as to whether this will confer enhanced efficacy or a longer duration of immunity thereby necessitating further evaluation.

The mechanism of action of the vaccine has been elucidated using animal studies with analogous papillomaviruses. These studies have deduced that the efficacy of L1 VLP vaccines is mediated by the development of a humoral immune response. Studies in animal models have demonstrated that these L1 VLPs induce high titres of neutralizing serum antibodies, particularly Immunoglobulin G (IgG), which protect against cutaneous and mucosal papillomavirus challenge[14]. Both Gardasil and Cervarix have demonstrated immunogenic potential via their production of specific neutralizing antibodies.

Suggested Use and Efficacy of the HPV Vaccines

Current guidelines set up by 'The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices' in America, exist for the use of the HPV vaccine. Both vaccines are administered in 3 separate doses over a 6 month period. Cervarix injections are administered at 0, 1 and 6 months, while Gardasil administration occurs at 0, 2 and 6 months. Three doses are necessary to confer immunity with the vaccine, with maximal efficacy achieved 1 month after the final dose[6]. The current recommended ages for administration of the vaccines are 10-25 years for Cervarix and 9-26 years for

Gardasil, ideally pre-coitarche. The optimal target age of vaccination is 10-15 years. These indications are the result of two studies; Pedersen et al 2007 and Block et al 2006 showed a higher antibody titre in girls given the vaccines at 10-15 years of age versus those given the vaccine at 15-25 years of age[15,16]. The higher antibody titre is expected to confer a longer duration of protection.

Studies investigating the effectiveness of both vaccines in the prevention of CIN and the development of cervical cancer have been undertaken. Gardasil, the quadrivalent vaccine, has been approved for the prevention of cervical cancer and CIN 2/3 related to HPV 6, 11, 16, 18[17]. To investigate Gardasil's effectiveness, four placebo-controlled, double blind, randomized control trials have been conducted. These included two Phase I trials: Protocol 005 and Protocol 007 and two Phase III trials: FUTURE I & II (Females United To Unilaterally Reduce Endo/Ectocervical Disease). FUTURE I & II and Protocol 007 evaluated the full quadrivalent vaccine while Protocol 005 investigated only the HPV 16 portion of the vaccine. Included in the studies were 20,541 women aged 16-26 in 29 different countries. Inclusion criteria were those who were HPV 6, 11, 16, and 18 naïve at onset, remained negative for HPV through to month seven, and completed the 3-dose course of the vaccine within 1 year. In all four trials, subjects received doses on day 0, at 2 months and again at 6 months. Combined data from the four trials, after an average follow-up of 3 years, indicated a significant reduction in the number of HPV 6, 11, 16 and 18 associated cases of CIN. The results were 0 new cases of HPV 16 or 18 related CIN 2/3 versus 53 cases for placebo, conferring a 100% efficacy. For HPV 6, 11, 16 and 18 related CIN1/2/3, 4 new cases were found versus 83 for placebo, yielding an efficacy of 95.2%[18].

Cervarix, the bivalent vaccine, has been approved for the prevention of cervical cancer and CIN 2/3 related to HPV 16 and 18[10]. The efficacy of Cervarix was assessed in two placebo-controlled, double blind, randomized control trials, one Phase II trial and one Phase III trial. A total of 19,778 women aged 15 to 25 years were studied. In the Phase III trial, the PATRICIA study, the efficacy of Cervarix was analyzed in the total vaccinated cohort[19]. The efficacy of Cervarix in the prevention of CIN 2 associated with HPV 16 and/or HPV 18 was assessed at 14.8 months following the last dose of the vaccine or control. This study showed a significant reduction in the number of HPV associated CIN cases, with 2 new cases of CIN 2 or greater in the vaccinated cohort versus 21 new cases in the placebo group, conferring a 90.4% efficacy[19].

The statistically significant reduction in cases of CIN 2 and CIN 3 associated with the administration of Gardasil and Cervarix is expected to lead to a reduction in the incidence of cervical carcinoma. However, it is not known at this time the length of protection that either of these vaccines will confer. Gardasil has demonstrated clinical efficacy for up to 5 years against HPV 6, 11, 16 and 18. Recently available data has indicated that Cervarix is highly efficacious in preventing most CIN 2 lesions caused by HPV 16 and 18 for up to 5.5 years [20]. In addition, some studies suggest that a continued cross-protection against HPV 45 and HPV 31 infections may also exist with Cervarix[20]. It is unknown whether or not a booster will be required to maintain immunogenicity. Therefore, continued surveillance of vaccinated individuals is necessary to assess the entire length of protection. The length of immunity conferred and the possible need for a booster are important aspects in assessing the long-term cost effectiveness of the vaccines.

Cost Effectiveness of the HPV Vaccines

The cost effectiveness of introducing a vaccination programme against HPV in Ireland has been a continued topic of debate and was recently examined in a report called "The Role of Human Papillomavirus Vaccines in Reducing the Risk of Cervical Cancer in Ireland," that was published by the Health Information and Quality Authority (HIQA). In this report, the cost effectiveness was calculated based on the cost of vaccination minus savings on unneeded treatment, due to prevention of HPV 16/18 dyskaryosis and neoplasia. Another consideration of the cost effectiveness calculation was the morbidity prevented. The decrease in morbidity expected was based on the number of cases of CIN 1, 2/3 and invasive carcinoma in 2004. Results were expressed as Incremental Cost Effectiveness Ratios (ICER) per Life Year Gained (LYG). An Incremental Cost Effectiveness Ratio (ICER) is the difference between the cost of the new treatment and the current treatment, divided by the difference between the effect of the new treatment and that of the current treatment. A Life Year Gained (LYG) calculates the difference in the cost of having a vaccination programme, compared to the cost of having no vaccination programme, divided by the average difference in survival (in years) across the population at which you are looking, allowing one intervention to be compared with another.

Vaccinating 12 year old girls against HPV 16 and 18 was found to have an ICER of approximately €17,383/LYG[6]. Had the benefit to quality of life associated with the prevention of malignancy been included, this figure would be lowered further[4]. This is a favourable result considering that the usual threshold for the provision of drugs in Ireland is €45,000/QALY

(Quality Adjusted Life Year)[6]. A LYG does not take into account the quality (in terms of health status) of the year of life gained whereas a Quality Adjusted Life Year (QALY) is a measure of the year of life adjusted for its quality. A year in perfect health is considered equal to 1.0 QALY. The HIQA report showed the HPV vaccine to be more cost effective than the universal hepatitis B vaccination in Ireland (€37,019/LYG)[6]. If the catch-up vaccination for 13 -15 year olds was also to be included in the programme, this would raise the ICER of annual vaccination to €52,968/LYG which exceeds the threshold[4]. However, if quality of life gain was included in the analysis, (expressed as a QALY) this addition would likely also be rendered cost effective[6].

Vaccination of 12 year old girls as outlined in the HIQA study will begin in September 2010.[6]. This programme will also include a once-off catch-up vaccination for 13 -15 year old girls. Although it will take at least 15 years after implementation of the programme before monetary savings will begin to be seen it is none the less economically justifiable. Vaccination of young females in Ireland would not only prevent the anxieties that accompany a diagnosis of CIN but also the subsequent development of sequelae.

Limitations and the Future

Both the quadrivalent and bivalent HPV vaccines have limitations. There are more than 100 different types of HPV and at least 15 of them are oncogenic for which no immunity is provided[21]. Although it is estimated that HPV 16 and 18 cause 71% of cervical cancers, a further 29% of cases are attributed to non-vaccine protected strains[21]. The development of a vaccine that incorporates these additional strains is a possible future development.

Another limitation of the HPV vaccines is that the 5.5 year follow-up study for Cervarix and the 5 year follow-up studies for Gardasil may not be long enough for cervical cancer to develop. However, with the prevention of CIN 2/3, it is believed that the subsequent development of malignancy is unlikely. Ongoing long-term studies are needed to assess the true effect in the reduction of the incidence of cervical carcinoma in the vaccinated cohort.

Finally, Gardasil and Cervarix do not prevent HPV infections already present at the time of vaccination from progressing to cancer, stressing the continued need for cervical screening[22]. Laboratory research and several human clinical trials are currently ongoing for the development of therapeutic HPV vaccines that could possibly eliminate existing HPV infection[23].

Conclusion

The national screening programme plays a pivotal role in reducing the incidence of cervical cancer, however, cancer of the cervix still remains a highly prevalent gynaecological cancer. HPV types 16 and 18 have been implicated in 70% or more of cervical cancers. With the advent of the HPV vaccines against these strains, it is possible to have a primary prevention programme to prevent neoplastic lesions from the outset[6]. Cervarix and Gardasil vaccines, which target both of these high-risk viruses, have been introduced in a number of countries over the past few years. The ability of both vaccines to prevent CIN 2/3 in pre-coital females and the cost effectiveness by which this can be achieved indicates that HPV vaccination would undoubtedly be a beneficial addition to the Irish healthcare system. According to the National Cancer Institute, "Widespread vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds if all women were to take the vaccine"[2]. The vaccine, however, does not eliminate the need for scheduled cervical cytology and it is essential that the vaccine be combined with regular cervical smears in order to gain the maximum synergistic benefit.

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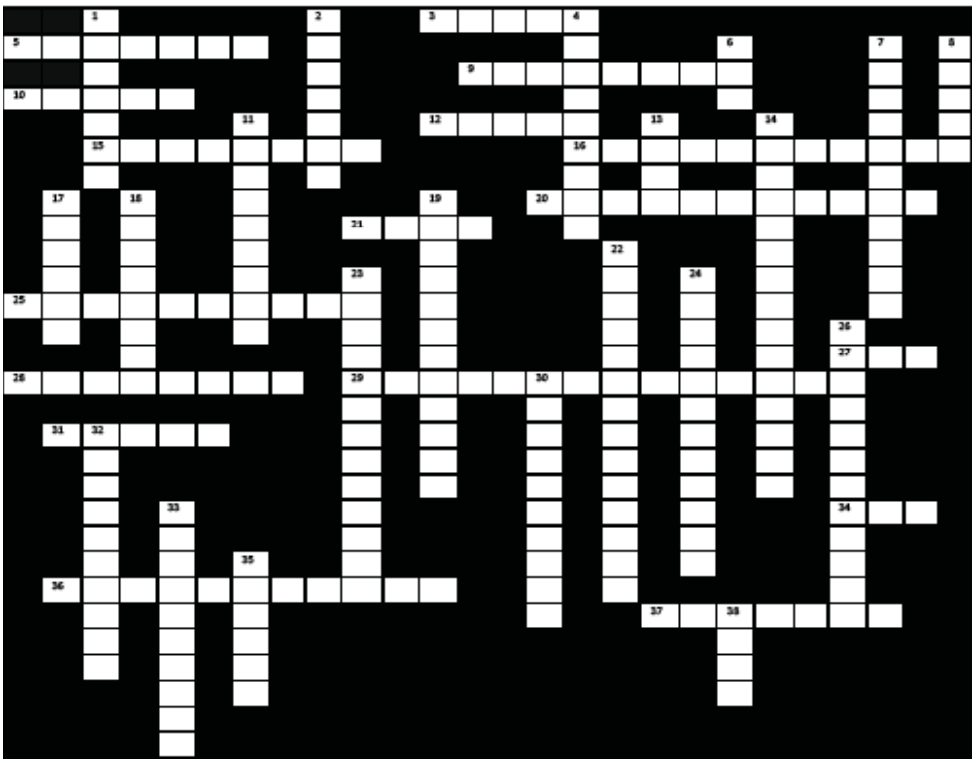
Created By Michael O'Sullivan *(Fourth Year Medicine, National University of Ireland, Galway)*



SOLUTION ON PAGE 89

ACROSS

3 **Postulates.(5)**
5 **Psoriasis is associated with this phenomenon.(7)**
9 Famous German Surgeon (8)
10 Earth (5)
12 **Wolff-Parkinson-White syndrome has this classic wave on E.C.G. (5)**
15 **Rupture of the middle meningeal artery may cause this haematoma.(8)**
16 **Form of focal dystonia following neuroleptics administration.(11)**
20 Spots in the iris of a Down Syndrome child.(11)
21 **This infection can cause spleenomegaly after kissing.(4)**
25 Antidote for malignant hypertension.(10)
27 Triplet repeated in Hungtinton's disease. (3)
28 **A syndrome characterized by postpartum hypopituitarism.(9)**
29 This antipsychotic can cause agranulocytosis. (15)
31 Second cranial nerve (5)
34 **Subsequent to a gastrectomy it is important to supplement the patient with this vitamin.(3)**
36 Bilateral lymphadenopathy and erythema nodosum would be suggestive of this diagnosis.(11)
37 **This clinical sign can be present with invasion of the sympathetic chain. (7)**

DOWN

1 **A type of prescription used to prevent antibiotic resistance. (7)**
2 **This fossa contains brachial contents.(7)**
4 **Type of conduction in myelinated nerves.(9)**
6 **The main psychoactive substance found in the Cannabis.(3)**
7 Cells promote the production of renin.(6,5)
8 **An important cycle in glucose metabolism.(5)**
11 **This type of breathing is associated D.K.A. (8)**
13 Palsy attributable to macrosomia.(4)
14 **Common infectious organism found in Lake Victoria.(15)**
17 Nerve that supplies the triceps.(6)
18 **If the hallux dorsiflexes this is a..... Babinski's sign.(8)**
19 **Spleenectomised patients are at increased of infection from this type of bacteria.(12)**
22 **"Shutter Eye".(9,5)**
23 Young Red Blood cells(13)
24 **A deep depression in the upper surface of the body of the sphenoid bone. (5,7)**
26 **1st choice antihypertensives in diabetics.(3,9)**
30 Causes slapped cheeks. (10)
32 **Painless jaundice and a palpable gallbladder in a patient is suspicious for this malignancy.(10)**
33 **The most lethal form of malaria.(10)**
35 **This score is use to predict whether induction of labour will be required. (6)**
38 Mature treatment for T.B.(4)

Recession blues: Investing in mental health despite no wealth

Maria Tempany *(Fourth Year Medicine, TCD)*

The human impact of the global economic downturn that hit in 2008 is only starting to be appreciated now. As people's jobs are lost and their assets plummet, it is clear that the mood of our society is falling equally fast. The relationship between our mental health and this global recession has yet to be addressed in an appropriate manner, or with the degree of compassion it warrants. Throughout this paper, I intend to highlight the importance of investing in mental health, especially in these current times of economic struggle.

It is difficult to dispute the fact that our health is deeply entwined with our wealth. The World Health Organization (WHO) takes a holistic definition of health as one that encompasses "physical, mental and social wellbeing [1]". The WHO further defines mental health in terms of functionality, as "a state of wellbeing enabling individuals to realise their abilities, cope with the normal stresses of life, work productively and fruitfully, and make a contribution to their communities [2]".

As a society, mental illness is not a condition that we entirely appreciate. This is largely due to the fact that it has been hidden under a veil of stigma and discrimination for a very long time. It is vital that all physicians have a strong grasp on mental health, as the prevalence of mental disorders among sufferers of chronic disease is considerably higher than it is among the general population, highlighting its relevance to all medical practitioners. While the prevalence of depression in the general population varies between 3% and 10%, prevalence rates of depression increase considerably in people with long-standing illness. It is estimated that 27% of diabetics, 33% of patients with cancer, up to 44% of people with HIV/AIDS and 46% of those suffering with tuberculosis have been reported to suffer from depression[2].

It is time to bring the issue of mental health out into the open, as the degree of suffering it imposes on individuals, their families, and society in general is astounding. In most countries, physical health receives most, if not all, of the funding set aside for healthcare expenditures. Globally, neuropsychiatric disorders account for 13% of health problems, yet receive merely 2% of the global health budget2. Action must be undertaken to treat this global depression, as we cannot overcome this recession without our mental health intact.

Several figures need to be highlighted to emphasize the global impact of psychiatric illness. As many as 450 million people suffer from a mental/behavioural disorder[2]. By 2020, unipolar depression alone will be the second largest disease burden globally[3]. One in four families has at least one member with a mental illness[2]. Almost one million people worldwide commit suicide every year and mental illness has been implicated as the leading risk factor[4]. Between 420 and 460 of these deaths from suicide are occurring here in Ireland each year, and suicide prevention experts state that both job losses and the recession may be linked to a 43% increase in the number of suicides recorded in the first 3 months of 2009[5]. According to Fine Gael TD Dan Neville, we spend 10 times more money on road safety measures here in Ireland than on suicide prevention, despite the fact that more people kill themselves annually than die on the roads[5]. With such staggering statistics, it is very difficult to argue against investing in mental health.

Mental health is closely related to physical and social health[1]. As previously mentioned, the prevalence rates of depression are consistently higher in people affected by chronic disease[2]. Furthermore, patients with depression, anxiety and substance use disorders, who also suffer from other co-morbidities, often exhibit poor compliance with medications[6]. Depressed patients are, in fact, three times less likely to comply with their medical regime than non-depressed patients[5]. Therefore, treating co-morbid depression could potentially increase adherence to interventions for physical illnesses, ultimately lessening the total disease burden on our already taxed health system and on the individuals themselves. In addition, depression has been indicated as a risk factor for heart disease[7]. Di-Matteo et al investigated the onset of heart disease in depressed males between the years 1993 and 2005. This study revealed that men with depression in 1992 were twice as likely to develop heart disease in the ensuing years, as compared to men with no history of depression[6]. This suggests that treating underlying depression might decrease the incidence of heart disease.

A specific example of the human cost of mental illness, and a huge factor in favour of investment in mental health, is the link between postnatal depression and Sudden Infant Death Syndrome (SIDS). In New Zealand,

a 3-year, multicentre, case-control study has demonstrated this association. Mitchell et al found that infants of mothers with either a self-reported use of medication for psychiatric disorders, a history of hospital admission for psychiatric illness or a family history of postnatal depression had a significantly increased risk of SIDS than infants of mothers without these conditions. All mothers of infants born in the study areas over a 1 year period were eligible to complete a questionnaire measuring maternal depression when the infant was 4 weeks of age. In the study, 33 infants subsequently died from SIDS as compared to 174 controls. 15 (45.5%) of the mothers of SIDS cases were depressed compared with 28 (16.1%) of the mothers of control infants. From this evidence, it was concluded that postnatal depression is a risk factor for SIDS[8]. This would suggest that targeted and effective treatment of postnatal depression could potentially cause a reduction in child mortality attributed to SIDS.

It is a well known fact that people with psychiatric illnesses have an increased incidence of engaging in risky activities ranging from substance abuse to shoplifting and sexual promiscuity[9]. At a more global level, those with mental disorders are at increased danger of being infected with HIV due to their poor understanding of risk factors and general vulnerability[10]. A study conducted in Nigeria analyzed the knowledge, attitudes, and risk behaviours of both schizophrenic and diabetic patients in regards to HIV/AIDS. This study revealed that schizophrenic patients had more misconceptions about HIV/AIDS, as well as an increased likelihood of engaging in high-risk behaviours. During the 12 months preceding the study, 34.3% of the sexually-active schizophrenic patients did not use condoms during sexual intercourse with sexual partners to whom they were not married, compared with 19.5% of the diabetic patients[11]. These reckless behaviours are also a feature of bipolar disorder and bulimia nervosa[9], suggesting that investing in the management of all these conditions could lead to a global reduction in sexually transmitted infections and particularly HIV/AIDS.

Worldwide, those suffering from mental illnesses are often the victims of discrimination[2]. In India, individuals with mental health conditions are often ostracized from their communities due to the extreme stigma associated with these conditions. A shocking example of human rights violations was the fire in an asylum in Erwadi, India, in August 2001. 25 people were charred to death when a devastating fire broke out that morning. There were 46 inhabitants with mental disorders and 40 of them had been chained to their beds. As part of their "treatment" in this asylum, people with mental disorders were often caned, whipped and beaten up in the hope of "driving away the evil[2]". Although this is an extreme example, all over the world people with mental disorders face employment and educational barriers as a result of their illness[2]. Investing in treatment that minimizes the symptoms that isolate mental health patients can improve their quality of life and increase their chances of being accepted by society.

There are many convincing reasons in favour of investing in mental health

but what is important to consider is: Does it work? Has investing in mental health proven to be successful? Does it decrease the global burden that mental disorders cause? The following are excellent examples of how investing in mental health has shown to improve the wellbeing of individuals affected by mental disorders, decrease economic and social burden and ultimately save lives.

Inpatient treatment of children and adolescents with serious mental health disorders has been associated with a substantial and sustained improvement in their health[12]. In the UK, 150 participants were recruited across 8 different hospital units. The children were admitted for varying durations and they were followed a year after their discharge. Their outcome was measured by clinicians according to the Childhood Global Assessment Scale (CGAS). A clinically significant 12-point improvement in CGAS following a mean 16.6 week admission was shown, and this improvement was sustained at 1-year follow-up. This improvement was seen across all diagnoses. In comparison, during the mean 16.4 week pre-admission period there was a 3.7-point improvement[7]. These results provide a strong indication of the positive impact of admission and treatment for complex mental health problems in young people.

Another reason in favour of early intervention in these illnesses is the fact that childhood mental disorders have also been shown to be responsible for huge costs in adult life. One study found that adults who had conduct disorder as children generated long-term expenses for a range of state agencies that were significantly higher than the costs incurred by a control group of adults. The most noticeable costs were those faced by the criminal justice system. These costs were 18 times greater than the costs for the control group[13]. By detecting and treating antisocial behaviour in its early stages in childhood, we could save on these costs in the future.

A final example of how effective investment can be was seen in a study carried out by Brown et al in the United States. This study determined the effectiveness of a 10-session cognitive therapy intervention designed to prevent repeat suicide attempts in adults who had recently attempted suicide. 120 adults were recruited and followed up for 18 months post-attempt. From baseline to the 18 month assessment, 24.1% of the cognitive therapy group compared to 41.6% of the group who did not receive therapy made at least one subsequent suicide attempt. Participants in the cognitive therapy group had a significantly lower reattempt rate and were 50% less likely to reattempt suicide than participants in the usual care group. The severity of self-reported depression was also significantly lower for the cognitive therapy group than for the usual care group[14]. This provides clear support of investing in cognitive therapy for suicide prevention. This evidence further highlights the success of early intervention and adequate investment, so why is it that we are not implementing these cost-effective and life-improving ideas?

Is it due to a lack of awareness? Insufficient funds? Stigma? There are many possible reasons for this. One may be that we are not acknowledging the extent of the problem globally. If we do not discuss mental illness openly, we cannot appreciate its impact on society, let alone the benefits gained from adequate investment. Another, and perhaps more pressing reason is the associated cost. Treating mental disorders has proven to be very expensive. A study carried out in the United States revealed that Alzheimer's Disease ($25,000/pt/yr) and Schizophrenia ($15,000/pt/yr) are the two most costly diseases to treat, their average cost per patient being higher than cancer ($13,000) and stroke ($11,000)[15]. In Ireland, the treatment of schizophrenia alone cost €460.6 million in 2006[16].

This expense obviously presents a barrier to investment in these times of economic struggle. There is no denying that financial resources are limited and they must be allocated according to need. If we change our strategies now and invest early in the treatment and prevention of mental illness, we can ultimately decrease the net cost to society. Moreover, we can also provide hope of a longer and more fulfilling life for individuals struggling with their mental health, thereby facilitating long-term economic gain for society as a whole.

Investment in mental health is needed now more than ever due to these "recession blues." People must be at their fittest mentally to cope with the demands and difficulties currently prevailing. Neglecting an individual's mental health will affect their ability to rebuild their life, search for employment, and overcome financial strain. This will ultimately prolong the recession because, as I addressed in the beginning, it is difficult to work towards lifting the economy if our mental health is not intact.

In these times of economic difficulty, when many other sources of wealth are rapidly dissolving, shouldn't we fight harder than ever to care for our greatest source of non-monetary wealth – our health?

I certainly wouldn't like to be the one to take that away from anyone.
Would you?

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LITERATURE REVIEW

The long-QT syndrome: A silent killer

Claire Crowley *(Fifth Year Medicine, UCC)*

CLINICAL POINTS

- The long-QT syndrome can be inherited or acquired.
- It affects the function of cardiac ion channels and is characterised by a prolonged QT-interval on ECG.
- High risk individuals, including those with a suggestive history and/or ECG and those with an affected 1st-degree relative, and athletes should undergo screening.
- Prophylactic treatments available include lifestyle modification, beta-blockade, gene-specific therapies, LSCD and ICDs.
- Research must continue to uncover all gene-mutations causing SCD in order to improve the diagnosis and management of those at risk.

ABSTRACT

Introduction: Sudden cardiac death is a striking phenomenon, affecting seemingly healthy individuals without warning. The long-QT syndrome is a common cause of sudden cardiac death that can either be inherited or acquired. While congenital long-QT syndrome comprises a heterogeneous group of hereditary disorders affecting ion channels in the heart, acquired long-QT syndrome is usually a result of pharmacological therapy.

Main Body: Various mutations in twelve different genes have been linked with the long-QT syndrome to date. This condition is characterised by a prolonged QT-interval on ECG, which signifies a delay in ventricular repolarisation. The clinical presentation of this syndrome can range from symptoms of dizziness and syncope to sudden death. Diagnosing long-QT syndrome is difficult due to variable penetrance in its inheritance and the existence of yet unidentified causative mutations.

Discussion and Conclusions: Accurate diagnosis of the long-QT syndrome is essential as this condition may predispose an individual to sudden cardiac death. Prophylactic therapy for the syndrome exists and therefore early identification of those at risk is crucial in reducing the number of preventable cardiac deaths. Research must continue to discover all mutations responsible for sudden cardiac death so that therapeutic strategies can be developed to combat this silent killer.

INTRODUCTION

Sudden cardiac death (SCD) is unexpected death due to cardiac causes usually occurring within an hour of the onset of symptoms [1]. Often the individual is previously well, with no knowledge of an underlying cardiac condition. SCD in young people, particularly athletes, is an issue that has come to public attention in recent years. More than 5,000 people suffer from SCD each year in Ireland, 15% of who are under the age of 35 [2]. Globally, SCD is thought to affect 4-5 million people per year [3]. Screening programmes are now available in Ireland and elsewhere, targeting those thought to be at risk of SCD. Although many causes such as coronary artery disease, cardiomyopathies and cardiac conduction defects have been recognised, in many cases, the cause of death cannot be established and grieving families are left without answers.

Congenital long-QT syndrome (cLQTS) is the most common hereditary cause of sudden arrhythmic death; underlying 23-28% of cases [4]. The first data-based estimate of the global prevalence of cLQTS was published recently by Schwartz *et al.* [7], estimating that it is present in 1 in every 2,500 live births. This condition is comprised of a group of heterogeneous disorders that differentially affect ion channels and proteins that regulate the cardiac cycle [5, 6]. More common than its congenital counterpart is acquired long-QT syndrome (aLQTS) [5, 6, 8]. This form of the condition mainly results from pharmacological therapy [6]. Hormone and electrolyte disturbances such as hypothyroidism and hypocalcaemia have also been implicated.[5]

This paper provides a brief overview of data accumulated to date on the genetics, pathophysiology, diagnosis and management of LQTS. It also serves to illustrate the need for continued research in order to identify all mutations responsible for the syndrome which will ultimately allow for the improved diagnosis and treatment of those at risk.

GENETICS OF CONGENITAL LONG-QT SYNDROME

Much progress has been made in the last decade in uncovering the genetic basis of cLQTS. In excess of 600 different mutations have been identified in twelve genes that result in this disorder (Table 1) [9, 10]. On this basis, twelve subtypes are currently

Sub-type	Incidence (%)	Gene	Protein	Effect of mutation	Triggers of cardiac events	Syndrome
LQT1	45	*KCNQ1*	KvLQT1α	↓ IKs	exercise, swimming	RW JLN
LQT2	45	*KCNH2*	HERG α	↓ IKr	sudden noise, emotional stress, postpartum period	RW
LQT3	8	*SCN5A*	Nav1.5	↑ INa	rest/sleep	RW
LQT4	1	*ANK2*	Ankyrin B	disrupts cardiac ion channel distribution	exercise, emotional stress	RW
LQT5	<1	*KCNE1*	β-subunit minK	↓ IKs		RW JLN
LQT6	<1	*KCNE2*	β-subunit MiRP1	↓ IKr		RW
LQT7	<1	*KCNJ2*	Kir2.1	↓ IK1	altered serum K^+ levels	Andersen-Tawil
LQT8	<1	*CACNA-1C*	Cav1.2	↑ ICa	sepsis, hypoglycaemia	Timothy
LQT9	<1	*CAV3*	Caveolin-3	↑ INa		RW
LQT10	<1	*SCN4B*	Navβ4	↑ INa		RW
LQT11	<1	*AKAP9*	A-kinase anchor protein-9	↓ IKs		
LQT12	<1	*SNTA1*	α1-syntrophin	↑ INa		

Table 1: Existing Subtypes of the Long-QT Syndrome [6-8, 13-25]

Legend
RW Romano-Ward syndrome
JLN Jervell-Lange Nielsen syndrome
IKs Slow component of the delayed rectifier K+ current involved in cardiac cell repolarisation
IKr Rapid component of the delayed rectifier K+ current involved in cardiac cell repolarisation
INa Na+ current involved in cardiac cell depolarisation
IK1 Inward rectifier K+ current involved in cardiac cell repolarisation
ICa Ca2+ current involved in cardiac cell depolarisation

thought to exist (LQT1-LQT12). LQT1, LQT2 and LQT3 are the most common. Together, they account for approximately 98% of all genetically characterised cases [6, 8].

Several variants of cLQTS have been described. The most commonly reported is the autosomal dominant Romano-Ward syndrome (RW), although a rare autosomal recessive variant, Jervell-Lange Nielsen syndrome (JLN), was the first to be described in 1957 [11]. The principle difference between these two conditions is that JLN is additionally associated with congenital sensorineural deafness and has a higher risk of sudden death than RW [5, 8, 11]. Furthermore, the inheritance of RW is not strictly mendelian; females are affected to a slightly greater extent [12]. Rarer still are variants such as Andersen-Tawil syndrome and Timothy's syndrome.

Pathophysiology of the Long-QT Syndrome

The pathological mechanism is different for each of the cLQTS subtypes, yet all have the same overall effect of delaying ventricular repolarisation through the retention of positively charged ions (K^+, Na^+, Ca^{2+}) in myocardial cells [8]. This creates electrical instability and predisposes to the ventricular arrhythmia *torsades de pointes* (TdP) (Figure 1). Although TdP resolves spontaneously in the majority of cases, a minority of patients will degenerate into ventricular fibrillation following TdP [8, 26]. Without immediate defibrillation, this can lead to SCD.

Acquired LQTS, as previously mentioned, can result from certain drug therapies, many of which are in common use. They include the antibiotics erythromycin, clarithromycin and suxamethoxazole; the anti-histamines terfenadine and oxatomide; and the anti-arrhythmics amiodarone, sotolol and quinidine [27]. These agents may block KCNH2 potassium channels causing a delay in cardiac repolarisation in a manner similar to cLQTS. A subset of patients with aLQTS were subsequently found to have an underlying genetic suscep-

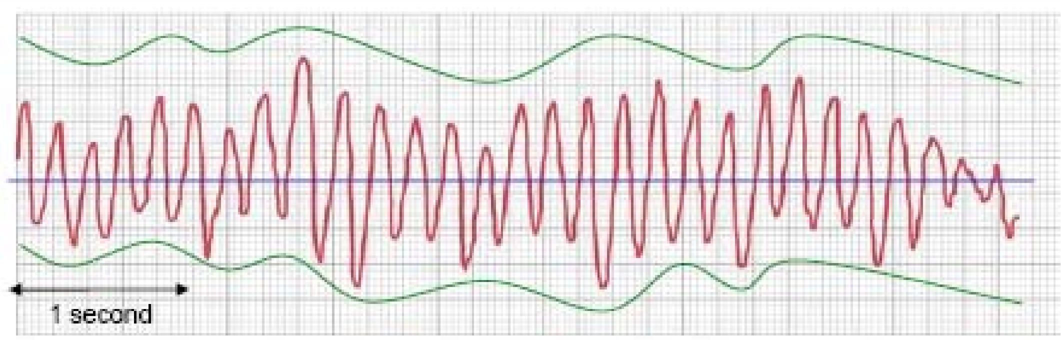
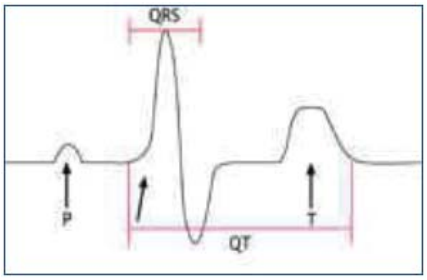
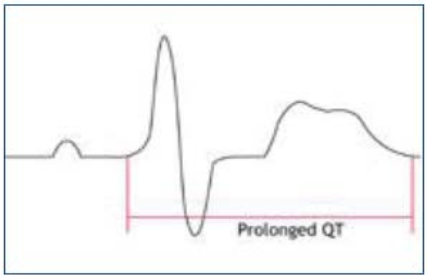


Figure 1: ECG recording showing an episode of the polymorphic ventricular arrhythmia torsades de pointes ("twisting of the points"). The curvy green lines show the characteristic "twist" of the QRS complexes around the isoelectric baseline in blue (adapted from Ashley and Niebauer, 2004) [27].



▲ **Figure 2a:** Normal ECG pattern depicting electrical activity of the heart as it contracts and relaxes. The QT-interval (beginning of the QRS complex to end of the T wave) is a measure of the duration of ventricular depolarisation and repolarisation.



▲ **Figure 2b:** Typical ECG of a LQTS patient. The QT-interval is prolonged and so the duration of the action potential is lengthened and repolarisation is delayed. (Adapted from "Cardiac Risk in the Young. SADS sudden arrhythmic death syndrome"[33])

tibility, having been silent mutation carriers until they were administered these drugs [4]. Evidently, physicians should exercise caution when prescribing these drugs, particularly when co-prescribing them as this would further increase the risk of arrhythmia.

Diagnosing the Long-QT Syndrome

The diagnostic methods available for LQTS can mainly be divided into clinical- and molecular-based methods. LQTS largely remains a clinical diagnosis made by detailed history-taking and ECG interpretation. The discovery of all LQTS mutations could ultimately alter this practice however to favour a molecular-based approach.

History

Congenital LQTS usually presents by the age of forty [4]. Common presentations include palpitations, dizziness, syncope, seizures and sudden death. Cardiac events can be precipitated by different activities, depending on the subtype involved. Exercise, particularly swimming, can trigger events in LQT1 whereas rest and sleep are triggers in LQT3 (Table 1) [8, 25, 26]. A detailed personal and family history enquiring about the circumstances surrounding cardiac events is therefore essential to recognise the syndrome and to deduce the likely genotype involved.

Electrocardiography

ECG is another important method used for diagnosing LQTS. As described earlier, LQTS causes a delay in ventricular repolarisation. This is signified on ECG by a prolonged QT-interval. A QT-interval corrected for heart rate (the QTc) using Bazett's formula ($QTc_{(ms)} = QT_{(ms)} / \sqrt{R\text{-}R}$, where R-R (sec) is measured from the onset of one QRS complex to the onset of the next) is considered prolonged if it measures ≥460 ms in a female or ≥440 ms in a male (normal range 380-440 ms) [5, 28]. In addition, it is important to recognise other ECG findings that can also indicate a diagnosis of LQTS as 25-35% of mutation carriers have a QT-duration of <440 ms due to incomplete penetrance and these individuals should not be overlooked [29, 30]. Moreover, up to 15% of the healthy population have a QTc in the 'borderline range' of 440-470 ms [31, 32]. Distinct T-wave patterns and poor accommodation of the QT-interval in response to an increased heart rate are also considered positive findings associated with the condition [5, 28]. The latter is noted upon exercise or epinephrine challenge testing [8, 29].

Diagnostic Criteria

The Schwartz diagnostic criterion is useful in the initial evaluation of a patient suspected of having cLQTS [28]. Points are allocated to various clinical, familial and ECG findings. Points for positive findings are added together to give an overall score that indicates the probability of a positive

		Points
ECG findings [a]		
QTc [b]	>480 ms	3
	460-470 ms	2
	450 ms (male)	1
Torsades de pointes [c]		2
T wave	T -wave alternans	1
	Notched T-wave in 3 leads	1
Low heart rate for age [d]		0.5
Clinical history		
Syncope	With stress	2
	Without stress	1
Congenital deafness		0.5
Family history [e]		
A	Family members with definite LQTS	1
B	Unexplained sudden cardiac death below the age of 30 amongst immediate family members	0.5

▶ **Table 2:** 1993-2006 LQTS Diagnostic Criteria [8, 28, 30]

Score < 1 point = Low probability of LQTS
1-3 points = Intermediate probability
>3-5 = High probability

a In the absence of medications or disorders known to affect these ECG findings

b QTc (the corrected QT interval) calculated by Bazett's Formula where $QTc = QT/\sqrt{R\text{-}R}$

c Mutually exclusive

d Resting heart rate below 2nd percentile for age

e The same family member cannot be counted in A and B

diagnosis (Table 2). With an intermediate probability, serial ECGs and 24-hr Holter monitoring should be done as the QTc can vary over time [30]. The ECG abnormalities previously mentioned should also be sought.

Molecular Diagnosis

Although genetic screening is considered the gold standard for diagnosing cLQTS, clinical diagnostic methods are largely regarded as sufficient in identifying affected individuals [5, 8]. Reasons for this are that screening is restricted by cost and time. A false negative rate of 30-35% [30] also limits its widespread use. Screening does however provide useful information where a previously reported mutation is implicated. In these instances, it is more useful than history and ECG at identifying the patient's genotype which strongly influences their risk stratification and management decisions.

In 1999, the European Working Group on Arrhythmias [34] recommended the use of genetic screening where it might: i) confirm diagnosis for an individual with borderline clinical criteria; ii) alter the management of a clinically diagnosed individual; or, iii) identify affected, asymptomatic first-degree relatives of a diagnosed patient. Variable penetrance means that asymptomatic family members cannot be regarded as being unaffected without being excluded from carrying a mutation. The proband should first be screened and their mutation identified. This will then allow for efficient screening of first-degree relatives and for the prophylactic treatment of those found affected [5].

Ideally all 12 LQTS genes should be screened when evaluating a patient for LQTS. However, this is not practical considering how rare some of the syndrome subtypes are as well as the cost and time involved. Different laboratories have their own protocols for screening varying numbers of the genes. Regions of the LQT1, 2, 3, 5 and 6 genes known to harbour LQTS-mutations are usually screened [35].

Limitations of Diagnostic Methods used for the Long-QT syndrome

Accurate diagnosis of LQTS is crucial given that it is a potentially lethal disorder for which prophylactic therapy exists. However, as with many diagnostic techniques, each of those used for the syndrome has limitations. The use of ECG as a diagnostic tool for LQTS has several shortcomings. The QTc is commonly miscalculated [36] and the potential exists for false positives and false negatives using current QTc cut-off lengths. Also, Bazett's formula may lead to over- or under-correction of the QT-interval at slow or fast heart rates respectively.[28] Genetic screening is not always reliable as not all LQTS-mutations are yet known. The overall message conveyed is that none of the diagnostic techniques currently available can be fully relied on and so history and examination should guide the physician's suspicions and the degree of evaluation needed.

Differential Diagnosis

The main conditions from which cLQTS must be distinguished are those affecting the structure of the heart and those affecting the cardiac conduction system. These conditions include; hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy, aLQTS, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular cardiomyopathy and Brugada syndrome [5, 28]. Non-cardiac differentials that should be considered include vasovagal syncope, situational syncope, orthostatic hypotension and epilepsy, depending on the symptoms reported.

Recommendations	Level of Evidence*	Comment
Avoid participation in competitive sports	I	For both clinically and genetically diagnosed patients
Beta-blockers	I	For patients with a prolonged QTc (>440 ms in a male and >460 ms in a female)
	IIa	For patients with a normal QTc
Implantable cardioverter-defibrillator	I	For survivors of cardiac arrest
	IIa	For patients with syncope despite beta-blocker therapy
	IIb	For high-risk patients, including those with LQT2, LQT3 or who have a QTc lasting >500 ms

▲ **Table 3:** Guidelines for the management of the Long-QT syndrome [5, 37]
* Levels of evidence:
I- conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective;

II- conditions for which there is conflicting evidence or divergence of opinion, or both, about the usefulness and efficacy of a procedure or treatment:

IIa- conditions for which the weight of evidence or opinion is in favour of usefulness and efficacy

IIb- conditions for which the usefulness and efficacy are less well established by evidence or opinion

THERAPEUTIC OPTIONS FOR CONGENITAL LONG-QT SYNDROME

The lack of data from large randomized control trials makes decision-making in the management of LQTS a challenge. Treatment options available to choose from include lifestyle modification, pharmacological therapy and surgery. In 2006, the major cardiology and electrophysiology societies in both Europe and America developed guidelines to aid physicians in their management of this syndrome (Table 3).

Lifestyle modification is universally considered essential for all patients whether symptomatic or not [37]. Recommendations include the avoidance of known triggers of cardiac events for the genotype in question and of all QT-prolonging drugs.

Beta-adrenoceptor antagonists remain the first-choice therapy for those with a prolonged QTc[28, 34, 37] as they prevent the acute rise of sympathetic activity that triggers most arrhythmias. Mixed opinions exist on the treatment of those with a normal QTc (Table 3).

Much research is currently underway into treatments targeted at specific genotypes. Although supported by experimental data, population studies confirming the efficacy of these treatments in protecting against arrhythmia are still lacking. At present, it might therefore be better to consider these as adjuncts to beta-blocker therapy rather than as a sole means of therapy [38].

Sodium channel blockers such as mexiletine have been proven to benefit patients with LQT3[27, 39] whereas flecainide was found to be useful for those with the D1790G mutation [40]. Flecainide is not, however, thought to be safe in treating those with other LQT3-mutations [41]. The therapeutic effects of L-type calcium channel blockers are also of current interest. They not only show promise for treating LQT8 and its associated gain-of-function mutations in cardiac calcium channels, but also for treating LQT3 as they additionally inhibit cardiac sodium channels [27, 38]. Experimental data also supports the use of oral potassium supplements, potassium-sparing agents, potassium channel openers and HERG (human *Ether-à-go-go* Related Gene) current enhancers in treating LQTS subtypes associated with reduced outward potassium current. Finally, gap junction coupling enhancers and the correction of protein trafficking defects are other therapeutic strategies under investigation.

Surgical options for the treatment of LQTS are considered in certain situations and include left cardiac sympathetic denervation (LCSD) and implantable cardiac defibrillator (ICD) insertion. The correct use of ICDs in LQTS is a heated topic. On one hand, they can reduce the risk of fatal arrhythmias in high risk patients [28]. On the other, they have a considerable effect on quality of life, particularly that of younger patients who require more battery and leads replacements. Additionally, their associated side effect of electrical storm caused by repeated electrical shocks has led to a substantial incidence of attempted suicide in adolescents [42]. Current guidelines strongly support their use in survivors of cardiac arrest, in conjunction with pharmacological therapy [35]. To a lesser degree, they are also recommend for other high-risk patients, including those with LQT2, LQT3, or a QTc >500 ms (Table 3). LCSD involves the removal of the first four thoracic ganglia which, like beta-blockers, reduces the rise in sympathetic tone that initiates arrhythmias. It should be considered where syncope is recurrent despite full-dose beta-blockade [28, 43]. It can also be used in conjunction with an ICD where beta-blockers are contraindicated and can dramatically reduce the frequency of ICD shocks and electrical storms in this instance [8, 28].

PROGNOSIS

The prognosis for patients with LQTS is dependent on a large number of factors including the syndrome subtype, the associated genetic mutation, the inheritance pattern, the degree of penetrance and whether or not the syndrome is recognised and treated. Most mutation carriers never experience symptoms [28]. As previously indicated, the majority of individuals that suffer a TdP arrhythmia usually recover. Approximately 13% of untreated patients suffer a cardiac arrest or SCD [44]. However, the prognosis for those who receive prophylactic therapy is usually good [28].

CONCLUSION

LQTS is a life-threatening disorder of the cardiac conduction system. It can be inherited or acquired and results in prolonged ventricular repolarisation which predisposes to fatal arrhythmias. In the past two decades, research has greatly advanced our understanding of the genetic, molecular and clinical aspects of LQTS. However, there still remain many shortcomings in our knowledge. Efforts must continue to unravel the genetics underlying this disorder and to improve the efficacy of prophylactic therapy.

In relation to disorders causing SCD overall, the ultimate goals of research include the development of automated screening which can definitively diagnose genetic predisposition to SCD, and of universal guidelines for the management of each disorder. This would hopefully lead to the enhanced recognition and treatment of those at risk and reduce the number of lives cut short.

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CASE STUDY

Going under the gamma knife: A case of intractable trigeminal neuralgia

Nessa Timoney *(Fourth Year Medicine, TCD)*

CLINICAL POINTS

- Trigeminal Neuralgia (TN) is the most common cause of facial pain in individuals older than 50 years of age.
- The pathophysiology consists of chronic irritation of the trigeminal nerve due to compressive or inflammatory causes.
- Diagnosis of idiopathic TN is based on clinical presentation, whereas secondary causes of TN may be confirmed by imaging techniques such as MRI, MRI with or without contrast, MR angiography, and 3D reconstructed MRI.
- It is estimated that more than 80% of patients respond initially to medical treatment but as time passes, medications may lose their efficacy, even when part of multiple drug therapy regimens.
- Surgical treatment is reserved for patients who have failed to achieve pain relief after adequate trials of two or three pain medications, when pain relief is attained but the patient is experiencing significant drug toxicity, or in the presence of symptomatic TN with a surgically amenable structural lesion.

Contributor: Michael K. Sowell MD
Associate Professor of Neurology and Pediatrics, Director of University of Louisville Comprehensive Headache Program, Director of University of Louisville Child Neurology Residency Program, Director of Medical Student Education in Neurology, University of Louisville Health Sciences Center, Louisville, KY

PRESENTATION OF CASE

KS, a 58-year-old male patient, presented to the neurology out-patient clinic in autumn 2008 at the University of Louisville where he was being followed for ongoing facial pain, having a three-year background history of Trigeminal Neuralgia (TN). At the time of presentation, he reported an eight month history of recurring facial pain despite pharmacotherapy, and was becoming increasingly concerned about the side effects of his medication, oxcarbazepine (Trileptal), which had become intolerable. The site of his pain was in the distribution of the maxillary (V_2) and mandibular (V_3) divisions of the right trigeminal nerve. Pain was intermittent, each episode lasting approximately 5 to 10 minutes on average and episodes occurring several times daily. KS described the pain as "stabbing", and rated the severity as 10 out of 10. He further reported that on six to seven occasions, he experienced an aching pain that lasted up to 25 minutes. His facial pain had gradually worsened over the last six months, with a more rapid deterioration of pain tolerance over the preceding one to two months. Pain was precipitated by chewing, brushing of teeth, talking, and combing hair. In addition, KS complained of TN associated headaches that "felt as though his head was in a vice constantly."

After several months of medical therapy with high-dose oxcarbazepine, which had been increased at a previous outpatient visit to alleviate worsening symptoms, KS had felt "terrible, doped up, and like a zombie." He reported being more clumsy, bumping into walls and was aware of a general decrease in his gross motor skills. He also reported finding himself isolated and increasingly depressed. This was particularly concerning for KS, who had a past history of bipolar disorder for which he was being treated. He worried that the isolation, pain, and depression would exacerbate his bipolar disorder.

At the time of the current presentation, KS's medications included: oxcarbazepine, an anticonvulsant, 600 mg three times daily and clonazepam, a benzodiazepine derivative with anticonvulsant, muscle relaxant, and anxiolytic properties, 1 mg daily for TN, sertraline hydrochloride (Zoloft), an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, 50 mg daily and lamotrigine (Lamictal), an anticonvulsant, 200 mg twice a day for bipolar disorder, and finasteride (Proscar), a 5-alpha reductase inhibitor, 5 mg daily for benign prostatic hyperplasia. KS noted he had an allergy to gabapentin.

Past drug history included 1600 mg carbamazepine (Tegretol), an anticonvulsant, taken daily when KS was first diagnosed with TN in 2005. He found temporary relief from the carbamazepine but pain persisted a few months thereafter despite dosage increase. Other drugs were added individually to the pharmacological regime over a nine month period. These agents included gabapentin (Neurontin), which he subsequently had an adverse reaction to, and ba-

clofen (Lioresal). He was then tapered off the carbamazepine, which was substituted for oxcarbazepine (Trileptal) at a 600 mg dose daily as carbamazepine had been ineffective for pain relief. On his next visit, despite pharmacological intervention, he complained of persistent pain. As a result, oxcarbazepine was prescribed up to a dose of 2400 mg daily at which dosage side effects became intolerable and still failed to achieve adequate pain relief. At this point, surgical intervention was considered.

KS's past surgical history included Gamma Knife Radiosurgery (GK-RS) at the University of Kentucky, in May 2006 (two years priors to current presentation). The GK-RS was performed due to a lack of symptom resolution with maximal pharmacotherapy for several months following initial presentation in 2005. Immediately following this surgical intervention, the patient was maintained on oxcarbazepine at a dose of 300 mg daily and remained pain-free for two years. During this pain-free period, KS was re-evaluated in the clinic for ongoing management of his condition in September 2007. At that time his TN was well controlled on 300 mg of oxcarbazepine daily and this dose was being tapered gradually since the patient had reported no pain in the preceding several months. Although his medications remained effective for several months at tapering doses, KS eventually began to experience recurrence of TN symptoms that led to his current presentation to the neurology outpatient clinic.

As previously mentioned, KS also suffers from bipolar disorder in addition to TN, and there was nil of note when asked about his family history. Social history revealed that KS is currently not working due to the distressing pain associated with his condition. He is, however, trained as a psychologist in a school setting. KS has no children

Classical TN	Symptomatic TN
A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of trigeminal nerve and fulfilling criteria B. and C.	A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes with or without persistence of aching between paroxysms, affecting one or more divisions of trigeminal neuralgia and fulfilling criteria B. and C.
B. Pain has at least one of the following: • intense, sharp, superficial or stabbing • precipitated from trigger areas or by trigger factors	B. Pain has at least one of the following: • intense, sharp, superficial or stabbing • precipitated from trigger areas or by trigger factors
C. Attacks are stereotyped in the individual patient	C. Attacks are stereotyped in the individual patient
D. No clinically evident neurological deficit	D. A causative lesion, other than vascular compression, has been demonstrated by special investigations and/or posterior fossa exploration
E. Not attributed to another disorder	

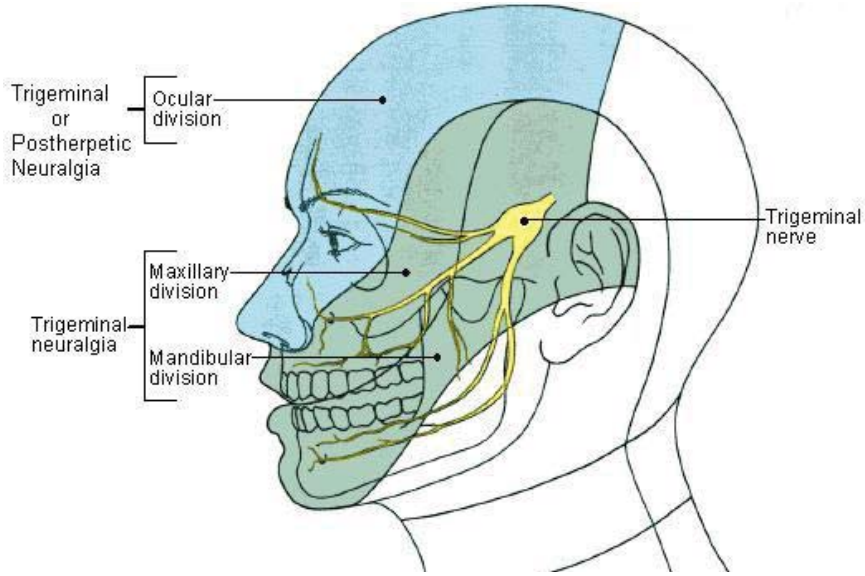
▲ **Table 1:** ICHD-II Trigeminal Neuralgia Classification © International Headache Society 2003/5

and no spouse or significant other, and he denies current or past use of tobacco, alcohol, or recreational drugs.

Review of systems was non-contributing. As would be expected in a patient with TN, no signs were elicited upon physical or neurological exam[5]. If there had been positive findings upon physical examination, this may have been suggestive of a diagnosis other than TN[1].

Investigations and Diagnosis

Diagnosis of idiopathic TN is typically made clinically because there is no routine and definitive laboratory, electrophysiologic, or radiologic testing indicated for a diagnosis of TN. Due to the characteristic symptoms associated with TN, a diagnosis can

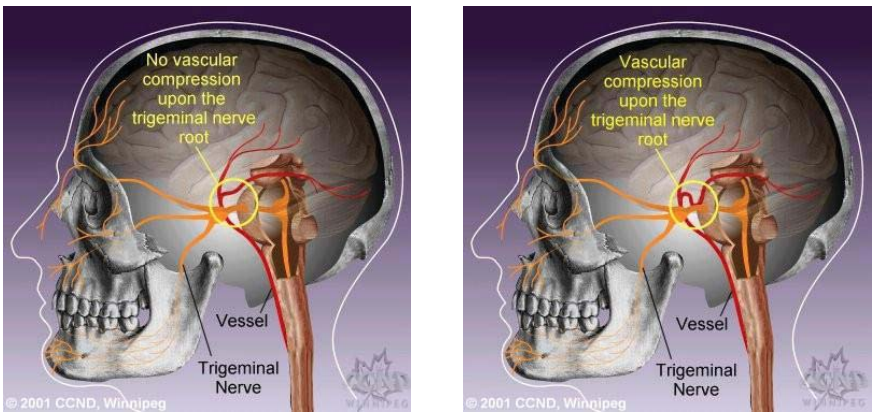


▲ **Figure 1:** Facial distribution of TN.

be made based on the clinical picture alone. Evidence-based reviews have demonstrated that clinical or laboratory testing is of limited use in the diagnosis of TN. In addition, routine neuroimaging may only identify an underlying cause for the TN in up to 15 percent of patients with TN-like symptoms[2]. As a result, such investigations are not carried out routinely unless the patient has failed a trial of medication and is a candidate for surgical intervention[2].

TN is a syndrome characterized by recurrent but brief, lancinating, paroxysmal attacks of facial pain. This pain is superficial, usually unilateral and restricted to the facial somatosensory distribution of the trigeminal nerve and its branches (Figure 1)[3]. Similar to the presentation of KS, TN tends to affect the right side of the face more commonly than the left, a finding that is believed to be due to the narrower foramen rotundum and foramen ovale (conduits for the maxillary and mandibular nerve, respectively) on the right[1]. TN pain is classically shock-like, stabbing, or sharp and usually lasts only seconds. Attacks may occur infrequently or as often as 100 times a day, with patients generally being asymptomatic between episodes. KS, however, noted an aching type of pain between episodes. As demonstrated in KS's case, non-noxious triggering factors may include smiling, talking, brushing teeth, and eating[1, 4]. Small areas in the nasolabial fold and/or chin may be trigger areas, particularly susceptible to precipitation of pain. Although pains usually remit for variable periods, the amount of time spent in remission tends to diminish as the disease progresses[5].

In the past, terminology for TN was problematic as attempts were made to classify the neuralgia based on its aetiology. However, in the first revision of the 2nd edition of the International Headache Society Guidelines, difficulties in proper classification were clarified and criteria for specific subtypes were explicitly outlined. Neuralgia caused by compression of the nerve by a vascular loop demonstrated during open surgery, is described as *secondary trigeminal neuralgia* (see Figure 2). Aetiology unrelated to vascular loop compression is classified as either *classical trigeminal neuralgia* or *symptomatic trigeminal neuralgia,* and may be differentiated based on the International Headache Society Guidelines in Table 1[5].



a) b)

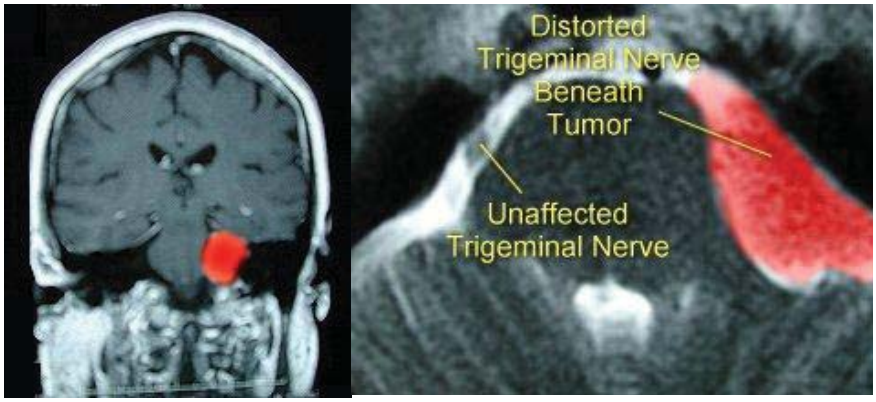
Figure 2
a) In people without TN, there is usually no vascular compression upon the trigeminal nerve root
b) In most sufferers of typical TN, vessels compress the trigeminal nerve root.

KS fulfilled most of the criteria for a diagnosis of classical TN, with the exception of the duration of his episodes, which lasted longer than two minutes (criterion A).

Imaging studies such as Brain MRI with or without contrast, MR angiography (MRA), and 3D reconstructed MRI can help distinguish secondary causes of TN from the idiopathic form of the condition. Thus, in addition to ruling out secondary TN (vascular loop), MRI also permits detection of symptomatic TN caused by lesions such as tumours or Multiple Sclerosis (for explanation, refer to Discussion: pathophysiology). Imaging is indicated in patients presenting with the condition when younger than 60 years of age, primarily to exclude tumour (see Figure 3)[6]. On initial presentation, KS underwent MRI with and without contrast as well as MRA, and no aberrant vascular loop or other lesion was identified, thus ruling out both secondary and symptomatic TN. Further confirming his diagnosis was the significant pain relief he experienced while on carbamazepine, an anticonvulsant, which according to some, is a good diagnostic trial medication for classical idiopathic TN[1]. A lack of response in his case would have suggested symptomatic TN or another diagnosis, both of which are less likely to respond to the drug[1]. Therefore, the negative findings on MRI in addition to the patient's response to a trial of carbamazepine confirmed the diagnosis of classical persistent idiopathic TN.

MANAGEMENT

Upon his current presentation to clinic, KS was instructed to continue oxcarbazepine at 600 mg three times daily (1800 mg) to mitigate the intolerable side effects that he had previously experienced when on the higher dose (2400 mg). Given the failure of previous pharmacological



▲ **Figure 3:** In these MRI images, a tumour responsible for compressing the trigeminal nerve is highlighted in red.

regimens prior to his first surgery and the patient's concerns about the side effects of high-dose oxcarbazepine and his current pharmacological regimen, he was then referred for surgical reevaluation at the University of Kentucky. KS discussed the surgical options with his neurosurgeon and opted for a second GK-RS rather than an open surgical modality. This decision was based on the patient's familiarity with the GK-RS procedure, his desire for a less invasive procedure and its improved safety profile as compared to the more invasive open-surgery modalities such as microvascular decompression (MVD).

Outcome and Follow-up

GK-RS provides safe and effective treatment of TN for certain patient prototypes. Currently, it is the least invasive surgical treatment for TN and side effects are usually limited to persistent trigeminal paraesthesias[5]. Despite its safety profile, pain recurrence after initial GK-RS treatment is a major concern and it would not be uncommon to undergo a second procedure, as in KS's case[8]. It has generally been considered a viable therapeutic option for the management of medically refractory idiopathic TN[9]. Following his second GK-RS, KS denied post-surgical numbness, and he was counseled about long-term outcome and possible recurrence. Thus far, he has had an excellent result. Since this second surgical intervention, KS has been maintained on the lower dose of Trileptal (1800mg per day) and instructed to follow-up with University of Louisville neurologists for routine visits or earlier if problems develop.

Discussion

Introduction

Trigeminal Neuralgia (TN) is a relatively rare but well-known cause of facial pain with a prevalence of 15.5/100,000 cases[4]. It can occur at any age but is more common in the elderly, with approximately 90 percent of cases occurring in those over the age of 40[4]. For reasons unknown, cases of TN are twice as likely in women as men (ratio of 2:1)[4]. Certain subgroups of the population are more likely to be affected. For example, TN has a prevalence of between one and two percent in patients with Multiple Sclerosis (MS), and a slightly higher prevalence in patients with hypertension than in the general population[1] (for explanation, refer to Discussion: pathophysiology).

Historical Perspective

Also known as "tic douloureux" or Fothergill disease, TN was first described in 1688, by Drs. Johannes Michael Fehr and Elias Schmidt as "*a sharp shooting pain in the maxilla which prevents eating solid food, varying in time – the person died of malnutrition*[10]." The syndrome was then described in greater detail by Dr. John Fothergill, a British physician who scrupulously described the symptoms and nature of the pain, onset, duration, aggravating factors, and predilections for certain age groups and gender[10]. It was not until 1820, however, when Sir Bell investigated the fifth cranial nerve, that the term "Trigeminal Neuralgia" was introduced. The distinguishing symptomatology, therapeutic debate, and evolution of recent therapeutic options, make this complex pain syndrome uniquely intriguing[11].

Pathophysiology

Walter E. Dandy demonstrated in 1925 that if the trigeminal nerve was sectioned in TN patients, relief of pain was noted. After performing over 500 operations, he consistently observed an anomalous vascular loop compressing upon the nerve[10]. Upon further scrutiny, it was noted that the pulsating nature of the compressing artery was traumatic enough to cause demyelination of the axon. This focal demyelination results in an abnormal conduction or ephaptic transmission, more simplistically referred to as a "short-circuit". Consequently, these demyelinated axons are prone to ectopic impulses, which in the case of TN, may be directly responsible for the typical characteristics of the pain experienced in those with the facial pain syndrome described as episodic, electric, lancinating pain[1]. The strong association of MS and TN further emphasizes demyelination as an underlying cause of the pain[11].

MEDICAL MANAGEMENT

The medical management of TN has evolved as its pathophysiology has been further elucidated and both imaging technology and surgical techniques have advanced. At the onset of the disorder, pharmacotherapy works extremely well and approximately eighty percent of patients achieve almost complete control of their symptoms on medication alone. Initial first line treatment is therefore medical[1, 4]. A derivative of phenytoin, used first in 1942, was later replaced by carbamazepine in 1962.

Carbamazepine is now the mainstay of medical treatment of TN based on recommendations of the European Federation of Neurological Societies and the Quality Standards Subcommittee of the American Academy of Neurology[12]. Carbamazepine is an anti-epileptic that acts by reducing sodium-conductivity thereby decreasing the responsiveness of peripheral mechanoreceptors. Eighty percent of patients benefit from this therapy and ninety-four percent report relief from symptoms in the first 48 hours[13]. Lack of efficacy or side effects such as nausea, vomiting, dizziness, drowsiness, or unsteadiness, may indicate the need to substitute carbamazepine for oxcarbazepine, a derivative of carbamazepine, but with a more favourable side effect profile[7,14]. Should a patient's TN pain be refractory to oxcarbazepine or if the patient finds the side effects of the indicated medications intolerable, alternative agents such as phenytoin, gabapentin, pregabalin, lamotrigine, topiramate, and baclofen may be added or substituted[4,7]. For fifty percent of medically treated TN patients, it is inevitable that drugs will progressively lose their efficacy because of drug resistance or drug tolerance necessitating increased doses, and thus surgical intervention must be considered[15].

SURGICAL MANAGEMENT

Referral to neurosurgery is imperative when the diagnosis is consistent with TN and the pain is refractory to pharmacotherapy. Surgical procedures consist of either open or percutaneous modalities. The most commonly used surgical procedures for TN patients include microvascular decompression, percutaneous radiofrequency rhizotomy, percutaneous glycerol rhizolysis, percutaneous balloon microcompression, and stereotactic radiosurgery using Gamma Knife. Each surgical procedure has its merits and limitations, and approaches must be based on the individual and what is best in their particular case.

Open techniques involve posterior fossa exploration such as partial trigeminal rhizotomy and microvascular decompression (MVD). These procedures carry a small risk of serious adverse events such as stroke, meningitis, and death. First introduced by Dr. Peter Jannetta in 1967, MVD is still considered the gold standard for treatment of TN as it provides the highest rate of long-term patient satisfaction with the lowest rate of pain recurrence[3, 11]. Complications of surgery are rare when the team is experienced but may include: cerebellar injury, hearing loss, cerebrospinal fluid leakage, facial weakness, and lower cranial nerve dysfunction[3, 11].

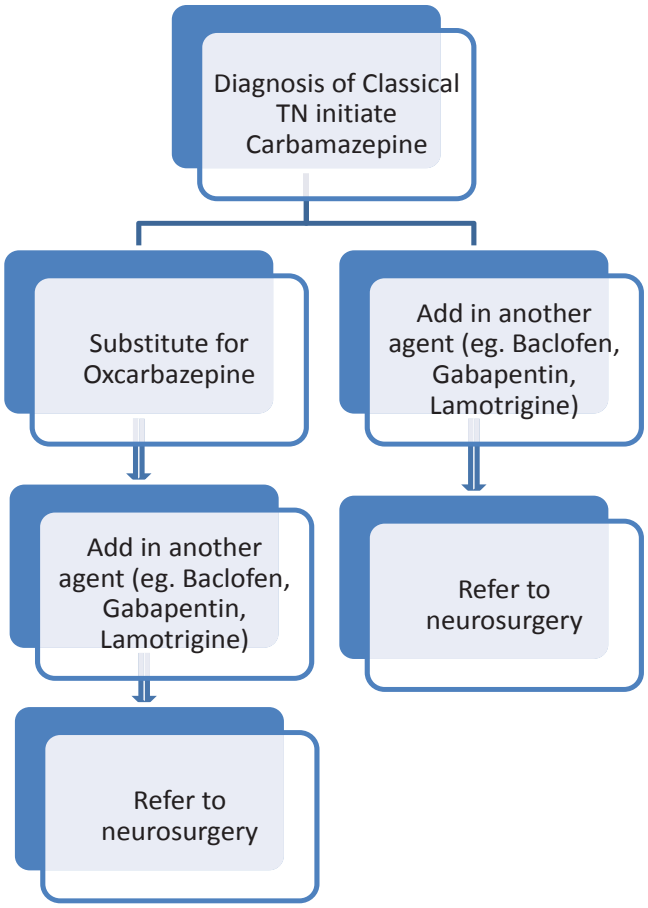


Figure 4: Algorithm for the diagnosis and treatment of TN.

Percutaneous techniques include glycerol injection, balloon compression, radiofrequency rhizotomy, and Gamma Knife Radiosurgery (GK-RS). These less invasive procedures carry reduced health risks and a shorter hospital stay compared to open procedures[3]. However, less invasive procedures do not provide as long lasting relief as that of the open procedures and have a higher incidence of sensory loss[1]. A summary of the diagnosis and treatment of TN is depicted in Figure 4[14].

MVD provides a higher and longer duration of relief than any of its counterparts. More than 70 percent of patients report consistent relief at 10 years post MVD[1]. Although both MVD and GK-RS result in pain relief, MVD is more likely to result in complete pain relief[16]. However, MVD may not be appropriate for all TN patients and is the surgery of choice for younger patients who are less likely to be at risk of complications. As a result, this procedure should be avoided in the elderly[17]. Furthermore, for the persistent idiopathic TN patient with continuous aching pain, MVD does not provide a favorable outcome. In this patient profile type of TN, GK-RS may be a better alternative to MVD. At the University of Maryland Medical Center, the majority of patients with persistent idiopathic TN undergoing GK-RS reported an overall improvement in quality of life, even if the pain returned[18].

The long-term results of the GK-RS procedure remain unknown as no high-quality studies have yet been performed with a follow-up of greater than five years. Therefore, it is difficult to predict the long-term outcome of KS's second GK-RS procedure and whether or not the neuralgia will reoccur. Good prognostic factors include a lack of the following three factors: previous surgery, post-surgical numbness, and typical pain; KS denied presence of the latter two[19]. Rates of initial pain relief with GK-RS approach those of MVD or percutaneous techniques in patients without previous surgery[19]. However, MVD continues to have a lower recurrence rate and is favoured as the treatment of choice for suitable patients. Repeat GK-RS has shown success rates for pain relief comparable to initial GK-RS, but results in fewer patients able to discontinue their medications[19]. This may be a concern for KS as he was intolerant to most of the medications commonly prescribed for TN.

To conclude, the minimal invasiveness of GK-RS makes it a good option for patients who cannot or should not undergo MVD. These include the elderly, those with medical problems that preclude neurosurgery, or patients such as KS who do not wish to undergo open surgery. The low rates of complication of GK-RS, coupled with good success rates and high patient satisfaction, favour its increasing use as a primary intervention for TN[13].

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LITERATURE REVIEW

Therapeutic hypothermia for neuroprotection after out-of-hospital cardiac arrest: Too cool for school?

Jack Collins *(First Year Medicine, UCC)*

CLINICAL POINTS

- Inducing mild therapeutic hypothermia in unconscious out-of hospital
- Cardiac arrest survivors after return of spontaneous circulation is found to improve survival and neurological outcome.
- Inducing mild therapeutic hypothermia appears to be a safe practice. Methods include application of ice packs and infusion of ice cold intravenous fluids.
- Mild therapeutic hypothermia for out-of hospital cardiac arrest continues to be underutilised despite much data indicating its efficacy.
- More research is required to elucidate the long term outcome of patients who initially benefit from mild therapeutic hypothermia.

ABSTRACT

Approximately 5000 people in Ireland suffer an out-of-hospital cardiac arrest annually, and surprisingly, only 5.4% are expected to survive such an event. A significant number of those who do survive to hospital discharge encounter varying degrees of neurological deficit. Many studies indicate that survival and neurological outcome after suffering an out-of-hospital cardiac arrest can be improved by inducing mild hypothermia for up to 24 hours following the return of spontaneous circulation. Although the exact physiological processes underlying this intervention are not clearly understood, hypothermia is thought to interfere with the mechanisms associated with ischaemic and reperfusion injury. Several methods to induce therapeutic hypothermia have been developed and include external cooling, intravascular cooling and combinations of both. Clinical trials examining the safety of therapeutic hypothermia suggest it presents little risk to patients. However, these studies have inherent limitations in their research methodology. A number of international surveys of physicians suggest that this treatment is underutilised due to a lack of both published data on its safety profile and the absence of local protocols. The use of therapeutic hypothermia in Ireland is yet to be analysed and there is little published data available on Irish out-of-hospital cardiac arrest survival.

INTRODUCTION

Cardiac arrest is described as a condition where absent or inadequate contraction of the heart, commonly due to ventricular fibrillation, causes circulatory failure, loss of consciousness and brain death within approximately 10 minutes if normal heart rhythm is not restored[1]. The Task Force on Sudden Cardiac Death advise that 5000 people experience an out-of-hospital cardiac arrest (OHCA) in Ireland each year, an event with a poor prognosis in terms of morbidity and mortality[1]. Patients in cardiac arrest who receive prompt interventions may be successfully resuscitated and experience return of spontaneous circulation (ROSC). ROSC is defined as the restoration of a palpable arterial pulse when cardiopulmonary resuscitation is paused[2]. While these patients demonstrate adequate cardiac function after ROSC, they often encounter some degree of neurological deficit.

Since the 1950s, a growing body of evidence has revealed that inducing mild hypothermia at a temperature of 32-34°C for 12-24 hours in comatose ROSC patients, improves both their survival and neurological outcome[3]. Traditionally, therapeutic hypothermia has been associated with the treatment of traumatic brain injury and raised intracranial pressure. Historical accounts of the initial use of hypothermia in the early 1800s describe one method of 'resuscitation' in Russia, which involved burial of the victim in snow while hoping for ROSC. It has since evolved into a novel neuroprotective therapy. Methods to induce hypothermia include the external application of cold packs or cooling blankets and administration of ice cold (4°C) intravenous fluids. Neuromuscular blocking agents are administered adjunctively to prevent shivering. This paper intends to review the current literature on efficacy, safety and implementation of mild therapeutic hypothermia for neuroprotection in adults who have experienced an OHCA.

PATHOPHYSIOLOGY

Patients who suffer a cardiac arrest and subsequent ROSC commonly encounter a number of detrimental neurological effects. These are a result of anoxic brain injury, an insult associated with the period in which

no oxygen is delivered to the brain. During an ischaemic episode, the cell resorts to anaerobic glycolysis for the production of energy, yielding only modest quantities of adenosine triphosphate (ATP). Accumulation of lactate, a product of anaerobic glycolysis, quickly ensues. This results in localised acidosis while the inactivity of ATP-dependant membrane pumps leads to electrolyte disturbance[4]. In addition, the excitatory neurotransmitter glutamate is released from neurones during cerebral ischaemia, causing further neuronal damage. A significant amount of damage also appears to be caused by the re-establishment of oxygen supply to the brain after an anoxic episode. This phenomenon is known as reperfusion injury. When oxygenated blood is reintroduced to an ischaemic area, a cascade of reactions occurs involving the release of inflammatory mediators and the production of deleterious oxygen free radicals[4,5]. The combination of these processes results in cell apoptosis.

Clinical trials involving animals in the 1950s indicated that the pathophysiological effects of ischaemia and reperfusion injury could be inhibited by hypothermia[3]. While the mechanisms of the neuroprotective properties of mild hypothermia are not yet clearly understood, animal trials indicate that mild hypothermia in the normal brain reduces the cerebral oxygen consumption by 6% for every 1°C reduction in temperature, thereby reducing ischaemic injury[6]. A decrease in electrical activity due to hypothermia also appears to suppress the chemical reactions associated with reperfusion injury. Aside from its use in neuroprotection, hypothermia has been utilised for its vasoconstrictive properties. This effect underlies its traditional therapeutic use in the treatment of traumatic brain injury and raised intracranial pressure. Therapeutic hypothermia has since fallen out of favour as a treatment for head trauma due to adverse events associated with its use in these patient groups[3].

While initial trials have focused on cardiac arrest in animal models, more recent studies have been conducted demonstrating the efficacy and benefits of mild therapeutic hypothermia (MTH) in OHCA survivors[7-12].

Efficacy

Two landmark papers, both published in the New England Journal of Medicine (impact factor = 50.017) in 2002, provide conclusive evidence that MTH has beneficial effects on the morbidity and mortality of OHCA patients. Bernard et al[7], in their Australian randomised controlled trail, assigned treatment of ROSC patients to one of two groups. Participants were randomly allocated to either group. The study group received MTH whereas the control group were subjected to normothermic treatment. The mean age of the study subjects was 65 years and 65% of those studied were male. Patient outcome was measured in terms of survival to discharge with good neurological outcome. The paper reported that 49% of the therapeutic hypothermia group (n = 21/43) survived to discharge with favourable neurological outcome, while only 26% of the normothermic group (n = 9/34) experienced an analogous recovery. It was impossible to blind the treating clinicians involved in this study however blind assessment of the participant's outcomes did take place. The second large study examining the use of MTH in human subjects provides comparable results. The Hypothermia After Cardiac Arrest Study Group (2002) conducted a multicentre, randomised control trial across Europe involving nine emergency departments[8]. Boasting a large sample size (n = 275, 76% males), the researchers compared the 6 month mortality and neurological outcome of consecutive OHCA patients who were treated with MTH compared to a control group treated at normothermic temperature. The assignment of patients to either group was randomised. A history of coronary heart disease was present in 37% of the sample whose mean age was 59 years. Blind assessment of patients was conducted to elicit the outcomes of those involves. Whereas 55% of the hypothermia group displayed a good neurological outcome 6 months after successful resuscitation, only 39% of the control group had a comparable outcome. The 6 month mortality rate among the hypothermia group was found to be 14% lower than that of the control group. Both of these initial studies utilised external cooling methods to induce hypothermia. The publications appeared to generate heightened interest in MTH and in 2003 the International Liaison Committee on Resuscitation (ILCOR) published an advisory statement suggesting that therapeutic hypothermia be considered for all comatose patients with ROSC after experiencing OHCA.

More recent studies also confirm the beneficial effects of MTH on both recovery rate and length of stay in hospital. A prospective observational study in Germany by Storm et al[9] examined the results of 52 consecutive ROSC patients treated with MTH against a historical cohort of 74 normothermic patients. Hypothermia was induced using a combination of external and intravascular methods. It was demonstrated that survivors in the MTH group spent an average of 14 days in the Intensive Care Unit (ICU). In contrast, members of the normothermia group spent an average of 21 days in ICU. These results are further supported by a recent Japanese study by Takeuchi et al[10]. While comparing the recovery rate of patients after the introduction of an MTH policy in their facility, it was found

that patients treated with MTH (n = 25) displayed an 80% recovery rate. Conversely patients in the normothermic group (n = 21) had a 38% recovery rate. This amounted to a very significant doubling in recovery rate for ROSC patients. This trial, along with other recent studies[13,14] examining the efficacy of MTH, has failed to employ a randomised study design, a shortcoming that should be addressed by future research. Despite this limitation, the literature provides clear evidence that MTH is a valuable therapy which offers ROSC patients a better chance of survival and a desirable neurological outcome. However, studies examining the long term (>1 year) advantages of MTH could not be identified and thus present an area that should be explored through further research. Although the literature presents much data concerning the efficacy of MTH, several papers also address its safety.

Safety and adverse events

The introduction of new interventions such as MTH must be deemed clinically safe prior to implementation to ensure the ethical principle of *Primum non Nocere,* or 'first, do no harm', is maintained. Older studies[3] have identified a higher risk of arrhythmia, pneumonia and coagulopathy with the use of therapeutic hypothermia. However, many modern trials examining its use for OHCA patients have suggested that it is clinically safe[12-14]. In fact, the incidence of adverse events encountered among patients treated with MTH is statistically similar to that of ROSC patients treated at normothermia[7,8]. Intravascular cooling was examined in an American study by Kim et al[13] who identified no adverse effects during or after the rapid intravenous administration of ice cold fluids. While monitoring core temperature and haemodynamic status of 17 ROSC patients during induction and maintenance of hypothermia, no cardiovascular detriment or side effects were encountered. The researchers used echocardiography and invasive manometry to monitor patients throughout treatment. Hypocoagulation and electrolyte disturbances were also out ruled with regular sampling and analysis.

While the above study provides strong evidence for the safety of inducing MTH, another trial by Nielsen et al[12] describes the prevalence of adverse events in ROSC patients who underwent MTH across 34 centres. The impressive sample size (n=975) had a mean age of 63 years and 74% of patients were male. Half of the sample survived, with over 90% displaying a good neurological outcome. Adverse events included 41% of patients developing pneumonia and 33% experiencing arrhythmia. Bleeding requiring a transfusion occurred in only 4%. Mechanically ventilated patients commonly experience adverse events such as pneumonia and it is difficult to interpret these findings without a control group. None of the recent studies which assess the safety of MTH were randomised controlled trials, limiting the quality of data and its application to clinical practice. Randomisation of participants ensures that results are valid and reliable by preventing bias. It also ensures that each study group is homogenous. The dearth of randomised controlled trials may inhibit the recognition of MTH as a safe practice and further restrain its implementation. However, as more evidence supports the use of MTH, it becomes difficult to ethically justify the inclusion of a control group, treated at normothermia, in such studies.

Too cool for school?

There is paucity in Irish data on the subject of OHCA and no studies could be identified to date that have examined the use of MTH. Some Irish studies have examined the frequency of OHCA and its associated mortality. A recent study conducted in the Mater Misericordiae University Hospital reported the results of a cardiac arrest registry maintained in the emergency department (ED)[15]. While this hospital serves a population of 170,000 people, the ED encountered 937 OHCAs between 2003 and 2008. The mean age of the sample was 61.1 years and 69% were male. A past history of coronary heart disease was present in 13% of the sample and 73% of cardiac arrests took place in the patient's home. An initially successful resuscitation was recorded in 15% of patients, while the overall survival to discharge rate was significantly lower at 5.4% (n=51). This equates to less than 10 patients per year surviving an OHCA. A recent retrospective study by Byrne et al (2008), conducted in Galway University Hospital, reported similar results[16]. The analysis included data from 212 OHCA patients over a period of one year. It was found that 6.1% (n=13) of patients were successfully resuscitated however only 3.8% (n=8) survived to discharge. The use of MTH was not discussed in either of these two modern studies and it may be inferred that it is not routinely utilised in the nation's EDs. The Irish emergency medical services regulator, The Pre-Hospital Emergency Care Council, has demonstrated some progression in this area and recently introduced a clinical practice guideline for MTH in the care of pre-hospital ROSC patients. This may be utilised by advanced life support providers for patients who are successfully resuscitated in the pre-hospital environment and involves the administration of ice cold intravenous fluids. The introduction of this practice in the pre-hospital environment is a promising development and will hopefully be replicated in EDs.

Despite substantial evidence supporting the efficacy and safety of MTH, current research suggests it is underutilised in clinical practice[17-20].

An anonymous internet survey by Merchant et al[17] of American, British, Australian and Finnish critical care physicians (n = 2248) evaluated the implementation of MTH. It was found that 74% of American and 64% of non-American physicians had never prescribed MTH. "Not enough data" was cited by 48% of physicians as the primary reason for poor endorsement of MTH. A more recent Canadian study published in 2008 shows a slightly higher MTH implementation rate than in other jurisdictions. Kennedy et al[20], in an internet survey of ED physicians (n = 247), found 47% had utilised MTH with 40.6% having access to a local policy directing its use. The research suggests that underutilisation of MTH in clinical practice is correlated to the absence of clear protocols directing it use.

Conclusion

MTH for neuroprotection is a pioneering intervention offering OHCA patients a better chance of survival and survivors a better quality of life. While the use of MTH is being rolled out in the pre-hospital setting, no empirical data is available to quantify the use of MTH in Irish EDs. The recent data reviewed offers persuasive evidence that MTH is a valuable tool, posing minimal risk to patients. Nevertheless, the quality of data examining its safety is consistently limited by non-randomised design. It is impossible to exclude physician bias in these papers and this presents a significant limitation in the studies assessing clinical safety. The physicians involved may have subconsciously assigned study participants with a worse prognosis to a control group in order to generate favourable results. Future research should address this issue by examining MTH in a randomised controlled clinical safety trial. Further investigation is also required to elucidate the long term outcomes (>1 year) of patients who are treated with MTH. International studies indicate MTH is under implemented, but it is clear that the presence a local policy is strongly linked to its use. While several thousand people will experience an OHCA in Ireland in 2010, it is impossible to say if any will be treated with MTH. The dissemination of supporting empirical data is critical to the development of MTH as a therapeutic option for patients in Ireland and the inclusion of MTH in local resuscitation guidelines will accelerate its national implementation.

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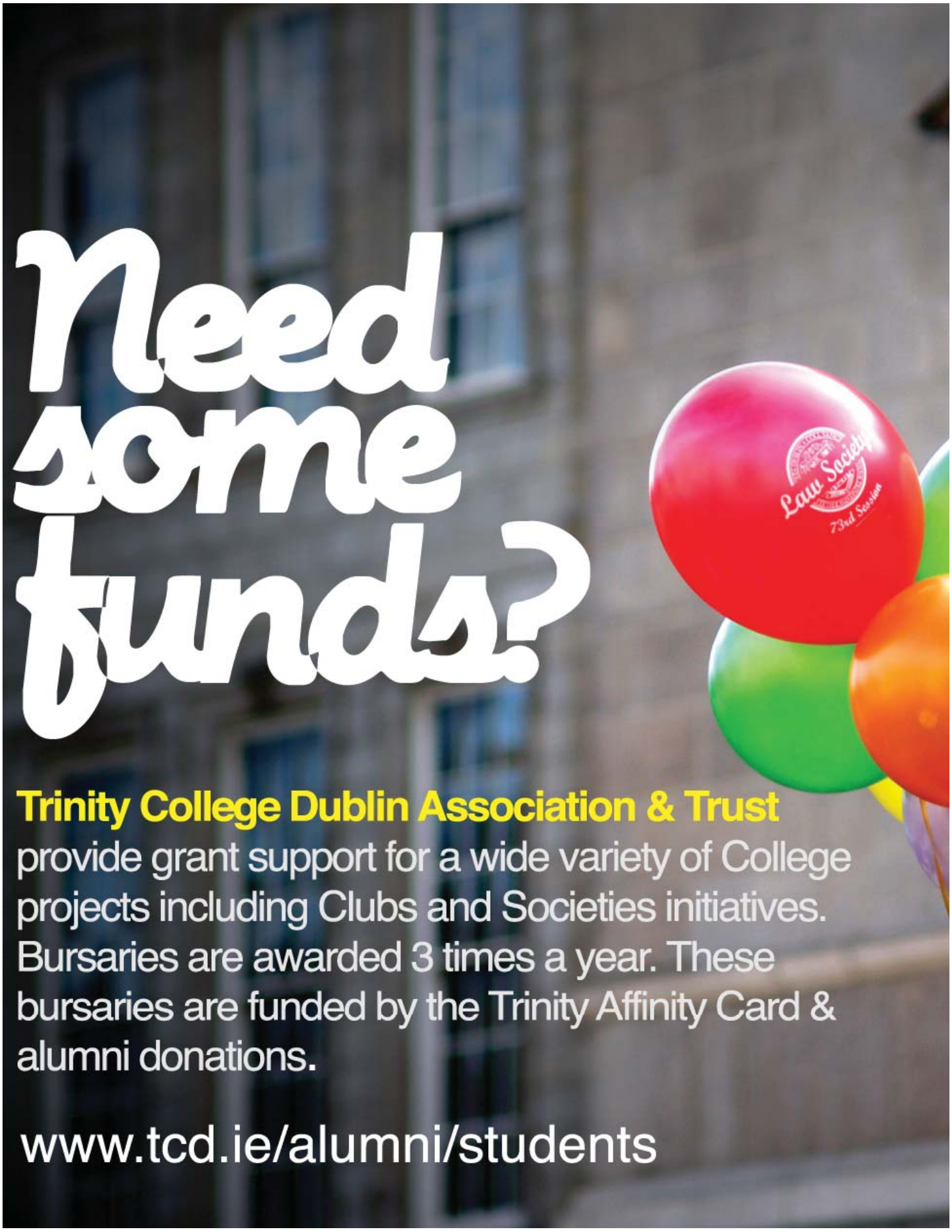
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Optimising secondary prevention: Effect of cardiac rehabilitation duration on cardiovascular risk profile modification

Jessie Elliott *(Third Year Medicine, TCD)*

CLINICAL POINTS

- Exercise-based Cardiac Rehabilitation is a valuable tool in the secondary prevention of cardiovascular disease.
- St. James's Hospital, Dublin, runs 6-week and 8-week exercise-based Cardiac Rehabilitation programmes aimed at improving the risk factor profile of discharged cardiac patients.
- Attendance at Cardiac Rehabilitation in St. James's Hospital is typically poor, with a completion rate of only 70%.
- Cardiac Rehabilitation programmes of longer duration have lower attendance rates and are less cost effective than shorter programmes. Limited current evidence suggests that programmes with increased duration are no more efficacious at reducing cardiovascular risk, when compared with shorter programmes.
- Healthcare expenditure and patient adherence might be optimised by employing shorter Cardiac Rehabilitation programme durations. This could increase the efficacy of cardiovascular risk factor reduction through Cardiac Rehabilitation by reducing the high withdrawal rate and increasing attendance.

ABSTRACT

Background: Cardiovascular disease is the leading cause of mortality in Ireland, accounting for 36% of all deaths. While it is well documented that exercise programmes are of benefit in risk factor modification in the cardiac population, the optimal exercise rehabilitation programme duration remains unclear.

Study Aim: This study aimed to analyse the effect of cardiac rehabilitation programme duration on cardiovascular risk factor modification in patients with established coronary artery disease, whilst assessing the effectiveness of existing programmes.

Methods: In this retrospective, observational study, subjects (male, low risk cardiac patients, aged 50-69 years, mean age = 59 ± 4 years) were randomised into a 6-week or 8-week exercise programme. Each programme consisted of 15 exercise sessions, of 50 minute duration, with equal time distribution on each of 7 exercise stations (treadmill, cross-trainer, exercise bicycle, ball, rowing machine, arm ergometer and weights) at 60% of maximal heart rate. During the programme, resting heart rate, blood pressure, waist circumference and body mass index were monitored at regular intervals.

Results: There was no significant reduction in any of the parameters for either the 6-week or the 8-week programme. There was no significant difference between the 6-week and 8-week programmes in modification of any risk parameters.

Conclusion: This study revealed no significant difference between a 6-week and 8-week cardiac rehabilitation programme in cardiovascular risk factor modification in the cardiac population.

Contributors:
Rachel O'Callaghan †, Mary Kerins ‡
† Physiotherapy Lecturer, Discipline of Physiotherapy, School of Medicine, TCD
‡ Cardiac Rehabilitation Manager, Cardiac Rehabilitation, Crest Directorate, St James's Hospital

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in Ireland, accounting for 36% of all deaths and 22% of premature deaths (under 65 years old)[1]. CVD is also a leading cause of mortality worldwide, accounting for approximately 16.7 million or 29.2% of deaths in 2003[2,3]. Furthermore, the World Health Organisation (WHO) estimates that CVD will be the leading cause of death in developing countries by 2010[2]. It is clear that CVD represents a serious worldwide health problem. There is strong evidence suggesting that Cardiac Rehabilitation (CR), involving exercise based interventions, with or without psychosocial counselling and education is an effective form of secondary prevention[4,5]. Epidemiological studies have demonstrated that risk factor modification using CR can result in a decrease in mortality of up to 50%, compared with population matched controls[6].

It is well documented that exercise produces improvements in cardiovascular health[7,8]. In addition, when prescribed as part of a CR programme, exercise has been shown to be beneficial to the cardiac patient, by optimising exercise tolerance, stroke volume, heart rate, blood pressure, serum low- and high- density lipoprotein levels, capillary density, psychosocial well-being and improving symptoms of angina[4,5,9]. A variety of

different exercise training paradigms are used as part of CR programmes, including aerobic exercise, anaerobic exercise and resistance training. While each has been shown to be beneficial[7,10,11,12,13], there is little evidence to demonstrate what training paradigms are most effective at improving cardiac risk profiles. It is clear that the mode of exercise influences the effect of exercise training within a cardiovascular (CV) population. However, it is also likely that intensity, frequency and duration of exercise are also significant factors affecting exercise induced CV risk factor reduction in the cardiac patient group. While it has been established that exercise session duration of 40-60 minutes is optimal in this target population[14], the most efficacious session frequency and programme duration have yet to be fully elucidated and literature in this area is sparse.

The optimal exercise programme must improve the CV profile of the patient, properly utilize hospital resources and be cost effective. Patient adherence to a CR programme is typically poor[15,16], due to a combination of motivational and logistic issues (e.g. lack of time), with the latter accounting for 47% of CR patient withdrawals[15]. Therefore, expediency to the patient must be considered when designing and analysing the efficacy of a CR programme. It is likely that shorter programme duration may both increase patient attendance and facilitate greater patient throughput, thus increasing the economic efficiency of such programmes and making CR resources available to a greater proportion of cardiac patients. This preliminary study aims to analyse the effect of CR programme duration on CV risk factor modification in patients with established coronary artery disease (CAD), whilst assessing the efficacy of the existing 6- and 8-week training programmes in St. James's Hospital. The objectives of this study were (a) to analyse the efficacy of existing CR programmes by taking easily accessible biometric readings before and after completion of CR, and (b) to compare the efficacy of a 6-week and 8-week CR programme to establish whether there is an optimal programme duration for CV risk factor modification.

This research should contribute findings for a more informed and evidence-based approach to exercise training in cardiac patients.

	Combined		6-Week Programme		8-Week Programme	
	n=13		n=8		n=5	
	Pre	Post	Pre	Post	Pre	Post
BP (mmHg)	129/80	131/79	127/80	132/81	131/79	129/78
SBP	±23.05	±18.41	±28.46	±20.15	±6.29	±18.32
DBP	±8.97	±7.35	±11.12	±8.66	±2.50	±5.79
RHR (bpm)	67.813	75.459	63.625	76.667	72	74.25
	±6.92	±16.86	±6.16	±16.86	±4.30	±3.77
BMI	31.68	31.757	30.461	30.347	32.9	33.167
	±4.24	±4.26	±4.53	±4.47	±3.60	±3.67
WC	107.95	106.28	105.57	101.89	110.33	110.67
	±8.35	±12.05	±6.35	±12.66	±13.01	±9.02

▲ **Table 1:** Summary of Data Showing Study Population Risk Factor Dynamics
BP: Blood Pressure, RHR: Resting Heart Rate, BMI: Body Mass Index, WC: Waist Circumference

MATERIALS AND METHODS

Study Design and Programme Overview

This was a retrospective, non-interventional study; all measurements were routinely taken as part of the CR programme. Cardiac patients enrolled in phase 3 of an outpatient CR programme in the Physiotherapy Department of St James's Hospital, Dublin, were recruited to participate in the study (n=13). Eligible subjects were male, low risk cardiac patients and aged between 50-69 years. Low risk was defined by the following criteria: no or stable angina, under 70 years of age and no positive exercise stress test (EST). Patients were excluded from the study if they were unable to give informed consent, had a positive stress test, had an existing co-morbidity which would affect their ability to participate in CR or they were a smoker. All medications were continued as per usual.

Patients were randomly assigned to either a 6-week or 8-week programme. Both programmes consisted of 15 exercise sessions, 3 and 2 sessions per week, respectively. Exercise sessions lasted approximately 50 minutes and consisted of a warm up, an exercise circuit consisting of aerobic and resistance exercise stations, and a cool down period. The exercise circuit included seven stations employing a treadmill, an arm ergometer, a cross-trainer, a rowing machine, an exercise bicycle, a ball and weights.

The warm up consisted of a 250m brisk walk with a series of dynamic upper limb movements. Thereafter, patients were guided through upper and lower limb muscle stretches. In accordance with standard recommendations[17], exercise prescription

was individualised such that patients exercised within their target heart rate (HR) range. Target HR was calculated using the Karvonen formula[i]. The exercise intensity was 60% of maximum, as determined by pre-CR stress testing. For the weights station, patients lifted 60% of their one repetition maximum. For safety purposes, patients were monitored throughout each session by telemetry[ii]. Following exercise, a cool down was performed in order to return the HR to within 10% of resting values, after which patients were guided through upper and lower limb muscle stretches. Following the exercise component of the CR programme, patients attended a 1 hour educational and personal development session. Educational and personal development sessions covered topics such as nutrition, cardiovascular risk, pharmacotherapy, stress management and exercise.

Measured Parameters

All measurements were taken in accordance with standard recommendations. Blood pressure (BP) and resting HR were measured at the start and end of the exercise sessions using upper arm automated BP/HR monitors[iii]. Patients were seated and at rest when measurements were taken. In addition to pre- and post-training measurements, HR was monitored by telemetry[ii] continuously throughout each exercise session. This was for both safety purposes and to facilitate individualisation of the exercise programme.

Body anthropometrics were measured at the start and end of each programme. Patient height data[iv] were inputted into an automated body composition analyser[v]. The body composition analyser measured weight and calculated body mass index (BMI)[vi]. Waist circumference (WC) measurements were taken around the patient's bare midriff or over a light layer of clothing. The measurement site was the midpoint between the inferior margin of the lowest palpable rib and the superior iliac crest, with the tape parallel to the floor and perpendicular to the long axis of the body. In obese patients, where it was not possible to palpate the body landmarks, WC was measured at the level of the umbilicus, in accordance with standard recommendations[18].

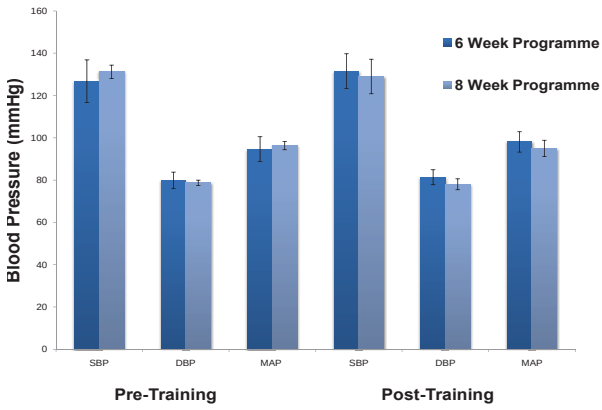


Figure 1: Effect of a 6-Week Vs. 8-Week CR Programme on BP
BP: Blood Pressure, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure
Data represent mean SBP/DBP/MAP values ± SEM for the 6-week (n=8) and 8-week (n=5) programmes before and after partaking in CR. There was no significant change in SBP (p=0.90), DBP (p=0.80) or MAP (p=0.90) with training and no significant programme effect was seen (p=0.92, 0.67, 0.95 respectively).

Statistical Analysis

Data were analysed using two-way repeated analysis of variance with Bonferroni *post hoc* tests. Statistical significance was $p < 0.05$. Data were analysed (a) to identify if there was a training effect and (b) to highlight any significant differences between the two CR programmes.

RESULTS

Subjects

Eight subjects were randomly assigned to the 6-week programme and five to the 8-week programme. Population risk factor dynamics throughout the study period are summarised in Table 1. The mean age of the participants Thirteen subjects were enrolled in this study in accordance with the study inclusion criteria. Eight subjects were randomly assigned to the 6-week programme and five to the 8-week programme. The mean age of the participants in the two groups was 58.8 years (59.5 ± 4.99 and 57.5 ± 2.65 for the 6-week and 8-week groups, respectively). All subjects completed the CR programmes and attendance rates for the 6-week and 8-week programmes

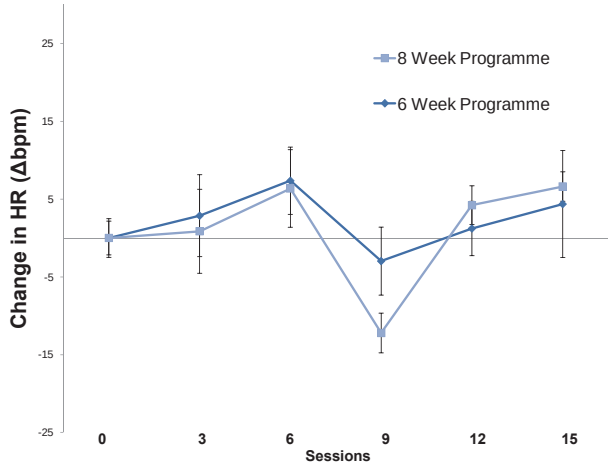
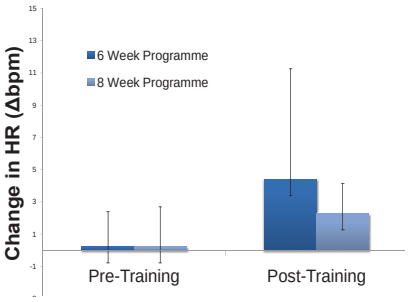


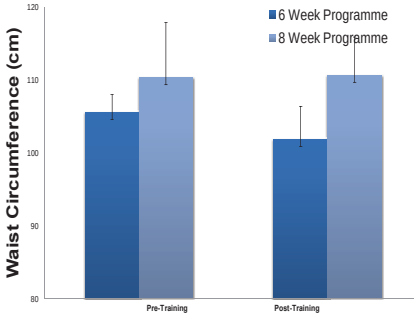
Figure 2: Effect of a 6-Week Vs. 8-Week CR Programme on HR

bpm: beats per minute
Data from sessions 3-15 represents change in mean heart rate from baseline ± SEM, for both the 6-week and 8-week programmes. Once data were normalised to baseline, training was shown to induce no significant change in resting heart rate (p=0.22). There was no significant difference between the effects of the 6- and 8-week programmes (p=0.18).



▲ **Figure 3:** Effect of a 6-Week Vs. 8-Week CR Programme on resting HR
HR: heart rate, bpm: beats per minute
Data represent change in mean resting heart rate from baseline ± SEM following attendance at CR for the 6-week (n=8) and 8-week (n=5) programmes. Training did not induce significant changes in heart rate (p=0.35). No significant difference (p=0.76) was seen between the effects of the 6- and 8- week programmes.

▲ **Figure 4:** Effect of a 6-week Vs. 8-week CR Programme on BMI
BMI: Body Mass Index
Data represent mean BMI values ± SEM for the 6-week (n=8) and 8-week (n=5) programmes before and after partaking in CR. There was no significant change in BMI (p=0.98) with training. No significant difference (p=0.23) was seen between the effects of the 6- and 8-week programmes.



▲ **Figure 5:** Effect of a 6-week Vs. 8-week CR programme on WC
WC: Waist Circumference
Data represent mean WC values ± SEM for the 6-week (n=8) and 8-week (n=5) programmes before and after partaking in CR. Training resulted in a moderate decrease in waist circumference in the 6-week group. This was not significant, however. No significant change was seen in the 8-week group, and there was no significant difference between the effects of the 6-and 8-week programmes (p=0.20).

were 77% (±6.28%) and 83% (±6.15%), respectively.

Blood Pressure

Systolic, diastolic and mean arterial pressure were analysed (Figure 1). Neither group showed a significant change in systolic blood pressure (SBP) with training (p=0.90) and no significant difference between the 6-week and 8-week programmes following training (p=0.92). There was no significant change in diastolic blood pressure (DBP) with training (p=0.80) and no significant difference between the 6-week and 8- week programmes following training (p=0.67). In addition, the CR programme did not produce any significant changes in mean arterial pressure (MAP) (p=0.90), with no significant difference between the two programmes (p=0.95).

Heart Rate

Resting HR at baseline was significantly greater in the 8-week group. To accommodate for this difference, HR data were normalised against baseline mean prior to analysis. Results showed that CR training had no effect on HR (p=0.35) and there was no significant difference between the two CR programmes (p=0.76) (Figure 2, 3).

Body Anthropometry

Neither CR training programme induced a significant change in BMI (p=0.98), as shown in Figure 4. In addition, there was no difference between the two CR programmes for BMI data (p=0.23). CR training resulted in a moderate decrease in WC in the 6-week group, but this was not significant (Figure 5). Results for WC showed no significant difference between the two programmes (p=0.20).

Medications

Table 2 summarises the use of anti-arrythmic and anti-hypertensive pharmacological therapy by both groups. 69% of subjects in this study reported using one or more anti-arrythmic agents (88% in the 6-week programme, 40% in the 8-week programme) while 92% of participants reported use of anti-hypertensive medications (100% in the 6-week programme, 80% in the 8-week programme).

DISCUSSION

While there is evidence to support the effectiveness of CR in reduction of risk factors for CVD[4,5], the optimal duration of exercise programmes remains unclear. When evaluating the efficacy of a programme, the following must be taken into consideration:

- Capacity to reduce CV risk factors
- Appropriateness to the needs of the patient
- Economic viability

Shorter programme duration has been demonstrated to be favourable in terms of the appropriateness to the needs of the patient, their lifestyle and ability to participate in CR[19], can increase patient adherence and may be associated with a reduction in healthcare costs. Therefore, it is essential that the effect of programme duration on risk factor reduction be assessed in order to facilitate an evidence-based approach to CR.

It is widely documented that exercise produces significant decreases in HR, BP, BMI and WC[3], even in an at-risk cardiac population. HR, SBP, DBP, MAP, WC and BMI were analysed in this study. Results indicated no significant change in any of these param-

eters following a 6-week or 8-week CR programme. However, 92% of patients were medicated for hypertension and 69% of patients were using an anti-arrythmic drug. The effect of poly-pharmacy on an exercising patient group is not known, though it is likely that these medications may have confounded the effects of exercise training in terms of the outcome measures employed. In addition, attendance of CR in St. James's Hospital is typically poor, with an initial average attendance rate of 89% and a completion rate of 70%[3]. It is expected that patients with poor compliance to a CR programme will not show a marked improvement in their CV risk factor profile on completion of the programme when compared with patients who attended all sessions. Poor patient attendance may have influenced the results in this study and may have contributed to the lack of observable improvements in CV risk profile following the two programmes. In addition, it is important to note that the sample size of the study was small (n=13), which may not accurately reflect the effects of a CR programme on the CV risk profile. It is clear that further research is warranted with a larger sample size and ensuring full attendance of participants to fully determine the effects of these CR programmes on the CV risk profile of medicated cardiac patients.

Although there were no improvements in the CV risk profile following either of the CR programmes, no significant differences between the programmes were observed. This result might suggest that there is no additional benefit conferred to the patient attending an 8-week CR programme as compared to a 6-week programme. Thus, healthcare expenditure and patient adherence might be optimised by employing a shorter CR programme duration. Current literature comparing the effects of long-term and short-term CR programmes is sparse. While Hevey et al (2003)[19] demonstrated that there was no significant difference in effect between a 4-week and a 10-week CR programme, and Reid et al (2005)[20] demonstrated that there was no statistically significant or clinically relevant difference between a 12-month and a condensed 3-month CR programme, few other studies have actively analysed the effects of varied programme duration. Review of the literature indicates a trend which suggests the efficacy of CR programmes of longer duration is more firmly established, when compared with short-term programmes. The current study suggests that CR programme duration does not influence outcome with regard to risk factor modification, aligning with the works of Hevey et al (2003) and Reid et al (2005). It must, however, be acknowledged that the difference in duration between the programmes analysed in this study was small. Future studies incorporating programmes with greater variance in duration are necessary to determine the minimum programme duration effective in modification of the CV risk factor profile. In addition, the potentially confounding effect of non-exercise interventions (education and personal development) must also be considered. Future studies should explore the role played by non-exercise based interventions in reducing CV risk factor profile.

	Combined	6-Week Programme	8-Week Programme
	n=13	n=8	n=5
% Patients Prescribed Anti-Arrythmic Agents (Vaughan-Williams Classified Drugs)	69	87.5	40
% Patients Prescribed Anti-Hypertensive Agents	92	100	80

▲ **Table 2: Summary of Anti-Arrythmic and Anti-Hypertensive Drug Use in Study Population**

CONCLUSION

No significant reduction in CV risk factor profile (HR, SBP, DBP, MAP, WC and BMI) was found following a 6-week or 8-week CR programme. In addition, there was no signicant difference in efficacy found between the two CR programmes. Expediency to the patient must be considered in the design of a CR programme in order to increase attendance and increase the degree of risk factor modification. It is likely that shorter programme duration is favourable in terms of adherence[3] and cost effectiveness, although this remains to be explored systematically.

Further research is warranted to accurately identify the CR programme duration that will produce optimal modification of the CV risk profile, while also optimising healthcare costs and remaining expedient to the patient. Importantly, future studies must incorporate more stringent monitoring of medications to elucidate the role played by poly-pharmacy. Employing shorter CR programmes would likely result in a significant reduction in healthcare expenditure, whilst increasing patient adherence. By reducing high withdrawal rates and increasing attendance, this straightforward change in protocol could increase the efficacy of cardiovascular risk factor reduction through CR and

hence prove most beneficial to the patient.

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APPENDIX

[i] Karvonen Formula: Target Heart Rate = [(max HR – resting HR) × %Intensity] + resting HR
[ii] Using either the IntelliVue TRx 4851A system (Philips Healthcare, Netherlands) or F1+ Polar monitors (Polar Electro, Finland)
[iii] Upper arm automated BP/HR Monitors (Microlife BP 3VTO-AP, Widnau, Switzerland)
[iv] Seca 222 height measuring instrument (Seca, Germany)
[v] Body Composition Analyser (Tanita BC-420MA, Illinois, USA)
[vi] BMI = [weight (kg) ÷ (height (m))^2]

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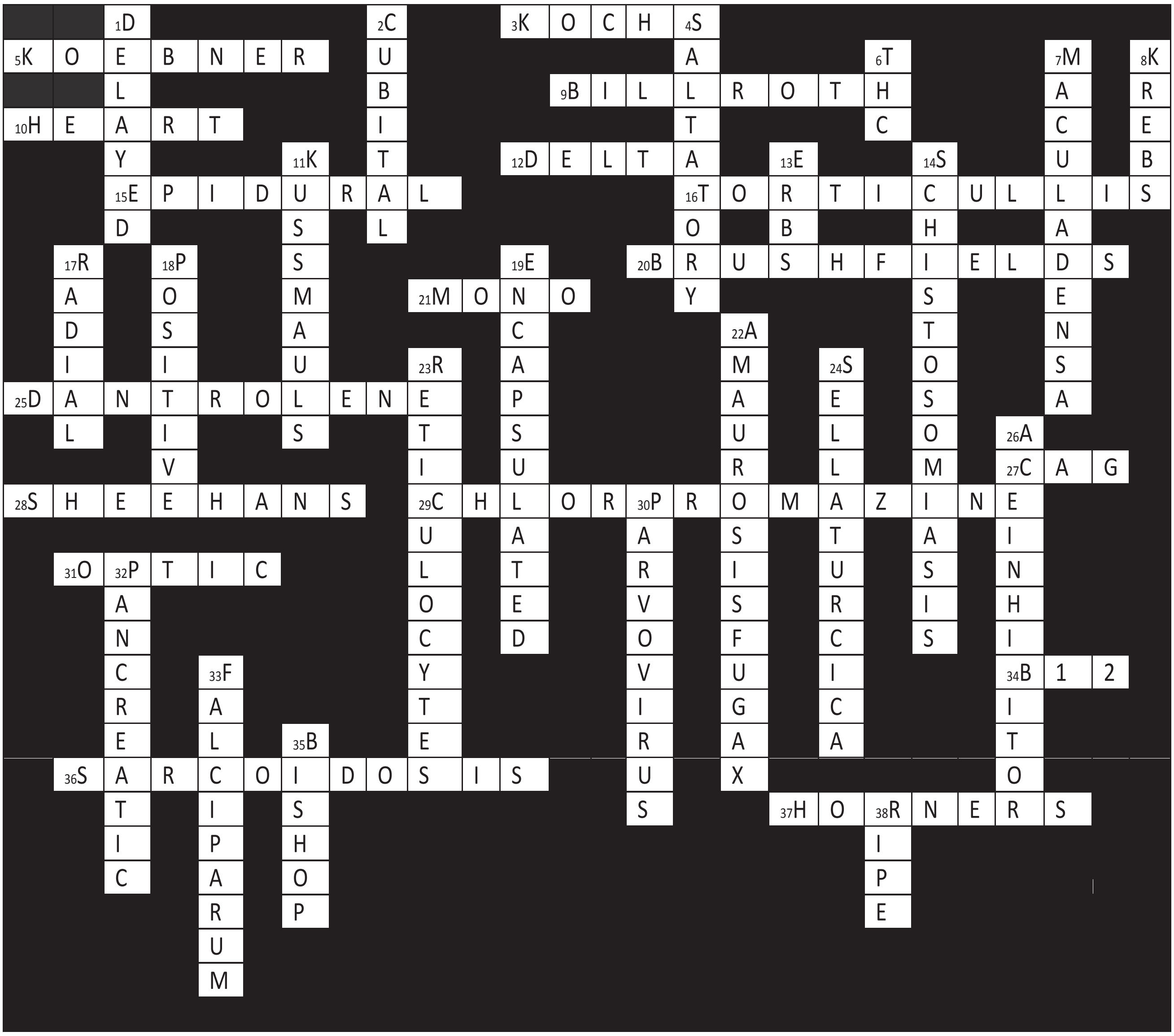

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