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Welcome message from the Editor-in-Chief, University of Dundee SUMJ

I am delighted to welcome you to the University of Dundee section of the inaugural issue of the Scottish Universities Medical Journal (SUMJ). This new on-line open access journal will provide a valuable platform for Dundee medical students to present peer-reviewed work undertaken during their undergraduate studies. Importantly, the SUMJ will remain both accessible and free for students and will allow them to gain some experience in medical journalism and publishing. The vision of the University of Dundee SUMJ is to publish high-quality articles and reviews from students that will be of broad interest and educational value to both students and junior doctors. This inaugural issue contains a wide variety of articles including a case study, clinical practice and service development reviews, primary research and literature reviews. We will also have regular Medical Education articles that will focus on Radiology and Clinical Anatomy.

I wish to extend my personal gratitude to all those who have contributed to the launch of this flagship student journal especially the consultant staff who have taken the time to review submitted articles. I would also like to thank the many student contributors and the Medical Defence Union for their generous sponsorship and support.

Lloyd David Hughes
Editor-in-Chief
4th Year Medical Student; University of Dundee Medical School
Intercalating at Napier University (BSc Care of the Elderly)

Contacting the SUMJ Dundee

General Enquiries  sumjdundee@gmail.com
Article Submission Queries  Lloyd Hughes [Editor in Chief] L.D.Hughes@dundee.ac.uk
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Submitting Articles to the SUMJ

The SUMJ is an online journal open to all medical students studying in Scotland. Our aim is to provide an accessible platform from which students are able to present peer-reviewed work carried out during their undergraduate years, and in the process gain experience in medical journalism. If you wish to submit to the SUMJ the deadlines for each of our editions are noted below:

Winter Edition February [Deadline for submissions is October 31st]

Summer Edition August [Deadline for submissions is April 30th]

Please attach copy of your submission to BOTH:

sumjdundee@gmail.com; L.D.Hughes@dundee.ac.uk

Please include the type of article (e.g. case report, research) you are submitting in the subject line. The guidelines for article submission can be found on the SUMJ Dundee website. The submitted article should be in Microsoft Word format and contain a declaration of your own work.

If you are submitting a case report you must submit a signed form by the patient in line with confidentiality considerations.
Licensed to Kill – The Impact of Legalising Euthanasia and Physician Assisted Suicide on the Training of UK Medical Students

Bhajneek Grewal (5th Year MBChB); Jennifer Harrison (FY2, Hairmyres Hospital East Kilbride) & Dr. David Jeffrey (Academic Mentor & Retired Palliative Care Consultant, University of Dundee)
Correspondence to: David Jeffrey: d.i.jeffrey@dundee.ac.uk

ABSTRACT

There have been a number of attempts to legalise euthanasia and physician assisted suicide (PAS) in the UK over the past decade. The potential impact of legalising euthanasia and PAS in the UK on the training of medical students, the next generation of doctors, is examined in this discussion paper.

Key Words: euthanasia, assisted suicide, medical students, education

Introduction

The terms used in the euthanasia debate are often confusing. We include the following definitions in Table 1.

Table 1 - Definitions

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<table>
<thead>
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<tr>
<td>Euthanasia</td>
<td>Translated literally from Greek to mean ‘good death’. Commonly referred to as ‘mercy killing’.</td>
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<tr>
<td>Active Euthanasia</td>
<td>Intentional administration of lethal substances to hasten death.</td>
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<tr>
<td>Voluntary Euthanasia</td>
<td>Euthanasia performed with informed consent from a competent person or by instruction of an advance directive</td>
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<tr>
<td>Involuntary Euthanasia</td>
<td>Euthanasia performed without consent.</td>
</tr>
<tr>
<td>Physician Assisted Suicide</td>
<td>A doctor assists another person to end his or her life e.g. by prescription of lethal drugs.</td>
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The debate surrounding the legalisation of euthanasia and physician-assisted suicide has become polarised. The principal arguments “for” and “against” euthanasia and PAS are well documented and will not be reiterated here.\(^\text{(2,3)}\)
Most people assume that if euthanasia and PAS are legalised, it will be doctors who will be prescribing the lethal medication or, in euthanasia, administering it. Thus it is of particular importance that medical students and doctors express their views on this contentious issue that could have an enormous impact on their clinical practice. This discussion paper examines the impact of legalising euthanasia and PAS in the UK on the training of medical students, the next generation of doctors.

Legal Background

There have been a number of attempts to legalise euthanasia and physician assisted suicide (PAS) in the UK. The present law strikes a balance by providing safeguards for the vulnerable and compassion for individual, extreme ‘hard’ cases.

**2003** Lord Joffe proposed the Assisted Dying Bill which would have legalised both euthanasia and PAS but it failed to progress.

**2004** Lord Joffe introduced another Bill (Assisted Dying for the Terminally Ill). It was referred to a House of Lords Select Committee.

**2005** House of Lords Select Committee chaired by Lord Mackay of Clashfern spent six months meticulously reviewing the evidence on the legalisation of euthanasia and assisted suicide. The committee failed to reach a consensus but did agree recommendations that any future legislation should take into account.

**2005** Lord Joffe presented his third Bill that now was limited to assisted suicide. It was defeated in the House of Lords by 148 votes to 100.

**2005** Jeremy Purvis MSP presented a consultation paper to the Scottish Parliament, “Dying with dignity”. This failed to achieve sufficient support to generate a full debate.

**2009** Lord Falconer’s proposed amendment to the Coroner’s and Justice Bill, designed to remove the risk of prosecution from those taking their relatives to a country where assisted suicide was lawful, was defeated by 194 votes to 141.

**2009** Law Lords unanimously agreed that Debbie Purdy had the right to know whether her partner would face prosecution if he helped her to end her life. The Law Lords instructed the Director of Public Prosecutions (DPP), Keir Starmer QC, to publish prosecution policy relating to cases of assisted suicide.

**2010** The DPP “Policy for Prosecutors in respect of cases of Encouraging or Assisting Suicide” was more focussed on the motives of the suspect rather than the characteristics of the victim. Starmer made clear that the policy did not change the law on assisted suicide nor open the door for euthanasia.

**2010** Margo MacDonald’s ‘End of Life Assistance Bill’, which allowed both euthanasia and PAS, was defeated in Scottish Parliament by 85-16.
Current training for medical students

The General Medical Council (GMC) in the UK has given a clear recommendation in Tomorrow’s Doctors that all medical students should receive core teaching on caring for the terminally ill. At present, provision of teaching on end of life care varies greatly from one university to another. It has been suggested that UK medical students have higher levels of awareness of palliative medicine than their US colleagues and that they have a more positive approach towards its role. Legalisation of euthanasia would undermine this progress.

Competition for undergraduate teaching time is fierce, and the new teaching would, at the very least, have to cover the following areas;

- the assessment of the euthanasia request
- attitudes to dignity
- the practicalities of ending life
- support of the family
- self-support
- support of colleagues

The undergraduate curriculum is already overloaded and it is possible that aspects of palliative care teaching would be sacrificed to make way for teaching on how best to end the life of patients.

Doctors in the UK have little knowledge of how patients could be euthanized and so far have never had to consider this on a practical level. Furthermore, the majority of doctors involved in end of life care want no part in this process. Perhaps if euthanasia and assisted suicide were legalised they should not be regarded as part of a doctor’s duty but instead be administered by lawyers and technicians trained to carry out euthanasia and assisted suicide.

Role contradiction

The Hippocratic injunction “first do no harm” is a cornerstone of the healthcare professional’s duty of care, a duty which legalisation of euthanasia would overturn so that the patient’s life could be ended. The importance of this paradigm shift in medical practice should not be underestimated. It would require a new ethos in medicine.

Students would require support to cope with the stresses involved in making decisions about euthanasia and assisted suicide. A number of students may be conscientious objectors to euthanasia and PAS. Recruitment and selection of undergraduates might be affected if euthanasia was legal in the UK. There have been no published large-scale surveys of UK medical students’ views on euthanasia and PAS.
Trust

Euthanasia legislation has the potential to affect the trust between the student/doctor and patient (Figure 1). Such trust is essential for medical care. The present law recognises this and protects patients and society by making it clear that doctors are not permitted to intentionally end a patient’s life or to assist in their suicide but rather they have a duty of care to act in the patient’s best interests until the end of their natural lives. However, once euthanasia and assisted suicide become legitimate ‘treatments’, doctors would be obliged to raise them as options with all dying patients. Such conversations would be bound to raise fears in some patients that the doctor had an interest in hastening their death.

Fig 1- Euthanasia legislation has the potential to affect the trust between the student and patient.

Value of life

The legalisation of euthanasia and PAS makes an underlying assumption that the worth of human life depends on features such as physical or mental ability, rather than being valuable in itself. Such legislation would send a message to people with disabilities or any chronic disease that because they are dependent on others they might reasonably consider their lives to be less worth living than those of their peers. Consequently they may feel obliged to choose euthanasia or assisted suicide in part because society tells them they are less valuable than others. Teaching students to carry out the task of judging whether life is ‘tolerable’ or ‘worth living’, goes against the current medical ethos and could inhibit patients from disclosing their concerns about physical, social, psychological or spiritual distress. Since it is often possible to resolve underlying issues that ultimately lead to suicidal desires, it is crucial that patients feel able to communicate openly with students and doctors.

Dignity and Choice

Choice is only one aspect of autonomy, but autonomy should not be confused with independence. We are dependent upon others for our existence throughout our lives and so dependence is an integral part of what it is to be an autonomous human being. Our mutual dependence is a part of our human dignity (12). Such a concept of human dignity is devalued by equating it with euthanasia or PAS.

Patient dignity is already threatened at times in hospital where there is often a lack of privacy for patients. Euthanasia would be an extremely sensitive topic to discuss.
behind curtains with the rest of the ward listening. It would distress neighbouring patients, and it is even possible that patients would be moved into a hospice. Hospices in the UK are places where patients place great faith and trust in their doctors and nurses, and PAS or euthanasia would change this therapeutic dynamic. Already many patients are apprehensive about coming to a hospice and legalisation of euthanasia and PAS would tip the balance even further in a negative direction.

**Practicalities**

It is often assumed that all euthanasia and assisted suicide deaths are peaceful and therefore “dignified”. Students may fail to take account of the complications that can occur in the process of assisted suicide and euthanasia. In a Dutch study, 3-16% of patients who had either euthanasia or assisted suicide had complications such as failure of completion, myoclonus or vomiting. Students would need instruction on how best to end a patient’s life. Practical skills in ending life would need to be tested and assessed. Training would need to be provided in developing the necessary communication skills to respond to the patient’s plea “Please help me to die!”

**Responding to a request for euthanasia**

Individual requests for euthanasia and physician-assisted suicide are complex in origin and demand careful attention with open and sensitive communication. Patients and families often experience great difficulty in discussing death and dying, how much more difficult it would be to discuss euthanasia and suicide. Sensitive exploration of the euthanasia request can help to identify the real needs of an individual patient. The request for euthanasia or physician-assisted suicide seems to point to a series of concerns that the patient has about dying; relating to loss of self, loss of dignity and the social context of dying. Understanding these concerns may help to improve the care of dying patients.

However, assessment of the euthanasia request can also create a barrier which subtly alters the doctor-patient relationship and may paradoxically impair the possibility of discussing the patient’s hopes and fears. Sometimes it can be difficult to assess a patient’s needs when the goal of euthanasia dominates the discussion.

At present, when faced with a patient saying that ‘life is not worth living’, medical students are taught to acknowledge the patient’s distress and then make an effort to address the factors underlying these feelings. This approach demonstrates that the patient is valuable in themselves and that the value of their life is not diminished by their loss of independence or disability. If euthanasia and PAS were legalised then an alternative approach becomes possible; where the doctor agrees that the patient’s life is intolerable and deliberately hastens their death. This confirms to patients that their lives really have lost meaning and purpose, not only in their own eyes but in the opinion of others and society at large. Legal endorsement of this approach teaches students and doctors, not only that there exists a category of people whose lives are not worth living, but also that it is proper for doctors to make judgements about who might be included in this group. Legalisation of euthanasia will encourage medical decisions that lead to its use rather than the current practice of addressing the causes of despair.
A change of mind

Patients often change their minds about their initial euthanasia request. In the quest for patient contact, medical students often have more time to listen to patients and in turn patients may reveal more to an individual student than they necessarily would to a ward round team. Would a sad expression or a throwaway remark qualify as a sign that the patient does not want to end their life? What would a student do in such a situation and what would be the implications if the student’s impression was not taken seriously by senior medical staff?

Wider impact

Legislation will change the way in which society views the sick, the disabled and the dying. There is a danger that such patients will be seen as an inconvenience to be disposed of. Patients might feel a burden to their families and society and so feel obliged to consider euthanasia. There is much for students to learn about the importance of a patient’s social circumstances in generating a request for euthanasia or assisted suicide (14). Rather than encouraging society to develop measures to address the suffering of patients, which affirms their intrinsic worth, legislation will encourage the attitude that human dependence and need actually devalue human life.

Role of Palliative care

Clinical experience shows that with the proper provision of palliative care services, and adequate and timely access to practical and necessary support for patients and their family, persistent requests for euthanasia are infrequent. Where they do exist, the solution lies in providing support and the best possible care to engage with issues such as hopelessness and suffering, not in euthanasia or physician assisted suicide. It is imperative that patients, their families and the public are clear that palliative care is fundamentally different from euthanasia and physician-assisted suicide.

Conclusion- A medical student’s view

When applying for a place in medical school we were filled with the hope of curing disease and alleviating suffering. These basic, humanistic ideas formed the basis for our career choice and hopefully will still be at the core of our clinical practice beyond graduation. If the above legislation had passed before I applied to medical school, and I had known that my future would include euthanizing patients this would have made me seriously question the fundamental principles of medicine. I wonder if, as a consequence of this legislation, Medicine would attract a different group of applicants; those who do not say at their interview, “I want to help people” but instead say, “I want to help people to die.”

Recent evidence suggested that the UK’s foundation doctors are inadequately prepared for dealing with dying patients on the wards (15). The study noted a tendency for medical students to shy away from encounters with the dying and an overall lack of undergraduate exposure to this patient group. In the era of ‘modern
We are still notoriously uncomfortable with patients who die as a consequence of disease progression; we are uncomfortable with natural law. Bearing this in mind, it is concerning to think that Parliament has repeatedly come so close to passing a law which would necessitate student attendance of compulsory sessions to educate us on the clinical ‘skill’ of assisting suicide. Student lectures would include the theory of euthanasia and provide instructions in humane methods that could be employed to end a human life. Communication skills sessions would involve counselling simulated patients on how we could hasten their death.

We are nowhere near being able to say we have mastered the art of palliative care, much of which is simply good care, much less being able to say we have overcome the need for it.

Politicians will continue to debate the theoretical and ethical issues surrounding euthanasia and PAS, but they will not be the ones offering euthanasia as a treatment option to patients. They will not be sitting by a patient’s bedside with their thumb on a lethal syringe. They will not go home at night knowing that a patient’s death was hastened on their watch. They will not have to live with the burden of these thoughts for the rest of their lives. (16)

We paint this picture not to enforce our views upon others but to encourage students to consider the practical implications of PAS or euthanasia legislation on our future professional and personal lives. Medical students are currently able to openly debate issues such as euthanasia and are still free to voice their opinions without legislation demanding competencies in PAS or euthanasia before or during foundation years. It is imperative that we do voice our opinions. This is said in multiple ethics articles and teaching sessions, but it is not simply to show that we are brave enough to have opinions on job application forms. Our voices are those of the next generation of doctors and will have an impact on future patient care.

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Medical Students and peer support: a discussion based on findings from a BMSc research project

Jocelyn Dick (4th Year MBChB, BMSc) Correspondence to: J.M.Dick@dundee.ac.uk

“There’s a big competitive drive for the first sitting. It might just be medics, it might be everyone, but it’s definitely “fend for yourselves”

ABSTRACT

Background

Little evidence of support schemes available to students following examination failure exists. Peer assisted learning initiatives in medical education have been shown to increase the engagement of students with learning and optimise academic achievement. The role of peers in supporting medical students has not been formally explored at the University of Dundee where this study was conducted.

Methods

A case study was undertaken exploring the perceptions of student support. Students who had failed a summative examination and academic support staff were invited to take part in an individual, semi-structured interview. Seventeen interviews were audio recorded, transcribed and thematically analysed by the researcher. This paper discusses the results from students related to peer support in the context of the relevant literature.

Results

Medical students can and do support each other after failing a summative examination. Working with same year and senior peers can help students to learn more efficiently in preparing for a re-sit examination. However, although peer interactions can reassure students about their academic performance they can also increase the insecurities of students regarding their knowledge.

Discussion

Peer interactions and group study may help to increase the efficacy of student study in preparation for examinations and encourage practice of behaviour conducive to a career as a health professional. Further research exploring the relationship between peer support and examination performance is required.
Introduction

This project explored the perceptions of students and faculty educators towards the support available to medical students after failing a summative examination at the University of Dundee medical school. This paper considers the findings related to the student perceptions of peer support. The research project process will be outlined and the relevance of peer support themes from the study considered. The results relating to peer support are presented and discussed in the context of the relevant literature.

Conducting a research project into student support

Literature to date\textsuperscript{1-3} indicates that students who have failed an examination are unlikely to seek support, and are arguably in more need of additional support following examination failure. Several studies\textsuperscript{4, 2, 4-7} suggest that the performance issues of medical graduates are rooted in the failure of universities to provide accurate feedback and guidance in undergraduate medical education. Despite the obligation of medical schools to provide general and academic guidance for poorly progressing students\textsuperscript{8}, there is little evidence of robust systems with effective remedial initiatives for medical students after they have failed an exam\textsuperscript{5}.

The extent to which student support is provided and integrated as part of the medical student experience after failing an exam has been addressed in few research studies but not at the University of Dundee. The research questions for the study were: (i) What support are students aware of after failing a summative examination? (ii) What were the experiences of students of support after failing an exam? (iii) What were the expectations of students at this time? (iv) Is there enough support in place and is support of value? (v) What should be changed, if anything, about the current support provision available to students after failing an exam?

A qualitative research approach is concerned with gaining an understanding of the accounts, opinions and experiences of an individual\textsuperscript{9}. Therefore, this was employed to explore the perceptions of participants. A holistic and humanistic approach\textsuperscript{10} was also appropriate for the sensitive nature of the study, as students were asked about their personal experiences related to failing a summative examination. Case study methodology permits an in depth exploration of individuals, processes and programmes\textsuperscript{11, 12}. The use of a case study for this research has provided a proficient archive of descriptive material, with the opportunity for future interpretation of findings by others and the potential to guide further revision and refinement of educational action\textsuperscript{13}.

Students in Years 1-3 who had failed a minimum of one summative examination at medical school were self-selected by agreeing to participate in response to a recruitment email sent to all students. Eight faculty educators were selected for interview based on their involvement in the provision of student support within the medical school. Participants were invited to attend a semi-structured interview that allowed the researcher to ask key research questions from an interview guide and explore emerging themes\textsuperscript{14}. Data saturation was reached after nine student interviews which lasted between 12 and 40 minutes. Interviews were recorded using
a digital audio recording device and transcribed by hand by the researcher. Transcripts were anonymised and thematically analysed.

**Consideration of peer support**

No formalised structure of peer support exists within the University of Dundee medical school. Although the term ‘peer support’ was not included in the research questions, students expressed their opinions related to interactions with peers in the medical school in response to being asked about their experiences of student support following examination failure. Students who acknowledged ‘peers’ in their responses understood ‘peers’ to be medical students in their own year, or senior years, at the same medical school.

Medical student peer interactions have been widely considered in the context of ‘peer assisted learning’ (PAL), where a student of the same or similar intellectual status facilitates group learning in an informal environment\textsuperscript{15, 16}. PAL is praised in medical education as it has been shown to improve examination performance, communication, team-work and the teaching skills of participants\textsuperscript{15-17}. Although Topping\textsuperscript{18} claimed that PAL improves the affective functioning of participants, the role of peers as an integral component of student support has not been explored within UK medical schools.

In addition, recent evidence concerning medical graduates suggests that building supportive relationships with fellow junior doctors helps them to respond to the challenges of training programmes\textsuperscript{19}. Prins et al.\textsuperscript{20} established that doctors find the emotional support received from other trainees to be of more value than support provided from designated senior supervisors or tutors. Peer support groups continue to be a popular component of well-being programmes and a fundamental element of support for graduate medical trainees in North America\textsuperscript{19}.

Students in frequent contact with their class peers engage more with learning activities, optimising academic achievement during undergraduate study and promoting student retention\textsuperscript{21}. As this research explored student perceptions of support provision following examination failure, it is appropriate to present the themes which relate to peer interactions and discuss the role of peers in supporting underperforming medical students.

**Results relating to peer support**

Six themes identified from nine student participants are presented below.

1- Senior peers providing reassurance and practical advice in preparation for a resit examination

Several students valued senior peers who had also failed a summative examination as this reassured them that they have an opportunity to rectify their underperformance in the resit examination:
‘Just talking to people who are in older years, they’ve done it. They’ve failed the exams but they’ve got through, they’re now almost...more than halfway through [medical school]. It’s really good to see that it’s possible.’ (Student 4)

Students considered senior peers to be a trusted source of guidance as they had experience of sitting that particular examination. Also students had encountered seniors who had taken time to advise them about revision:

‘It’s really great being able to go over stuff with an older student who’s already sat the exam, and is able to give you loads of little hints and tips.’ (Student 8)

2- Peer support helps individuals to gauge their level of knowledge in relation to the required standard

Students perceived that sharing work with same year or senior peers helped them to judge how their understanding and knowledge compared with the standard required to pass a summative examination:

‘Talking it over with a peer [is] great. When it’s just questions and answers, you can see... do I know that? Don’t I know that?’ (Student 4)

3- Same year peers who have failed help to reduce the burden of a resit examination

Students considered that others who had failed the same examination shared a mutual understanding of their predicament. The knowledge that their peers were experiencing the same difficulties was comforting and reduced their sense of isolation:

‘There was quite a sort of family of people at the library every day...it’s like, you know, ‘now we need to help each other.’’ (Student 9)

4- Same year peers who have failed help each other to augment learning in preparation for a resit examination

Several students noted that they had revised for their resit examination with peers in their year who had failed the same examination:

‘We got together sometimes as a group...and [we would] go through things, without like a peer tutor or a doctor or anything with us. I find that to sit down and chat to someone else about [a subject], makes it easier for me to understand about it.’ (Student 5)

5- Failing an exam reduces the need to impress peers

The majority of students acknowledged secretive behaviour of students surrounding seeking academic support. Students perceived that there is a need to impress peers, for fear that admitting to struggling will compromise their position in later years. Competition exists amongst students for better examination performance:
‘It might just be medics…but for the first sitting it’s definitely fend for yourselves.’ (Student 3)

After facing academic failure students are more inclined to admit their difficulties to one another and learn co-operatively:

‘Since we all failed, well, we all know we had trouble. So it’s like suddenly you’ve got rid of all that kind of farce...Competition really goes out the window ‘cause you’ve not got so much to prove.’ (Student 9)

6- Peer study groups can be counterproductive

Some students stated that in studying with peers prior to a resit examination, some group members would become anxious from peers demonstrating their superior depth of knowledge, whilst others felt that they could not rely on student knowledge to further their own learning:

‘...we just got so confused and we were just going in tangents, it’s literally like the blind leading the blind...I don’t know why we thought that was a good idea.’ (Student 4)

Discussion of findings related to peer support

Students appreciated their ability to learn more efficiently with trusted peers before their resit examination. Similar to Ashgar’s findings, peer to peer interactions enabled students to be more explicit with each other regarding uncertainties in their knowledge and understanding in a more amenable way than with a senior tutor in an esteemed position of authority. This may be of particular value for students who are preparing for a resit examination, who may require fundamental principles from the curriculum to be clarified. Students reported that working with same year and senior peers helps them to be more aware of their own learning. This is supported by the work of Topping who found that peer learners are capable of monitoring and regulating their own learning strategies. For students who have limited time to study prior to their resit examination, they may benefit from having an increased awareness of their study techniques. Students regarded discussions with older peers to be useful in providing them with some degree of feedback on the extent to which their knowledge met the standard required to pass an exam. Feedback is constructive to learning when it highlights disparities between the perceived performance and actual performance of the student. This is of particular relevance to students who have been unsuccessful in their first attempt at an examination where a lack of insight into their own academic ability often contributes to poor performance.

Over-competitive students contribute to creating a negative atmosphere, which leads to increased stress and anxiety amongst students; factors known to impede academic performance. Students indicated that in preparation for a resit examination, where it is common knowledge that individuals have failed, inter-student competition diminishes. This may help to explain why students in this
medical school preparing for a resit examination were more likely to collaborate with one another. Advocates of PAL\textsuperscript{17} have found that peer teaching reduces stress levels, which may further benefit students who are working with peers in preparation for a resit examination.

Students found relief in the knowledge that several of their fellow classmates had failed the first sitting of a summative examination. Shared learning carries emotional aspects with it and enables students to share empathy for failure and enjoyment in their successes\textsuperscript{22}. Topping\textsuperscript{18} and Cushing et al.\textsuperscript{23}, considering PAL, demonstrated that working with peers can increase learner motivation and self-esteem, desirable qualities for students with the intention of passing their resit examination.

It is clear from the opinions of students that some medical students respond positively to studying in an informal environment. Students were happy to organise their own group study sessions whilst preparing for their resit examination. Devoe et al.\textsuperscript{25} found that medical students consider peer study groups to be an effective learning strategy preferably when they are not mandated. This suggests that medical students can acquire skills to self-direct their learning, which are of benefit, during preparation for a resit examination.

The results from nine students showed that there are some negative aspects associated with peer interactions following examination failure. Students commented that they may feel intimidated by the perceived knowledge of others when revising with their peers. These are consistent with findings from Topping, who argued that dominant individuals can cause other members to feel that their competence is under threat. Topping also affirmed that students do not always have confidence in their peers as tutors\textsuperscript{18}.

**Limitations of this work**

The findings related to peer support presented here from this study are limited. Concepts related to peer support emerged from the responses of student participants to questions about their experiences of student support after failing a summative examination. This study was concerned with support provision in the context of examination failure and there may be further aspects of peer support that were insufficiently explored. The study has explored the perceptions of a small number of medical students within one medical school. As the sample size is small, the findings may not be extrapolated to other student groups at different institutions. However, case studies aim to understand a case in their own right\textsuperscript{11} and readers should consider the findings within the context of this research.

**Conclusion & Recommendations**

A summary of the major points that would encourage effective peer relationships is summarised in Table 1. Students at the University of Dundee are allocated into tutorial groups for Years 1-3 according to alphabetical order of their name. Students
work in these groups for compulsory academic commitments only thus excluding peer tutoring. There is potential for group based learning to have a positive affect on the academic performance of students but this may also become counterproductive with loss of synergy in the group’s dynamics. Based on the findings presented in this paper, it may be of value for the medical school to reconsider student group allocation.

**Table 1- Encouraging supportive peer relationships in Medical School**

| • Make a point of identifying one of your own peers in the Medical School that you could approach |
| • It is unlikely that others know you are struggling until you tell them, there is no shame in asking for help |
| • If you think that you could prioritise giving your time to help a junior student with their work, make them an offer |
| • Allocated ‘peer tutors’ can take the opportunity to encourage students to pursue group study in addition to formal peer tutoring/P.A.L programmes |
| • Faculty support staff should encourage students to consider their peers for academic support |

Whilst several students perceived their interactions with same year and senior peers to be both emotionally and academically supportive after failing a summative examination, peer support was considered informal. Whilst medical schools are committed to ranking students by academic merit as part of the foundation application process,, it may be appropriate for medical schools to encourage students to work with their peers outwith curricular encounters in order to facilitate less competitive learning behaviour and increase the sense of accountability of students.

**What this work has shown**

The findings presented from the author’s consideration of results relating to peer support have shown that medical students can and do support each other after failing a summative examination. Working with peers helps some students to learn more efficiently. Peer interactions contribute to students feeling more reassured about their academic performance but can also increase the insecurities of students about their knowledge.

The behaviours demanded of students interacting with peers in light of failing an examination include sharing knowledge, altruism and team-work and these are some of the fundamental traits that are key in the initial selection of medical students. Working with peers after failing a summative examination allows students to
develop characteristics conducive to a career as a health professional. Raising awareness of the value in peer support, in further studies and in encouragement from medical schools, may contribute to a more positive learning environment for medical students in the future. Further research that primarily explores peer support, and considers its influence on examination performance may help to strengthen the author’s findings from this study.

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An analysis of factors contributing to poor outcomes in Cystic Fibrosis

Kirsten Murray (3rd Year MBChB) University of Dundee

Correspondence to: K.A.Z.Murray@dundee.ac.uk

ABSTRACT

Cystic fibrosis (CF) is one of the most common inherited conditions in Europeans and affects 1 in 2381 births in the UK.\(^1\)\(^2\) It is an autosomal recessive condition resulting from a mutation in the CFTR (cystic fibrosis transmembrane conductance regulator) gene on chromosome 7.\(^3\) This affects the transport of chloride ions leading to disruption of sodium and water movement with the resultant generation of abnormally thick secretions.\(^3\) These thick secretions cause inflammation and cell damage and adversely affect organ functioning.

Introduction to Cystic Fibrosis

There are many different clinical presentations of cystic fibrosis and this now includes neonatal screening as every child born in the UK undergoes a Guthrie test one week after birth. Blood is collected via a heel prick and tested for several inherited conditions including cystic fibrosis which is demonstrated by a raised immunoreactive trypsin activity.\(^4\)\(^5\) In a study by Jackson et al. (2010) it was shown that, in the absence of a neonatal screening programme, cystic fibrosis presents with meconium ileus (18.5%), symptoms (gastrointestinal, respiratory or both) (66.4%) or family history (15.1%).\(^6\) Gastrointestinal symptoms include malnutrition (failure to thrive), steatorrhoea (foul stools due to fat malabsorption) or both.\(^5\)\(^6\) Respiratory symptoms include wheeze and cough productive of sputum.\(^5\) Infants with meconium ileus present early (median age of presentation 0.47 months) whilst those with a family history or gastrointestinal/respiratory symptoms tend to present later (1.3 months and 11.0 months respectively).\(^6\)

The diagnosis of cystic fibrosis is based on the clinical features, genetic screening for a CFTR gene mutation and an abnormal sweat test indicated by repeatedly elevated chloride levels.\(^5\) In addition, faecal elastase is measured to help identify patients with pancreatic insufficiency.\(^7\)

Treatment includes chest physiotherapy twice daily to aid clearance of the thick secretions from the airways.\(^5\)\(^7\) Patients are treated with prophylactic antibiotics, for example young children receive oral flucloxacillin to protect against Staphylococcus aureus infection.\(^7\) Patients with pancreatic insufficiency take pancreatic enzymes with each meal and fat-soluble vitamin supplements; pancreatic sufficient patients may also need fat soluble vitamin supplementation.\(^5\)\(^7\) Some patients are also treated with inhaled bronchodilators and steroids.
At every clinic appointment at a specialist CF centre the patients are reviewed by a team including a consultant, nurse specialist, physiotherapist, dietician and a psychologist. They will also have contact with a social worker and pharmacist if necessary. A cough swab or sputum sample from the patient is sent to microbiology for culture and treatment with antibiotics is given based on the culture and sensitivity results. For example, amoxicillin can usually be used for Haemophilus influenzae or Streptococcus pneumoniae infection. BMI is recorded at every clinic appointment to monitor nutritional status. Patients undergo an annual oral glucose tolerance test to screen for cystic fibrosis related diabetes (if aged over 12 years), spirometry testing to review lung function (if aged over 5-6 years) and a chest X-ray to screen for bronchiectasis. Every 2 years, they undergo a liver ultrasound to screen for liver disease (if aged over 5 years) and every 1-3 years, a DEXA scan is carried out to measure bone mineral density (if aged over 10 years).

Analysis of factors associated with poor outcome

A- Infection

There are certain pathogens which correlate with a poor prognosis, such as Pseudomonas aeruginosa and Burkholderia cepacia that are both gram negative organisms. McCloskey et al. (2001) carried out a study involving 3 groups of patients: group 1 had grown Burkholderia cepacia and Pseudomonas aeruginosa on sputum culture, group 2 had grown Pseudomonas aeruginosa only on sputum culture and group 3 had grown neither organism. It was shown that the lung function of patients in group 1 declined much faster (5.4% average decrease in FEV1 over 9 years) than that of patients in group 3 (1.6% decrease) and also faster than that of patients in group 2 (3.9% decrease). Burkholderia cepacia is also associated with a higher mortality rate. In the study 28 patients died over the 9 years; 16 of which had grown Burkholderia cepacia and 8 of which had grown Pseudomonas aeruginosa. Burkholderia cepacia infection is associated with increased morbidity and mortality because it is very difficult to treat. It is resistant to many antibiotics with different strains of the pathogen being susceptible to different antibiotics. According to the CF Trust, antibiotics which can be useful for the treatment of Burkholderia cepacia infection include ceftazidime, piperacillin, tazobactam, meropenem, imipenem, ciprofloxacin, trimethoprim, cotrimoxazole and tetracyclines. The Tayside Guidelines suggest that ceftazidime and gentamicin should be used for a paediatric exacerbation of cystic fibrosis due to Pseudomonas aeruginosa infection.

However, there are now policies to segregate cystic fibrosis patients in clinics and in hospital according to bacterial colonisation and this has led to a reduction in the spread of infection, including Burkholderia cepacia. As a result, Burkholderia cepacia infection is less prevalent but management remains difficult. Patient segregation cannot eradicate the infection as it can still be acquired from the environment, for example, from water or soil.

Cepacia Syndrome is when the pulmonary function of patients who have grown Burkholderia cepacia on sputum culture declines quickly; some patients also develop
“fulminant necrotising pneumonia” and die very quickly. Some strains of Burkholderia are more likely to cause Cepacia Syndrome than others, for example Burkholderia cenocepacia, multivorans and dolosa.

B- Cystic Fibrosis Related Diabetes

Another factor associated with a poor outcome is cystic fibrosis related diabetes which affects approximately 20% of adolescents and 40-50% of adults with cystic fibrosis. CFRD cannot be classified as type 1 diabetes (because it is not autoimmune) or type 2 diabetes (because the problem is insulin insufficiency, not insulin resistance) and it is thus placed in a category of its own. CFRD is due to thick secretions causing inflammation and damage to beta cells of the Islets of Langerhans in the pancreas. The mass of the Islets of Langerhans decreases by approximately 50% leading to reduced insulin production and insulin insufficiency. Patients with CFRD are, however, unlikely to develop diabetic ketoacidosis as the residual Islets of Langerhans still produce small amounts of insulin and there is also damage to alpha cells thus leading to decreased glucagon production.

CFRD is associated with increased morbidity and mortality as it leads to microvascular complications such as peripheral neuropathy which is present in approximately 50% of cystic fibrosis patients who have had CFRD for more than 10 years. Nephropathy and retinopathy are not as frequent in CFRD as in type 1 and 2 diabetes. However, the main reason why CFRD patients have increased morbidity is because CFRD worsens CF lung disease. For example, it adversely affects nutrition by increasing the breakdown of fat and protein that has a negative impact on lung function. Also, hyperglycaemia caused by CFRD encourages the growth of bacteria in the lungs.

C- Socioeconomic Status

A study by Schechter et al. (2001) indicated that low socioeconomic status was associated with a poor outcome. In this study, a low socioeconomic status was indicated by a requirement for coverage by Medicaid insurance (as Medicaid entitlement is based on income). Results showed that Medicaid patients were more likely to have a lower FEV₁ (78.1%) and a lower weight (28.6 percentile) than non-Medicaid patients (84.8% and 34.3 percentile respectively). Medicaid patients were also much more likely to have a pulmonary exacerbation (44.5%) and be hospitalised (43.4%) than non-Medicaid patients (28.6% and 25.9% respectively). Over the 8 year study period, 8% of Medicaid patients died compared to 6% of non-Medicaid patients.

Balmer et al. (2008) also showed a correlation between low socioeconomic status and poor lung function in children. They split patients into 3 groups: socially advantaged (household income >$75,000 per year, living with 2 parents and parental education of at least a college degree), socially disadvantaged (household income <$20,000 per year, living with 1 parent or parental education of less than a high school degree) and not socially disadvantaged. It was found that children in the socially advantaged group had a higher weight, BMI and FEV₁ than the other two
groups. They also had less hospitalisations per year and less absences from school.

Although this is American data, this also applies to Scottish patients. Poorer lung function in low socioeconomic status patients may be due to smoke (which can cause deterioration of lung function in children), as smoking is more common in low socioeconomic status households. Poorer understanding of the condition or of the treatment may be more frequent in less educated families, which could lead to non-compliance with medical treatment. In households with only 1 parent or with several children, time constraints may lead to poor compliance with disease management, especially physiotherapy. Non-compliance or poor compliance with treatment may cause poor nutrition leading to poor weight (if pancreatic enzyme replacement therapy is not taken) and poor lung function (if prophylactic antibiotics are not taken or physiotherapy is not completed). Children with several siblings (especially siblings with cystic fibrosis) or children who spend time at nursery/school will perhaps be more exposed to infection, which may have a negative impact on lung function over time.

D-Genotype

Genotype also predicts prognosis in cystic fibrosis. The mutations on the CFTR gene were divided into 6 classes by Welsh et al. (1993). Class I mutations due to insertions (for example, stop codons), deletions, splice site mutations or nonsense mutations lead to abnormal production of the CFTR protein with absent protein production or production of a non-functioning protein. Class II mutations lead to incomplete glycosylation of the CFTR protein resulting in an abnormal protein that is broken down. This class includes the delta F508 mutation which is the most common mutation seen in European patients. Class III and IV mutations lead to the protein channel not reaching the cell membrane. Class III mutations lead to defects in the nucleotide binding sites on the protein, thus the channel cannot be controlled properly and class IV mutations lead to reduced ion flow through the channel. Class I, II and III mutations lead to a severe disease phenotype as they are associated with pancreatic insufficiency. In contrast, class IV, V and VI mutations lead to a mild disease phenotype as they are not associated with pancreatic sufficiency.

Cleveland et al. (2009), examined the link between genotype and pulmonary disease using chest radiographs, FEV₁ and FVC. Patients were divided into groups depending on the class of their genotype. Group S contained the severe disease (pancreatic insufficient) patients and was divided into subgroups A, B and C: subgroup A had two class I mutations, subgroup B had one class I and one class II or III mutation and subgroup C had either two class II mutations or one class II and one class III mutation. Group M contained the mild disease (pancreatic sufficient) patients with at least one mutation from class IV, V or VI. The chest radiographs and FVC of group S declined more rapidly (-0.174 and -1.080 decline in points per year respectively) than those of group M (-0.064 and -0.179 respectively). Subgroup A declined faster than subgroup B and subgroup B declined faster than subgroup C as expected. Therefore, genotype does have a negative impact on pulmonary function as well as pancreatic function. However, it should be noted that pancreatic
insufficiency may be a factor in poor lung function as pancreatic insufficiency can lead to malnutrition, which has an important negative impact on lung function.

Table 1: Summary of genotype classification summarised from Table 1. Classes of CFTR Mutations That Cause CF (Welsh et al. 1993)\textsuperscript{15}

<table>
<thead>
<tr>
<th>Class</th>
<th>Defect</th>
<th>Examples</th>
<th>Frequency</th>
<th>Clinical Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Protein production</td>
<td>Insertions</td>
<td>G542X</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Splice site mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsense mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Protein processing</td>
<td>Incomplete glycosylation of the CFTR protein</td>
<td>ΔF508</td>
<td>67.2</td>
</tr>
<tr>
<td>III</td>
<td>Regulation of protein trafficking</td>
<td>Defect of binding sites</td>
<td>G551D</td>
<td>2.4</td>
</tr>
<tr>
<td>IV</td>
<td>Channel conduction</td>
<td>Reduced ion flow</td>
<td>R117H</td>
<td>0.8</td>
</tr>
</tbody>
</table>

E- Ethnicity, gender, age at diagnosis and BMI

In the UK, Asian patients have a poorer prognosis than patients of other races.\textsuperscript{18} McCormick et al. (2005) demonstrated that female Asians have a worse FEV\textsubscript{1} than male Asians and both groups have a worse FEV\textsubscript{1} than their matched UK white controls.\textsuperscript{18} This may be a result of the Asian genotype (many of which remain unknown) or a combination of diet, socioeconomic status and barriers to quality healthcare such as language.\textsuperscript{18}

Verma et al. (2005) stated that gender did not affect prognosis in cystic fibrosis.\textsuperscript{19} However, Gee et al. (2003) found that although BMI and FEV\textsubscript{1} did not differ between genders, females described a worse health related quality of life with regard to “chest symptoms, emotional functioning, concerns for the future and career issues”.\textsuperscript{20} Males described a worse health related quality of life with regard to “body image”; this may be due to the fact that males prefer to be heavier whereas females are content with a low BMI.\textsuperscript{20} Also, male cystic fibrosis patients are more likely to be infertile (due to an associated congenital absence of the vas deferens) than female cystic fibrosis patients.\textsuperscript{16} Age at diagnosis also has an impact on long term prognosis. Patients diagnosed at an early age by screening have a better height and weight at diagnosis, and these differences are maintained in the long term.\textsuperscript{21} A greater weight
and height (and therefore, BMI) correlates with a better lung function and this reinforces the value of screening tests as they improve prognosis by allowing patients to be treated earlier.  

**Conclusion**

In conclusion, there are many factors that contribute to a poor prognosis in cystic fibrosis. The prevalence of severe infections, such as Burkholderia cepacia, can be reduced by patient segregation and by sterilising equipment after use. However, the infection is very difficult to eradicate when established. CFRD can be controlled and the long-term effects of diabetes reduced by insulin therapy and good glucose control. Factors associated with a low socioeconomic status could be reduced by teaching patients and their families about the disease and treatment in order to optimise compliance with treatment. Health promotion and disease prevention in the form of smoking cessation could also improve prognosis in this group. Genotype, gender and ethnicity cannot be modified, but perhaps patients with a more severe genotype require more aggressive therapy to improve their prognosis as much as possible. Screening programs are important for early detection of the disease as they allow patients to receive prompt treatment.

**Table 2: Summary of factors contributing to poor prognosis in cystic fibrosis**

There have been many developments to the management of cystic fibrosis and there are more future treatments under development, including drugs to block ENaC channels (epithelial sodium channels) to reduce the transport of sodium and water out of the airways. This would lead to less viscous secretions which could be more easily cleared from the airways. Other improvements in cystic fibrosis management
for the future include gene therapy that aims to restore the expression of intact functional CFTR protein. All of these advances will continue to contribute to the ever-improving prognosis for cystic fibrosis patients.

**References**

Primary Brain Tumours – Everything a Medical Student Needs to Know

Joseph Timmons (4th Year MBChB) University of Dundee

Correspondence to: J.G.Timmons@dundee.ac.uk

ABSTRACT

A brain tumour is an illness that inspires fear and foreboding in the general population. They can strike at any age and can often have devastating consequences. They are however relatively uncommon and perhaps this is why many undergraduate medical students do not have much in depth teaching in this area. In this review, we will consider all that an undergraduate student needs to know to have a good understanding of this complex and varied pathology.

What are brain tumours and how common are they?

Primary brain tumours can be defined as benign or malignant growths that arise in intracranial tissue. As a group, they are heterogeneous, varying from benign tumours which can be removed with surgical resection through to inoperable malignant lesions which have a very poor prognosis. They are relatively uncommon, accounting for only 2% of adult tumours. In the UK around 4,400 people are diagnosed with a primary brain tumour annually and this translates to an overall annual incidence of around 7 per 100,000.1 Although brain tumours affect all ages and both sexes, they do become more common as people age, rising in incidence from the age of 30 onwards1 with the incidence peaking at the age of 65 to 79 years.2 The incidence of brain tumours is slightly higher in men than women, with men having a life-time relative risk of 0.65% as opposed to 0.5% for women.2 However, women have a higher incidence of meningioma than males.1 Despite their rare incidence, primary brain tumours have a relatively high mortality rate, being the leading cause of cancer death in children and the third leading cause in young adults aged 15 to 34.3 Tumours need to be classified pathologically, and staged, as this will determine the treatment that will be of most benefit to the patient. Up to half of brain tumours are benign, however the most common malignant primary brain tumour is glioblastoma multiforme (GBM) which has a poor prognosis.2,3 In this review, we shall explore the presentation of primary brain tumours, their investigation, diagnosis and treatment options. We shall then consider the outcomes for patients with these tumours following optimal treatment.

Presenting features: History and Examination

Brain tumours present with signs and symptoms primarily due to three factors: mass effect, parenchymal infiltration and tissue destruction.3 Headache due to mass effect is the most common presenting feature occurring in 23 to 56% of adults4 and in 41%
of paediatric cases.\textsuperscript{5} There are certain characteristics of a headache which must immediately raise the suspicion of a sinister cause such as a brain tumour. If the headache is associated with nausea and vomiting (the second commonest presenting feature in children) then the suspicion of a brain tumour must be considered. There can be worsening of the headache at different times of the day, with a typical worsening of symptoms first thing in the morning and during the night. At night the patient may complain of being awoken by the pain. This is due to decreased respiration during REM sleep, which then leads to an increase in blood carbon dioxide levels. The resultant cerebral vasodilatation further increases intracranial pressure exacerbating headache symptoms. Certain actions such as coughing or straining also exacerbate the headache from a brain tumour. A new onset of headaches in later life or a changing intensity or character of headache can also signify the presence of an intracranial tumour.\textsuperscript{3} Patients may present with seizures. Indeed the incidence of seizures is as high as one third of all patients in certain tumours such as gliomas (particularly low grade gliomas).\textsuperscript{3} In younger adults new onset seizures carry a 1.2% risk of being associated with an intracranial tumour and this rises further to 2.3% in the over 65s.\textsuperscript{4} Other symptoms which commonly occur with brain tumours include confusion, dysphasia, motor weakness, personality change and memory loss.\textsuperscript{5} In the history of presenting complaint, these red flag symptoms should help distinguish a sinister headache due to raised intracranial pressure (ICP) from much more common benign headaches.

A general examination should be performed, with particular attention paid to the neurological exam and the examination of the cranial nerves. Visual fields should be assessed to look for bitemporal hemianopia often found in pituitary gland tumours. It is important to assess the optic discs by fundoscopy. This can provide valuable information as to the level of intracranial pressure. Particular attention should be paid to whether papilloedema (swelling of the optic disc) is present or not. Additionally the presence of retinal venous pulsation as the veins turn into the disc should be assessed, as when present, this indicates normal intracranial pressure. Although this is normally evident in around 90% of the population, it may be absent in 10% of the population.\textsuperscript{6} Focal neurological deficits may be present when there is raised intracranial pressure due to a tumour. It is difficult however for doctors to decide when to investigate potential symptoms of a brain tumour further.\textsuperscript{4} Nevertheless, further investigation must then proceed if several of these symptoms are present, if there are clinical signs of raised intracranial pressure or there is a strong suspicion of an underlying tumour.

**Investigations**

Investigation is necessary to confirm the presence of an intracranial tumour and specify its location and radiological features as this can assist in diagnosis of the lesion. MRI scanning is the scan of choice for primary diagnosis of a brain tumour. The administration of intravenous Gadolinium contrast enhances some lesions such as glioblastoma multiforme. MRI can also provide other useful features aside from T1 and T2 weighted images. For example, MR spectroscopy can provide metabolic and biochemical information regarding suspected tumours. The levels of choline (a marker of cell membrane turnover), lactate and lipid are elevated in high grade gliomas.
compared to normal brain tissue. Also, the neuronal marker N-acetylaspartate (NAA) typically decreases in malignant tissue.\(^7\)

CT scanning provides an alternative imaging modality and will typically reveal a mass lesion. However, mass lesion sin the posterior fossa in particular may not be readily identifiable, as it is difficult to obtain an artefact free image of this area.\(^3\) Additionally, this imaging modality exposes the patient to ionising radiation.\(^3\) Imaging outside the CNS is unnecessary since CNS primary tumours do not tend to metastasise due to the blood brain barrier. Only occasional case reports of primary CNS tumour metastasis outwith the CNS have been reported and these generally involve disruption of the blood brain barrier as in patients with ventriculoperitoneal shunts.\(^8\) However, certain primary brain tumours such as primitive neuroectodermal tumours (e.g. medulloblastomas) can spread via the subarachnoid space and an MRI scan of the spine should be undertaken to exclude such eventualities.\(^3\) When a tumour is identified by MRI, it can then be biopsied to obtain a definite tissue diagnosis, so as to better inform the MDT as to how best to proceed with treatment.

**Pathology and classification of Brain Tumours**

In order to discover the exact pathology underlying a brain tumour, it is essential that it is biopsied and sent for analysis to an experienced neuropathologist. This biopsy can be done via a stereotactic technique, which allows tissue to be sampled from the lesion in a relatively safe way. This deploys a co-ordinate system based on scans, which allows the surgeon to access the tumour for biopsy in a minimally invasive approach. The other alternative is that a biopsy is performed as part of the debulking or excision of a tumour.

Broadly speaking, brain tumours can be classified as either gliomas or non-gliomas. These are either tumours of the glial cells of the brain or tumours of the other intracranial cells. The vast majority of lesions in adults tend to be supratentorial (above the tentorium cerebelli) and 86% of these falls into the category of gliomas. This includes astrocytomas, oligodendrogliomas and ependymomas.

### 1. Gliomas

Astrocytomas are the most common type of glioma and are graded according to the WHO scale of grades one to four. Grade 1 astrocytomas include pilocytic astrocytomas which are benign. Grade 2 astrocytomas are low grade infiltrating tumours. Grade 3 anaplastic astrocytomas exhibit mitoses. Finally, the grade 4 glioblastoma multiforme (GBM)\(^3\) is the most aggressive primary brain tumour in humans and has a median survival of 14 months following diagnosis even if given optimal therapy.\(^9\) GBM can arise as a first presentation or a secondary presentation to a lower grade astrocytoma. The gliomas most commonly encountered in adults are neoplasms of astrocytic or oligodenocytic lineage. Mixed tumours also occur, the most common of which is termed anaplastic oligoastrocytoma.\(^10\) In US studies, glioblastomas formed around 50% of these tumours. This was followed by oligodendrogliomas (9.2%), other astrocytomas (9.1%) and ependymomas (5.6%).\(^3\)
2. Non-Gliomas

Non-gliomas form the remainder of brain tumours. This includes meningiomas, which arise from the meninges and compress the brain thereby creating a mass effect. With an incidence of around 2 per 100,000, over 90% of these tumours are benign and are therefore potentially curable through resection. Loss of chromosome 22 is a characteristic genetic feature of these tumours. Pituitary adenomas also fall into the category of non-gliomas and are either functioning or non-functioning. If functioning, they may secrete hormones causing endocrine disturbance. The clinical manifestation of the tumour depends on the hormone secretion. Sexual dysfunction and galactorrhoea occur in prolactinoma. A “buffalo hump”, “moon face”, acne, weight gain, hypertension and diabetes mellitus occur in Cushing’s disease (ACTH hypersecretion). Acromegaly can result from an over-secretion of growth hormone with the typical changes that occurs with soft tissue growth in adult sufferers. Rarely, other secreting pituitary tumours such as TSHomas occur. Non-functioning pituitary tumours may exert a mass effect due to their proximity to the optic chiasm and can cause visual disturbance such as bitemporal hemianopia. Medulloblastomas are primitive neuroectodermal tumours which are rare in adulthood but much more common in children, accounting for 20% of childhood brain tumours. These tumours are generally located in the cerebellum and therefore present with signs of cerebellar dysfunction. They can involve the 4th ventricle and lead to the development of hydrocephalus. With the correct initial treatment of medulloblastoma, long-term survival may be achieved in around 40-60% of all patients. These tumours can however spread in the subarachnoid space to involve other parts of the CNS.

Primary CNS lymphoma is another tumour within the grouping of non-gliomas. These constitute 2-3% of total brain tumours in people of normal immunity. Patients with immunodeficiency are at an increased risk of developing this form of cancer.

**Treating Brain Tumours**

The options for treatment of a brain tumour depend on several factors. The location, type of tumour and overall health of the patient must be taken into consideration when formulating a treatment strategy. We will now consider the treatment options in 4 main categories:

1. **Surgery**

The first line of treatment in brain tumours is usually a surgical approach. The goals of surgery are as follows: (i) to obtain a histological diagnosis, (ii) reduce the mass of the tumour whilst preventing iatrogenic neurological deficit as effectively as possible and (iii) to treat hydrocephalus if present. Surgery can be curative for most benign tumours whilst debulking improves prognosis for malignant tumours provided the tumour is not infiltrating essential areas of the brain such as language areas. If this approach is not possible, simple biopsy is the second option and modern stereotactic...
approaches mean that this is now possible, even in neurologically critical areas of the brain, where attempting a resection would lead to death or a major neurological deficit. Problems can arise with higher grade tumours in ensuring that as much of the tumour is removed as is possible. Novel approaches include photodynamic techniques such as fluorescence image guided surgical resection (FIGS). Photosensitizers administered pre-operatively accumulate selectively in the tumour. The visible tumour is then surgically removed under white light before a blue light longpass filter is then used to allow the surgeon to visualise and remove as much of the remaining residual tumour as possible. The more of the tumour resected, the better the prognosis. This technique therefore offers more effective treatment to patients with high grade tumours. Excision of at least 98% of a GBM improves life expectancy by a median of 4.2 months compared with patients who have 2% or more of residual tumour remaining post operatively.

2. Radiotherapy

Radiotherapy provides another option in brain tumours. External beam radiotherapy remains an important tool either in addition to surgery or, in some cases, as an alternative. In certain tumours it can be curative and in the majority of cases it will prolong survival. There are various different approaches with this therapy. Whole brain radiotherapy is used in certain tumours like medulloblastoma and primary CNS lymphomas. “Involved field” radiotherapy is used in other tumours such as gliomas. Stereotactic radiosurgery is another method of radiotherapy, which delivers a large dose of radiation to the tumour in one dose, based on imaging that has accurately outlined the lesion. This technique is therefore useful in well-defined tumours such as meningiomas. Another form of radiotherapy used in brain tumours is stereotactic radiotherapy, which carefully targets the radiation towards the tumour tissue, but also exploits the different radiosensitivities of neoplastic cells compared to normal brain cells via the process of fractionation.

3. Chemotherapy

Chemotherapy is increasingly being used in the treatment of primary brain malignancies. The most commonly used agent is temozolamide, an alkylating agent which has good penetration of the blood brain barrier thereby allowing access to brain tissue. Certain regimens in combination with radiotherapy have shown a survival benefit in gliomas compared to controls. Chemotherapy can be used also in the treatment of oligodendrogliomas.

4. Other therapies

Other treatments are beneficial in brain tumours such as corticosteroids to reduce mass effect and thus help to alleviate symptoms and improve the quality of life. Anticonvulsant therapy can be used in patients with seizures. Clinically apparent DVT or pulmonary embolism occurs in around 20-30% of patients with brain tumours. This is perhaps due to the release of thromboplastins when brain tissue is injured. In these patients, anticoagulants can be used to prevent further thrombotic events.
Outcome and Prognosis

Outcome depends very much on the type of brain tumour. Benign tumours, such as meningiomas and pituitary adenomas, can be excised and are thus amenable to cure with an excellent prognosis. Astrocytomas, however, particularly higher grade tumours, are much more aggressive and therefore survival in the long-term is less likely. Median survival times (MST) vary with the grade of the tumour: the higher the grade, the poorer the prognosis. According to a Swiss study, pilocytic astrocytomas (WHO grade 1) have a very good prognosis, with 96% of patients surviving ten years. Grade 2 astrocytomas have a MST of around 5.6 years, while grade 3 anaplastic astrocytomas have a MST of 1.6 years. Grade 4 glioblastoma multiforme had a mean survival time of only 4 months in this study. Oligodendrogliomas generally have a better prognosis, with a MST of 11.6 years for WHO grade 2, and 3.5 years for WHO grade 3. Medulloblastoma outcome depends, among other factors such as whether there has been spread within the CNS to the spine. Non-disseminated medulloblastoma carries a relatively good long-term prognosis in children with a 5-year survival of 80%. This compares favourably to survival rates in adults which are around 50 to 60%. In ependymoma, survival rates vary depending on whether the tumour is differentiated or anaplastic. Overall, in a retrospective study of the disease, survival was 57% and 46% at 5 and 7 years respectively following diagnosis.

Conclusion

Brain tumours come in many varieties, with varying prognoses and management options. In this review I have tried to provide an overview of the different pathology that is included under the term of brain tumours. This is an area of much research and hopefully further developments will provide improved outcomes for patients and new techniques to improve morbidity and mortality from even the most aggressive tumours.

References

9 Adamson, C, et al. "Glioblastoma multiforme: a review of where we have been and where we are going." Expert opinion on investigational drugs 18.8 (2009): 1061-1083.
Elective Surgical Management of Aortic Abdominal Aneurysms – An Overview

Jennifer Ma (5th Year MBChB) University of Dundee

Correspondence to – J.Ma@dundee.ac.uk

ABSTRACT

Abdominal aortic aneurysms (AAAs) represent a degenerative process of the abdominal aorta that is often attributed to atherosclerosis; however, the exact cause is not known. In American autopsy studies, the frequency rate of AAA ranges from 0.5-3.2%. The frequency of rupture is 6.9 cases per 100,000 persons in Sweden, 4.8 cases per 100,000 persons in Finland, and 13 cases per 100,000 persons in the United Kingdom. Importantly, patients have a high mortality if an aneurysm ruptures so elective surgical management is of vital importance for the long-term health of many patients.

Introduction

An aneurysm is a degenerative disease in which there is abnormal local dilation of the artery greater than 50% of its normal diameter. In the case of an abdominal aortic aneurysm (AAA), this would be a dilation more than 3cm as the normal diameter of the abdominal aorta is 2cm. A study by Singh et al showed that men are 4 times more likely to suffer from AAA than women and it is more frequently seen in the elderly population. 5-10% of men between the age of 65 and 79 years were reported to have AAA according to a Cochrane review. It can be broadly classified as the ‘true’ variant in which all layers of the vessel are involved or as the ‘false’ variant in which an extravascular haematoma is formed instead. Another classification is by its location - most cases of AAA are infrarenal with the less common suprarenal AAA being more difficult to manage. Sometimes, the shape of an aneurysm may be described with fusiform AAA being seen more frequently than saccular aneurysms.

The management of a patient with AAA depends on the disease presentation with patients presenting with a ruptured AAA requiring prompt resuscitation and immediate open repair. Patients with non-ruptured AAA require monitoring and appropriate surgical management further explored in this article.

Aetiology

While its exact aetiology is uncertain, atherosclerosis which involves plaque formation, destruction of the tunica media and loss of elastic recoil, plays a key role in AAA development. Less common associations are infection, trauma, arteritis and

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Aetiology

While its exact aetiology is uncertain, atherosclerosis which involves plaque formation, destruction of the tunica media and loss of elastic recoil, plays a key role in AAA development. Less common associations are infection, trauma, arteritis and
connective tissue diseases such as Marfan’s syndrome and Ehlers-Danlos syndrome.\textsuperscript{4} A positive family history, smoking and hypertension are some of the other risk factors identified.\textsuperscript{5}

**Clinical Presentation**

AAA can present in a number of ways. A ‘text-book’ presentation familiar to many medical students is that of a ruptured aneurysm. This patient experiences severe abdominal pain that typically radiates to the back often associated with hypotension and eventual hypovolaemic shock. Patients with a complete AAA rupture are unlikely to survive long enough to reach hospital. However, the retroperitoneal structures in patients with a ‘leaking’ AAA exert a tamponade effect that acts to limit blood loss so that patient may reach hospital. Patients with an intact AAA may still have abdominal tenderness whilst a large non-ruptured AAA may compress local structures such as the ureters. Turbulent blood flow within the AAA may promote thrombus formation that may embolise to distal structures. For example, the patient could develop gangrene of the feet (also known as ‘trash feet’) as a result of distal embolisation. Despite the above, it should be noted that approximately 75\% patients are asymptomatic at the initial diagnosis of the AAA with the majority of cases being identified incidentally as a result of imaging investigations.\textsuperscript{6} Indeed, many patients remain untroubled by the condition for the rest of their lives.

**Management**

The aim of treatment for the intact AAA is to prevent aneurysmal expansion as this increases the risk of potentially life threatening rupture. The medical management of these patients, regardless of whether they are surgical candidates, must not be neglected. Cardiovascular risk factors should be assessed, as they often have a higher risk of peri-operative cardiovascular mortality. Correction of these risk factors also helps reduce operative mortality.\textsuperscript{6} Cessation of smoking, good control of hypertension and the statin therapy are also likely to be beneficial.\textsuperscript{6}

**Elective Surgical Management**

The risk of aneurysmal rupture and the potential mortality from the intervention must both be weighed carefully. In general, elective surgical intervention of AAA is indicated for a AAA with a diameter of 5.5cm or above, if the AAA increases in diameter by greater than 1cm every year or if the aneurysm becomes tender.\textsuperscript{7} The indication based on the size if the AAA is particularly important due to the high number of incidental findings of AAA. The figure of 5.5cm or above has been adopted from the UK Small Aneurysm Trial (UKSAT) that involved 93 UK hospitals. This study in investigated whether early elective open surgery or regular ultrasound surveillance was more suitable for small AAA.\textsuperscript{7} The study showed that aneurysms less than 5.5cm in diameter could be safely monitored, unless the diameter increased by greater than 1cm per year or they became tender.\textsuperscript{7,8} However, as studies have also reported a higher risk of rupture in women, the threshold for surgery in female patients may be lower.\textsuperscript{9}
Open repair versus endovascular aneurysm repair

The two main commonly used interventional approaches are open surgical repair or an endovascular aneurysm repair (EVAR). An open repair of the aorta is commonly adopted in an emergency setting. After laparotomy, the neck of the aneurysm is identified and the proximal affected aorta is clamped. This is followed by the incision of the AAA and the clearing out of thrombus from the aneurysm. A synthetic graft, usually Dacron (Fig 1), is stitched within the aorta while the outer wall of the aorta is then sutured up. The mortality rate for an elective open repair of the AAA is 5-7.8% in the UK compared to an approximates 50% mortality rate for an emergency repair.¹

Fig. 1 Picture showing the use of Dacron graft to repair an AAA in open repair
(Image from Cambridge University Hospital. Abdominal Aortic Aneurysm (AAA), Vascular Surgery.)

The alternative EVAR procedure employs a stent-graft system to divert blood flow through its lumen and to allow aneurysm to thrombose (Fig. 2).¹ Many centres have seen the use of EVAR becoming more prominent than open repair and reports suggest that at least 65% of AAA patient are suitable for EVAR.¹ According to the British Heart Foundation, an adequate neck length of 1.2cm is needed for fixation of the stent.¹ The EVAR intervention is much less invasive, although follow-up visits with imaging such as ultrasound are necessary to ensure correct position of the stent.¹⁰ In one study by Greenhalgh et al, the perioperative mortality for EVAR was 1.7% compared to 4.7% in those who underwent open AAA repair.¹¹ Hospital stay was also less for patients who had EVAR.¹¹ However, the United Kingdom EVAR trial reported subsequent rupture of aneurysm after its repair in patients who underwent EVAR such that further intervention became necessary: 23% who underwent EVAR required further intervention whilst only 9% needed another operation after an open repair.¹² The benefits of an open repair include the lack of requirement for long term follow-up after surgery and the absence of any potential stent-related complications, such as stent migration and stenosis, observed in patients after EVAR.¹⁰, ¹² In the same EVAR trial, the total mortality or aneurysm-related mortality after 4 years were reported to be very similar between these two techniques.¹²
Fig. 2 Picture showing the use a stent-graft system in EVAR to direct blood flow

(Image from Cambridge University Hospital. Abdominal Aortic Aneurysm (AAA), Vascular Surgery.)

Conclusion

The decision on whether a patient is a candidate for repair of an intact aneurysm is complex. Numerous factors, including the risks and benefits of any proposed intervention and the consequence of a ‘wait and see’ approach have to be considered. The particular treatment adopted should be tailored to the specific disease presentation of each patient and take into account other patient factors such as age and comorbidities. While EVAR has become a more popular treatment choice, doubts regarding its effectiveness remain, mainly due to insufficient data on the long-term outcome of patients. In order to provide the best care for patients with non-ruptured AAA, more controlled trials are still necessary, especially with regards to the long term prognosis of patients who have undergone these operations.

References

Efficacy and Safety of Deep Brain Stimulation for Tremor in Multiple Sclerosis Patients – A Literature Review

Vishnu Jeyalan (5th Year MBChB) University of Dundee; Prof. Sam Eljamel (Consultant Neurosurgeon, NHS Tayside)

Correspondence to Vishnu Jeyalan– V.Jeyalan@dundee.ac.uk

ABSTRACT

Background

Tremor is a complication frequently associated with multiple sclerosis and can be severely disabling in up to 15% of these patients. Deep brain stimulation has been proven effective in other tremulous conditions though it’s efficacy and safety in multiple sclerosis patients is not well documented.

Methods

Identification of relevant studies published via established databases like MEDLINE, EMBASE and Google Scholar. A quantitative and qualitative review was done on all studies obtained that met the inclusion and exclusion criteria specified.

Results

Tremor suppression achieved at late follow-up across the studies was 85.2% and of those 69.1% documented to have sustained tremor suppression over a one year period. 75% were reported to have gained functional benefit and only 65.5% documented to have sustained improvement over a one year period. Associated adverse effects more prevalently documented were infection at site of implantation, intracerebral haematoma, exacerbation of MS, dysarthria and peri-operative seizures.

Conclusion

Deep brain stimulation is effective in the symptomatic relief of tremor in multiple sclerosis patients. The benefits gained depend on long-term stimulation and require patients to be compliant with regular follow-up. The subthalamic region has proved to be a more efficacious target as compared to the traditional ventral intermedius nucleus. Despite the good outcome, this procedure is associated with risk and has to be weighed against potential benefits.
**Introduction**

Multiple sclerosis (MS) is one of the most common central demyelinating disease globally, especially in Northern European and American regions. Tremor is a frequent complication of MS seen to be affecting 25% to 58% of MS patients. It is associated with involvement of the upper extremities (55%), lower extremities (8%), head (7%) and trunk (5%). Matsumoto et al. defines MS tremor as intermittent or continuous, involuntary movements of the upper extremity that appeared rhythmic and oscillatory to visual inspection in a patient with clinically definite MS. Anatomy of the basal ganglia and the specific thalamic nuclei is very important to understand when considering the pathophysiology of MS tremor and deep brain stimulation (DBS) (fig 1).

The tremor is postulated to be caused by synchronisation of discharging motor units due to complex interactions between neuroanatomical structures with the MS related pathological peripheral reflexes and central oscillators. It is also hypothesised that there is a direct effect based on location of these lesions manifesting in MS tremor. Tremor in MS is thought to be caused by lesions at the cerebellar level and it’s associated tracts, thus manifesting in tremor that is based on the lesions neuroanatomical location. A study in the past though, showed a correlation between lesion burden in the pons, rather than the cerebellum with tremor amplitude. These lesions can lead to other clinical manifestations such as ataxic features of dysmetria, dysarthria or eye movement disturbances. The tremor usually has a proximal and distal component with a large amplitude (2.5-7Hz) postural and kinetic component to it, though concurrent ataxic involvement can make tremor evaluation very difficult. Proximal involvement of the upper extremities can cause large displacements of limbs while the kinetic tremors are enhanced by visually guided goal-directed movements. Thus, tremor in MS can be very severe and tend to dramatically affect quality of life and lead to disability with an approximate of 3% to 15% of MS patients with tremor succumbing to such severity.

Medical treatment aimed at tremor in multiple sclerosis is less than satisfactory and on most occasions are medication resistant. The progressive nature of the disease generally makes the pharmacological options of little functional benefit. Thalamotomy on the other hand is an ablative surgical procedure which has yielded results in certain patients though may not produce long term benefits in some. The procedure has been documented to relieve contralateral limb tremor in 65-96% of MS patients though tremor relapse was noted in approximately 20% of patients within 12 months. Thalamotomy has been associated with side effects such as dysarthria, swallowing difficulties and balance disorders which ranges from 0 to 45% in different case series. Due to the drug resistant nature of MS tremor and complications associated with thalamotomy, DBS is a form of treatment which has resulted in good success rates for tremor associated with Parkinson’s disease (PD) and essential tremor (ET), is now being used in some cases for treatment of tremor in multiple sclerosis. DBS is thought to cause less side effects than thalamotomy and is reversible compared to the permanent lesioning function of it’s counterpart. This new intervention in MS patients is thought to have a dual effect via stimulation of
the targeted nucleus within the thalamic or subthalamic region and produces a ‘microthalamotomy’ like effect which persists for a variable duration. The target of stimulation which is commonly used to produce relief of tremor is the ventral intermedius (VIM) nucleus though there have been various studies proving other targets to produce better alleviation. Although this modality of treatment seems promising, the data behind the effectiveness of it has been inconsistent and variable. This paper is a review of the efficacy and safety of DBS on MS related tremor by analysing published reports related to this subject.

Figure 1- Anatomy of the basal ganglia and the specific thalamic nuclei

Methods
Case reports and clinical studies were obtained using relevant keywords and search terms (deep brain stimulation, multiple sclerosis, tremor, thalamic stimulation) in Medline (1966 to March 2011), EMBASE (1988 to March 2011) and Google scholar. Additionally, the reference list of each study obtained and existing published reviews was then browsed through to extract papers relevant to the subject matter. Papers obtained were than filtered via certain inclusion and exclusion criteria. Studies were included if it encompassed patients with a diagnosis of MS, tremor of any degree, underwent procedure of deep brain stimulation, as well as documented pre-operative and post-operative follow up on tremor. Studies that were excluded were those that did not meet the inclusion criteria, had insufficient data documentation or those studies that were duplicates. Studies of mixed patients populations with other tremor causing conditions such as PD and ET were included if separate data for MS patients outcome were available from the results.

Results
Description of Studies
Among the 28 studies identified there were a total of 151 patients that were suitable for this review. There was variability in patient population sizes ranging from 1 to 15 patients. Studies encompassed largely patients purely with MS treated with DBS though some studies included patients with mixed movement disorder aetiologies or
were comparative studies to thalamotomy. Most studies did not specify detailed inclusion and exclusion criteria. Among the more commonly used criteria were severe upper extremity tremor, tremor of an action, postural or intention component, medication refractory tremor, clinically stable MS for at least the past six months and a measure of poor functional capacity (Expanded Disability Status Scale (EDSS) mean of >7). Studies were excluded commonly if patients had sensory loss, muscle weakness, cognitive dysfunction (Mini Mental State Examination (MMSE)<24), ataxia or cerebellar hypermetria, contraindications to surgery or a previous thalamotomy.

Various outcome measures were used across the studies though there was no consistency in terms of assessment scales used. Tremor scoring was carried out with different rating scales that were either designed by the author or a previously established one such as the Fahn-Tolosa-Martin(FTM) rating scale, Tremor-Clinical Rating Scale(TCRS), or the Bain-Finchest tremor scale. Benefit gained by patients were analysed via assessment guides of functional capacity such as Activities of Daily Living(ADL) Index, EDSS, related questionnaires or general patient feedback on surgery and outcomes. Other secondary outcome measures were included in the studies are neuropsychological assessment and post-surgical MRI scans.

Follow-ups periods were variable across all studies and ranged from a period of 2 months to a mean period of 5.2 years in some studies. In majority of studies initial tremor reduction was 100% that were attributed to a “microthalamotomy” like effect. Thus in some studies follow-ups were done at a “safe” period when this effect was postulated to have relieved. In another instance, a regression line was drawn at one month as to negate the “microthalamotomy” effect on the outcome.

Surgical Procedure
The VIM has been the selected surgical target for DBS implantation in most of the studies (16 studies) reviewed. The fundamental concept behind DBS is illustrated in fig 2. Some series documented stimulation of other targets like the Ventrocaudal nucleus(Vc) as an indirect effect on VIM stimulation. Other common thalamic targets are the Ventral oralis anterior(VOA), Ventral oralis posterior(VOP) and the ventrolateral thalamus(VL). Subthalamic region especially the Zona Incerta(ZI) has become an increasingly used locus of stimulation in DBS for MS tremor as were seen in 7 studies. Some series documented various targets curtailed for specific tremors and different proximities of limb tremor. Majority of studies had reported specifics of intraoperative procedures and on techniques used for neurophysiological location of the optimal point of tremor suppression in the selected target. Some studies specified the use of macroelectrodes, microelectrodes or semi-microelectrodes. The usage of both microelectrode for mapping, and macroelectrode for confirmatory purposes and avoiding stimulatory side effects in certain cases were reported.

Neurophysiological location of intra-operative tremor suppression was detailed via different avenues such as somatosensory mapping, identification of tremor cells, use of Field Potentials(FP), accelerometry or Electromyography(EMG) reading, or
achieving a “microthalamotomy” effect. Few studies gave details on final parameters of electrode implantation as well as optimal stimulation settings in pre-operative and post-operative setting. Majority of studies conducted unilateral implantations for contralateral tremor control though some studies had stimulation performed bilaterally, either simultaneously or staged. Implantation was not undertaken in certain patients due to the inability to map optimal point of tremor suppression intra-operatively\textsuperscript{15}, a benefit from microelectrode insertion alone relieving tremor\textsuperscript{15,16} or side effects like the development of an intracerebral haematoma\textsuperscript{9}, intra-operative seizure\textsuperscript{17} or unmanageable wound infection\textsuperscript{18}. Some studies used CT, MRI or X-ray to determine final stereotactic coordinates of electrodes that were inserted.

![Figure 2: Illustrative overview of Deep Brain Stimulation](image)

**Outcome on Tremor And Daily Benefit**

Table 1 summarizes the core details from each of the 28 studies. A degree of tremor suppression and improvement in quality of life was achieved in most of the studies. Studies that had clear documentation of percentage of patients whom obtained an extent of tremor suppression were 23, and of those there were 98 patients from a possible 115(85.2%). Among the 8 studies that had mean follow-up periods of more than 1 year, patients that acquired tremor suppression were 38 from a total of 55(69.1%). Functional benefit on daily living obtained via DBS was reported only in 60 patients out of a population of 80(75%). While of those, 19 patients from 29(65.5%) were reported to have maintained functional benefit at follow up mean period of more than a year.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study size (n)</th>
<th>Mean Age(years) / Sex (Male:Female)</th>
<th>Mean MS duration (years)</th>
<th>DBS Specifics</th>
<th>Tremor Suppression⁴</th>
<th>Functional Benefit⁵</th>
<th>Follow-up⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brice and McLellan 1980¹⁹</td>
<td>2</td>
<td>23-34 / 0:2 n/r*</td>
<td></td>
<td>Unilateral Subthalamic</td>
<td>100%</td>
<td>100%</td>
<td>5-6 months</td>
</tr>
<tr>
<td>Nguyen and Degos 1993¹¹</td>
<td>1</td>
<td>35 / 0:1 n/r</td>
<td></td>
<td>Unilateral VIM</td>
<td>100%</td>
<td>100%</td>
<td>17 months</td>
</tr>
<tr>
<td>Benabid et al 1996²⁰</td>
<td>4</td>
<td>n/r</td>
<td></td>
<td>VIM</td>
<td>Inconsistent, less significant or not improved**</td>
<td>50%</td>
<td>3 and ≥6 months</td>
</tr>
<tr>
<td>Geny et al 1996²¹</td>
<td>13</td>
<td>37 / 5:8 9</td>
<td></td>
<td>VIM Unilateral</td>
<td>69.2%</td>
<td>92.4%</td>
<td>13.4 months mean n/r</td>
</tr>
<tr>
<td>Whittle et al 1998¹⁶</td>
<td>5</td>
<td>n/r</td>
<td></td>
<td>VLl thalamus</td>
<td>n/r</td>
<td>n/r</td>
<td>&lt;3 months to &gt;12 months</td>
</tr>
<tr>
<td>Montgomery et al 1999⁹</td>
<td>14</td>
<td>42.3 / 8:6 12.4</td>
<td></td>
<td>Unilateral VIM</td>
<td>100%</td>
<td>n/a</td>
<td>2 months</td>
</tr>
<tr>
<td>Hay 1999⁵</td>
<td>1</td>
<td>37 / 1:0 9</td>
<td></td>
<td>Unilateral thalamic</td>
<td>100%</td>
<td>n/a</td>
<td>6 months</td>
</tr>
<tr>
<td>Taha et al 1999²²</td>
<td>2</td>
<td>n/a</td>
<td></td>
<td>Bilateral VIM</td>
<td>100%</td>
<td>n/a</td>
<td>10 months</td>
</tr>
<tr>
<td>Schuurman et al 2000²³</td>
<td>5</td>
<td>36.6 n/a</td>
<td></td>
<td>VIM</td>
<td>≥40%^</td>
<td>2.9% increase in FAIπ</td>
<td>6 months</td>
</tr>
<tr>
<td>Matusmoto et al 2001⁸</td>
<td>3</td>
<td>No separate data for DBS</td>
<td></td>
<td>Unilateral VIM</td>
<td>100%</td>
<td>n/a</td>
<td>12 months</td>
</tr>
<tr>
<td>Berk et al 2002¹⁸</td>
<td>12</td>
<td>34.5 / 5:7 n/a</td>
<td></td>
<td>Unilateral VIM</td>
<td>Significant mean reduction by 40%</td>
<td>100%</td>
<td>12 months</td>
</tr>
<tr>
<td>Hooper et al 2002⁶²</td>
<td>10</td>
<td>41 / n/r 13.3</td>
<td></td>
<td>Unilateral Thalamus</td>
<td>100%</td>
<td>68% or 78% benefited or remained the same based on functional scales</td>
<td>12 months</td>
</tr>
<tr>
<td>Nandi et al 2002²⁴</td>
<td>1</td>
<td>35 / 0:1 4.5</td>
<td></td>
<td>Unilateral ZI</td>
<td>100%</td>
<td>100%</td>
<td>12 months</td>
</tr>
<tr>
<td>Schulder et al 2003²⁵</td>
<td>9</td>
<td>43.4 / 0:9 7.4</td>
<td></td>
<td>Unilateral VIM</td>
<td>89%</td>
<td>33%</td>
<td>32 months</td>
</tr>
<tr>
<td>Loher et al 2003²⁶</td>
<td>2</td>
<td>71.4# n/a</td>
<td></td>
<td>Unilateral VIM</td>
<td>100%</td>
<td>100%</td>
<td>9 months</td>
</tr>
<tr>
<td>Wishart et al 2003¹⁷</td>
<td>4</td>
<td>46.5/ 3:1 9</td>
<td></td>
<td>Unilateral thalamus</td>
<td>100%</td>
<td>n/a</td>
<td>22 months</td>
</tr>
<tr>
<td>Moringlane et al 2004⁷⁷</td>
<td>1</td>
<td>34 / 0:1 14</td>
<td></td>
<td>Unilateral thalamus</td>
<td>100%</td>
<td>100%</td>
<td>4 years</td>
</tr>
<tr>
<td>Study</td>
<td>Study size (n)</td>
<td>Mean Age (years) / Sex (Male:Female)</td>
<td>Mean MS duration (years)</td>
<td>DBS Specifics</td>
<td>Tremor Suppression</td>
<td>Functional Benefit</td>
<td>Follow-up</td>
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</tr>
<tr>
<td>Nandi et al 2004</td>
<td>15</td>
<td>39.4 / 8:7</td>
<td>10.4</td>
<td>Unilateral VOP and ZI</td>
<td>Mean reduction postural (63.7%), intention (36%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n/r</td>
<td>15 months</td>
</tr>
<tr>
<td>Lim et al 2007</td>
<td>1</td>
<td>42 / 0:1</td>
<td>9</td>
<td>Bilateral VIM and VOA&lt;sup&gt;a&lt;/sup&gt; Mixed regions</td>
<td>100%</td>
<td>100%</td>
<td>9 months</td>
</tr>
<tr>
<td>Hyam et al 2007</td>
<td>6</td>
<td>34.2 / 4:2</td>
<td>3.7</td>
<td>Bilateral Ventrolateral or Subthalamic VIM</td>
<td>100%</td>
<td>100%</td>
<td>3.67 years</td>
</tr>
<tr>
<td>Hammel et al 2007^&lt;sup&gt;4&lt;/sup&gt;</td>
<td>No separate report for MS</td>
<td>n/a</td>
<td>Bilateral Ventrolateral or Subthalamic VIM</td>
<td>100%</td>
<td>No separate report for MS</td>
<td>3 months to ≥1 year</td>
<td></td>
</tr>
<tr>
<td>Herzog et al 2007</td>
<td>11</td>
<td>41.5 / 6:5</td>
<td>10.1</td>
<td>Bilateral ZI</td>
<td>100%</td>
<td>≥50%&lt;sup&gt;β&lt;/sup&gt;</td>
<td>1 year</td>
</tr>
<tr>
<td>Plaha et al 2008</td>
<td>4</td>
<td>40.3 / 1:3</td>
<td>5</td>
<td>Unilateral VIM</td>
<td>100%</td>
<td>100%</td>
<td>n/r</td>
</tr>
<tr>
<td>Moore et al 2009</td>
<td>1</td>
<td>47 / 0:1</td>
<td>7</td>
<td>VOP and ZI</td>
<td>63%</td>
<td>54.5%&lt;sup&gt;Ɨ&lt;/sup&gt;</td>
<td>5.2 years</td>
</tr>
<tr>
<td>Thevathasan et al 2010&lt;sup&gt;33&lt;/sup&gt;</td>
<td>11</td>
<td>38.7 / 3:8</td>
<td>12.2</td>
<td>VIM</td>
<td>36.4%&lt;sup&gt;Ɨ&lt;/sup&gt;</td>
<td>n/r</td>
<td>31 months</td>
</tr>
<tr>
<td>Torres et al 2010&lt;sup&gt;7&lt;/sup&gt;</td>
<td>10</td>
<td>38.1 / 4:6</td>
<td>15.1</td>
<td>VOP and ZI</td>
<td>63%</td>
<td>54.5%&lt;sup&gt;Ɨ&lt;/sup&gt;</td>
<td>5.2 years</td>
</tr>
<tr>
<td>Mandat et al 2010&lt;sup&gt;32&lt;/sup&gt;</td>
<td>5</td>
<td>37 / 2:3</td>
<td>6</td>
<td>Indirect VIM</td>
<td>100%</td>
<td>100%</td>
<td>3 months</td>
</tr>
<tr>
<td>Johnson et al 2010&lt;sup&gt;33&lt;/sup&gt;</td>
<td>1</td>
<td>33 / 0:1</td>
<td>11</td>
<td>Unilateral Thalamic</td>
<td>100%</td>
<td>n/r</td>
<td>4 years</td>
</tr>
</tbody>
</table>

<sup>S</sup> Tremor suppression and functional benefit measured as percentage of patients gaining any extent of benefit from DBS µ follow-up recorded as mean unless a range is given

<sup>μ</sup> not reported

<sup>**</sup>reported with another 13 patients with other dyskinetic forms of tremor

<sup>^</sup> other 60% had tremor relapse though tremor scores were still better or same as pre-operative scores

<sup>Ɨ</sup> Frenchay Activity Index

# Data mixed with other tremor aetiologies

<sup>a</sup> Only 10 from 15 patients tremor outcome documented

<sup>Ɨ</sup> Assessment also done with VIM and VoA separately which both produced similar results to simultaneous stimulation

<sup>β</sup> Only two patients were reported to of not being wheelchair bound any longer after DBS, while other two patients did not have functional benefits documented

<sup>Ɨ</sup> Data at early(<1 year) post-operative no data reported for late follow up
Adverse Effects

Among the 28 studies reviewed, there were 4 cases of intracerebral haematoma where in two cases the patient developed a microhaematoma (use of microelectrode and semi-microelectrode respectively) and other two cases developed small thalamocapsular haematoma (use of macroelectrode). The 2 patients with the thalamocapsular haematoma were left with hemiparetic deficits at one year. One of the patients (not implanted) with the microhaematoma acquired it during surgery and was left with a temporary dysarthria. Though it was postulated that for these 3 patients, the intracerebral bleed gave them better function of their hand via reduction of tremor severity. The remaining 1 patient’s microhaematoma resulted in an acute deficit which waned off in 3 months.

Dysarthria was evident persistently in 4 cases where it ranged from mild to severe with one documented case of worsening of an existing dysarthria. There were also 4 cases of transient dysarthria which all alleviated within a range of 3 months. Infection at the site of implantation was recorded in 6 patients with an overall incidence of 3.85%. Among those, there was documentation of attempted antibiotic treatment in all patients of which 4 (67%) being successful, though in one patient failure was attributed to cognitive state and behaviour of patient. A single case of memory deterioration was recorded in all studies.

Exacerbation of MS was reported in 4 studies among 8 patients of which occurred within a month of DBS surgery. 3 of those patients was reported to respond to intravenous steroids. The occurrence of seizures was 5.6% across all studies. Some studies, reported patients complaining of paresthesia at initial stimulation which settled in about 1 minute though adjusting stimulation parameters provided relief as well. Other transient side effects that was associated with DBS in a minority of patients were hemiparesis, monoparesis, diplopia, swallowing difficulties and abnormal bladder control. Some patients were left with chronic sequelaes like hemiparesis, ataxic features and asthenia.

Neuropsychological studies were done in a small number of series mostly yielding unremarkable results, though Benabid et al postulated that stimulation of the left VIM affected verbal fluency while the right side affected spatial performance. Loher and associates reported reduced short memory recall (episodic memory) on stimulation of it’s left side.
<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Number of Cases (n)</th>
<th>Mean Incidence (range)*</th>
<th>Overall Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Dysphagia</td>
<td>1(^{19})</td>
<td>20%</td>
<td>0.64%</td>
</tr>
<tr>
<td>Dysarthria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>4(^{6,17,19,29})</td>
<td>17.1%(6.7%-25%)</td>
<td>2.56%</td>
</tr>
<tr>
<td>Permanent</td>
<td>4(^{12,23,19,27})</td>
<td>15.6%(6.7%-20%); 100%(^\ast)**</td>
<td>2.56%</td>
</tr>
<tr>
<td>Urinary Complications</td>
<td>5(^{18,19})</td>
<td>33.4%(6.7%-60%)</td>
<td>3.21%</td>
</tr>
<tr>
<td>Transient Monoparesis</td>
<td>4(^{16,17,21})</td>
<td>17.6%(7.7%-25%)</td>
<td>2.56%</td>
</tr>
<tr>
<td>Transient Acute Deficit</td>
<td>1(^{20})</td>
<td>25%</td>
<td>0.64%</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>2(^{11,29})</td>
<td>11.7%(6.7%-16.7%)</td>
<td>1.28%</td>
</tr>
<tr>
<td>Permanent</td>
<td>2(^{16})</td>
<td>20%</td>
<td>1.28%</td>
</tr>
<tr>
<td>Transient diplopia</td>
<td>1(^{17})</td>
<td>25%</td>
<td>0.64%</td>
</tr>
<tr>
<td>Transient Initial Stimulatory Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyesthesia</td>
<td>13(^{21})</td>
<td>100%</td>
<td>8.33%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>Cannot ascertain</td>
<td>Most(^1); Most common(^{18}); Some(^{16}); (n=1)25%(^{17})</td>
<td>Cannot ascertain</td>
</tr>
<tr>
<td>Arm ataxia</td>
<td>1(^{13})</td>
<td>20%</td>
<td>0.64%</td>
</tr>
<tr>
<td>Ataxic gait</td>
<td>2(^{23})</td>
<td>40%</td>
<td>1.28%</td>
</tr>
<tr>
<td>Impaired mobility</td>
<td>1(^{13})</td>
<td>25%</td>
<td>1.28%</td>
</tr>
<tr>
<td>Intracerebral haematoma</td>
<td>4(^{9,16,20})</td>
<td>17.2%(6.7%-25%)</td>
<td>2.56%</td>
</tr>
<tr>
<td>Wound Site Infection</td>
<td>6(^{7,12,16,18})</td>
<td>12.2%(10%-15.4%)</td>
<td>3.85%</td>
</tr>
<tr>
<td>Wound Inflammation or Erosion</td>
<td>2(^{17,31})</td>
<td>16.7%(8.3%-25%)</td>
<td>1.28%</td>
</tr>
<tr>
<td>Intra-operative Hypoxia</td>
<td>1(^{16})</td>
<td>10%</td>
<td>0.56%</td>
</tr>
<tr>
<td>Memory deterioration</td>
<td>1(^{25})</td>
<td>25%</td>
<td>0.56%</td>
</tr>
<tr>
<td>Seizure</td>
<td>10(^{7,12,16,17,31,33})</td>
<td>18%(6.7%-30%)</td>
<td>5.6%</td>
</tr>
<tr>
<td>Exacerbation of MS</td>
<td>8(^{9,17,21,25})</td>
<td>22.1%(7.1%-33.3%)</td>
<td>5.13%</td>
</tr>
</tbody>
</table>

*Incidence recorded only among studies with the specific reported side effect
** Only one patient in this study, thus data not incorporated into mean incidence(range) as may skew values, but included in the overall incidence
Discussion

Evidence suggests that DBS provides relief of tremor in patients with MS enhancing further the notion of DBS as an effective form of stereotactic surgery for these patients. Based on the data, DBS also has a proven effect in increasing patient’s functional capacity to facilitate better quality of life. Despite the evidence compiled, some pitfalls throughout the studies reviewed have translated onto the quality of data retrieved. Documentation of outcomes especially of functional benefit gained, have not been practiced in many of the studies in which 47% of patients failed to be reported on that aspect. Inclusion criteria’s and exclusion criteria should encompass inclusion of patients with clinically stable MS for at least 6 months, drug refractory disease, severe upper extremity tremor with no signs of sensory loss or weakness in the tremulous limb and free of ataxic features. A criteria of clinically stable MS aids in ensuring that the disability status of a patient is assessed purely in terms of DBS efficacy and is not affected by progression of disease. Muscle weakness may have a “false positive” effect on tremor suppression post-DBS. Hyam et al identified a significance between pyramidal weakness and attenuation of intention tremor hence the need for the utilisation of an established muscle strength assessment like the Medical Research Council (MRC) Scale as a filter for only suitable patients to partake in these studies. An underlying ataxic complex needs to be excluded as tremor alleviation can unmask an underlying cerebellar syndrome making assessment of tremor difficult and at the same time severely affecting disability scoring.

Success of DBS would stem from not only from improving tremor control but returning a beneficial amount of patient’s functional capacity as well. Outcome measures used differed among studies preventing standardised assessment of patients and efficacy of DBS. Scales used such as EDSS must be used with caution especially in patients with MS, while the tremor scales allowed for examiner biasness and does not assess the functionality aspect. Matsumoto et al describes the use of Quantitative Movement Analysis (QMA) to eradicate these two limitations of orthodox tremor scales. In the same study, the author suggested a multi-dimensional battery of test to quantify outcomes accurately. Herzog and associates carried out neurophysiological assessment of postural tremor using electrophysiological measures via accelerometry and of intention tremor using kinematic analysis on top of a conventional lateralised TCRS. This allowed assessment of tremor in terms of spatial variability and allowed for assessment of cerebellar features of MS on tremor control through kinematic analysis. These measures allow for evaluation of functional gain as well through tremor analysis. Validated health-related questionnaires is usually best suited to assess overall functional benefit.

The effectiveness of DBS has been debatable in terms of longevity of benefits reaped by patients. DBS is good value for in the first year of treatment though long term effects have not been as encouraging. Torres et al documents a 50% tremor suppression at one year to a 20% suppression at 3 years among it’s patient population and a separate 20% suffered from tremor relapses at less than 2 years. Wishart et al reported 4 patients whom acquired tremor suppression initially, though 3 patients had effectiveness declined over time but still remained at
beneficial levels. Hyam et al\textsuperscript{29} reported initial tremor reduction in 83% of patient population, to 33% at 2 years or more. These all show marked decline with cases of relapse. Despite that, Thevathasan and associates\textsuperscript{31} have showed evidence that long term effective stimulation can provide staggering improvement in mean tremor score of 61.7%, even with a mean late follow up period of 5.2 years. In the same study 80% of patients assessed with stimulation OFF showed no improvement of tremor score in the first year of follow-up, however 60% of the same group went on to achieve tremor reduction in OFF at the late follow-up. Another instance, would be the report of single patients in two studies\textsuperscript{27,33} of whom both achieved sustained tremor control for four years, even though in one of the cases it was found that the battery generator had run out.

This points that DBS has long term efficacy with proper compliance, though the stimulatory effects of DBS seems to have a major role in the initial stages of treatment but in the long run a ‘persistent microthalamotomy’ like effect takes place producing mirrored tremor relief in OFF and ON parameters. In a post-explantation MRI study of 2 patients, lesions were found along the course of electrode tracts in the patient that developed permanent tremor reduction and not in the other. Schulder et al\textsuperscript{25} conducted MRI scans that were unremarkable in his studies, though the only histopathological study of post-DBS in MS patients done by Moore et al\textsuperscript{10} indicated demyelination of grey matter spreading out from the stimulation site which is vaguely visible on MRI. This goes hand in hand with the theory of stimulation induced demyelination producing the postulated “persistent microthalamotomy” effect. This raises cost-effective questions of the redundancy of battery generator replacements in cases where there is development of this phenomenon. In majority of the cases, reprogramming to optimal parameters were required especially in the first few weeks post-operatively due to the effect of “tolerance”.

Brodkey et al.\textsuperscript{34} have reported 5 times more Tremor Related Activity(TRA) cells per unit thalamus in PD as compared to MS being one of the reasons for the obvious difference in effectiveness of DBS in tremor of PD as compared to in MS. VIM stimulation has proven results previously and the documentation of it’s somatotopic organisation allowed precise stereotactic parameters for an end effect on a specific region\textsuperscript{12}. There have been studies done comparing the efficacy of other thalamic targets like the VOA with VIM which showed similar results\textsuperscript{28}. Evidence of DBS effects on VIM were shown through the study of motor evoked potentials(MEP) via the cerebello-thalamic-cortical (CTC) pathways with VIM stimulation, and it’s effect in restoring motor inhibition within the CTC\textsuperscript{35}. In recent times, the subthalamic region has reported to be largely more effective than thalamic targets. Hamel et al\textsuperscript{14} and Herzog et al\textsuperscript{30} have documented the effectiveness of the subthalamic region in DBS as compared to thalamic stimulation in tremors of postural and intention components. The subthalamic region is thought to be most effective due to it’s afferents, the CTC that are projected to the VIM via a narrowed region, hence only requiring a smaller stimulatory field. Subthalamic stimulation though has been reported with higher risk of side effects of dysarthria, paresthesia and gait ataxia.
accentuated especially with bilateral stimulation when compared to VL thalamus targeting\textsuperscript{14}.

DBS has proven to be effective and has trumped thalamotomy as it was said to have a smaller risk profile. In a comparative review done by Yap et al\textsuperscript{3}, initial tremor suppression recorded in both were approximately similar though functional improvement in DBS dwarfed that of thalamotomy, though the risk of haemorrhage in DBS seemed to be higher, 3.09% to 0.62%. This review though estimated a haemorrhagic complication rate of 2.56% for DBS which is still substantially high. Despite this, the irreversibility, the ability to have complete control over degree of tremor suppression and it’s longer lasting benefits make DBS more attractive as a treatment option. Though recently, Johnson and associates\textsuperscript{33} reported an 8 fold increase in the incidence of seizures in MS patients whom completed DBS compared to other disease groups. From the literature gathered there seems to be an increased risk among the group whom have undergone thalamic procedures rather than subthalamic ones. The seizures seem to be a one off incident with good response to a loading dose of phenytoin. This begs the question whether could this be due to the fact of the prevalence of epilepsy in MS patients (2.3%) with it’s natural demyelinating progression, or from an initial stimulatory effect from the DBS device. The overall cost of DBS is estimated to be very high and the average visit per patient for reprogramming was approximated to be $5\textsuperscript{36}$. Combined with the phenomenon of “tolerance” it is clear that patients need to be committed to treatment highlighting the shortcomings of DBS.

\textbf{Conclusion}

This review has highlighted the efficacy and safety of DBS in the treatment of MS related tremor. It is documented to provide tremor suppression in 85.2% and functional benefit in 69.1% of these patients. Despite that, the long-term outcome depends on the chronicity of implantation as well as patient compliance. Neurophysiological assessment modalities have introduced improved simultaneous evaluation of the multivariable components of MS tremor and functional capacity of the tremulous limb. The subthalamic region should be given consideration as an alternative target to the VIM nucleus in this subgroup of patients. Despite the obvious benefits of DBS, the associated risk of intracerebral haemorrhage(2.56%) and wound infection(3.85%) remains considerable and needs careful exploration to ascertain the safety of this surgical procedure. Of recent, the recognition of MS exacerbation(5.6%) and seizures(5.13%) associated with DBS has highlighted the need to further evaluate these complications to better understand the risk profile of DBS.


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Approaches to Radiology- *Radiology and Shortness of Breath*

Dr. Nicola Schembri (Clinical Fellow in Medical Education & SpR in Radiology NHS Tayside)

Correspondence to: nschembri@nhs.net

**ABSTRACT**

This is my first in a series of articles aimed at improving medical students’ approach to interpretation of different imaging modalities. As medical students, and likewise also as fresh foundation doctors, despite probably adequate exposure to clinical images requested as part of the patient management pathway during ward-based attachments, not many feel confident in their interpretation skills. Moreover though, two things that I find interesting is that medical students and junior doctors find it difficult to prioritise imaging requesting in the context of the clinical problem presented, and

(1) lack verbal fluency in describing their findings, no matter how barn-door the findings are.

The essential point to make is that the aim is not to make mini-radiologists, but to ensure that junior doctors can practice safely.

The key teaching points during this issue will focus on the following:

- Tackling a core clinical problem and discussing its medical work-up.
- Discussion of the imaging work-up emphasising on investigation prioritisation.

A self-assessment section will supplement this, with a case study in future issues, to put knowledge acquired to practice.

**Editorial Update – Dr. Schembri 8th February 2012**

Since this article went into press, the requesting system within NHS Tayside has undergone drastic changes with the system going electronic as I write. The principles in image requesting with respect to IRMER still hold and the same approach should be taken when making electronic radiology requests. The paper copies will be phased out by spring 2012 as the system goes live throughout all of NHS Tayside. All clinicians are entitled to submit any radiology request with no restrictions made irrespective of their level of training even with regards to CT requesting. Having said that though, if junior doctors are submitting the request it would be helpful to indicate in the “Clinical Details” section that the patient was reviewed by the senior clinician who made the decision to request CT/MRI.
Core Clinical Problem – Shortness of Breath

78-year-old woman admitted to the A&E resuscitation bay at 3am complaining of sudden onset shortness of breath that woke her up from sleep associated with central chest pain. She was found by the paramedics to be very distressed, cold and clammy. Her relevant past medical history is that of hypertension controlled by medication and an anterior myocardial infarction back in 1999. She had been getting mild anginal attacks over the past couple of weeks precipitated by moderate exertion, which settled with GTN spray. 12-lead ECG shows sinus tachycardia of 100bpm and left axis deviation with left bundle branch block.

What is your differential diagnosis given this history?

The differential diagnoses given by the University of Dundee for the core clinical problem of “shortness of breath” is rather broad:

- Cardiac failure
- COPD
- Pneumonia
- Asthma
- Pulmonary embolism
- Pleural effusion
- Pneumothorax
- Pulmonary fibrosis
- Lung cancer
- Anaemia
- Metabolic
- Acidosis (e.g. acute renal failure/diabetic ketoacidosis)

What salient information might you want to know to narrow down your differential list and prioritise your list in a relevant ranking order?

**History of presenting complaint**

Are there any cardiac symptoms – exertional, paroxysmal nocturnal dyspnoea?

Are there any high risk factors for pulmonary embolism such as long haul flight, previous or known carcinoma, hypercoagulability state, recent surgery, pregnancy/postpartum?

Are there any infective symptoms including overseas travel, exposure to TB, immunosuppression?

**Past medical history**

Are there known cardiovascular risk factors (previous MI, DM, HT, hypercholesterolaemia, smoker), renal history?
**Occupational/social history**

Is this patient a smoker (if yes, how heavy)? Does patient have a current or past occupational exposure risk for interstitial lung disease?

**What imaging investigations might you want to do depending on the differential?**

In the setting of chest and cardiovascular disease, the differentials for shortness of breath may fall under the following headings:

- suspected heart failure and/or myocarditis
- suspected pulmonary embolism
- pneumonia
- acute exacerbation of asthma
- acute exacerbation of COPD
- suspected pleural effusion
- suspected diffuse/infiltrative lung disease
- upper respiratory tract infection

**Key Point**

"Making the Best Use of Clinical Radiology Services" is a reference guideline published by the Royal College of Radiologists that helps clinicians decide on the most appropriate investigation in a particular clinical setting. Clinicians in NHS Tayside have free access to this publication online via “Staffnet”.

So getting back to the case presented above we will re-capitulate and ask the same question again:

**What is your differential diagnosis given this history?**

Given this information it is likely that the patient is suffering from a severe attack of cardiac failure, which could have been precipitated by a new myocardial infarction (we do not know yet if this is new left bundle block or of longstanding till old notes are made available). It could have also been a lower respiratory tract infection that is now increasing the demands on the heart precipitating heart failure in an already compromised heart.

We can now access the guidelines under the heading of “Chest and Cardiovascular System”, sub-heading “Suspected Heart Failure and/or Myocarditis”. This will list the investigation of choice in priority order for that clinical entity supported by evidence-based recommendation (see Fig 1).
Based on this guideline, what is the investigation to request in the first instance in this case?

CXR

Depending on the clinical condition of your patient you will need to assess whether your patient is fit enough to be taken round to the radiology department to obtain a posteroanterior (PA) CXR. If they are too unwell then a portable anteroposterior (AP) CXR may be appropriate. Bearing in mind that the patient is being cared for in the resuscitation bay in A&E, it is likely that she is too unwell so a portable AP CXR will be requested in this instance.
How will you now go about requesting this investigation?

There are a few things to consider first:

- Choose the appropriate request card.
- Complete all necessary parts especially patient demographics, patient location in the hospital/clinic, referring team.
- Tell us what the question is that you want us to answer based on detailed relevant clinical information given.
- Make sure that clinician contact details are legible in the event that the radiologist might want to communicate significant clinical findings urgently.
- Sign the card ONLY if you are eligible to do so. For instance in some centres like NHS Tayside, CT and MRI cards can only be signed off by clinicians at registrar level and above.

Choice of request cards in NHS Tayside

Figure 2 – General radiography request card for requesting CXR, AXR, fluoroscopy such as barium enema, CT and US studies.

Figure 3 – Request card for requesting nuclear medicine studies such as V/Q scans, bone scan.
Which of the request cards above would you choose? Is it Figure 2, 3 or 4?

Answer is Figure 2.

Who can sign the card?

Answer is any level of clinician from FY 1 up.

Once that you have chosen the first line imaging investigation of choice you would then move on to second line imaging investigations pertaining to the specialist field of interest, such as dedicated cardiac imaging like echocardiography for cardiac function analysis and/or nuclear imaging to assess myocardial perfusion in this instance. The same approach would apply to any other differential diagnoses suspected clinically.

During this issue we have touched on

- Tackling a core clinical problem and discussing its medical work-up.
- Discussion of the imaging work-up emphasising on investigation prioritisation.

In the next issue of this journal we will consider

- Discussion of image findings expected related to “Shortness of Breath” pertaining to the different imaging modalities implemented appropriate to a junior doctor level of training.
- A systematic approach towards chest radiograph interpretation in the context of a specific core clinical problem.
Self-assessment section

– Some local researching may be required to answer some of these questions
– One, some or all answers may be correct

1. Can anyone sign off any request card in NHS Tayside?
   a. Yes or No?
   b. If “No” who can sign off which card(s)?

2. If a patient presents with shortness of breath what would be the first line imaging investigation of choice if
   a. Heart failure is clinically suspected?
      i. CT chest with contrast
      ii. Echocardiogram
      iii. Chest radiograph
   b. Pulmonary embolism is suspected?
      i. CT pulmonary angiogram
      ii. Chest radiograph
      iii. Ventilation/perfusion scan

3. If in doubt as to which investigation to go for, where would you seek help?
   a. Ask your senior colleague
   b. The cheapest investigation on offer
   c. The investigation with least ionisation radiation
   d. Consult “Making the Best Use of Clinical Radiology Services”

Answers

1. a) No
   b) Registrars and above can sign off CT and MRI request cards in NHS Tayside.

2. a) Chest radiograph
   b) Chest radiograph

3. Ask your senior colleague and/or consult “Making the Best Use of Clinical Radiology Services”. 

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**Glycaemic Control & Heart Failure Development - Importance of Health Promotion in the Diabetic Patient**

Mohammed Farik Jabir (5th Year MBChB) University of Dundee & Prof. Chim Lang (Professor of Cardiology) University of Dundee

Correspondence to Mohammed Farik Jabir: M.F.Jabir@dundee.ac.uk

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**ABSTRACT**

**Background**

In diabetes, poor glycaemic control is associated with increased risk of cardiovascular events. The relationship between glycaemic control and chronic heart failure (CHF) is less well defined. There is controversy regarding the importance of glycaemic control in patients with type 2 diabetes-mellitus (T2DM) and CHF with recent evidence suggesting that tight glycaemic control may be associated with worse survival.

**Aim**

The aim of this study was to examine the relationship between HbA1c and the risk of incident CHF and examine the relationship between HbA1c and outcome in T2DM with established CHF.

**Methods**

This study was carried out in the population (approximately 400,000) of Tayside in Scotland using the Diabetes Audit and Research in Tayside information system. The incidence of new CHF in the DARTS database was determined during the study period (Jan 1994 to Dec 2003). CHF was defined as the presence of a hospital discharge code for CHF or the prescription of CHF medication following a myocardial infarction. A prospective case control study was performed with each case of CHF. Development of CHF was modelled using conditional logistic regression with a proportional hazards model used to consider the impact of HbA1c on survival of the cases.

**Results**

Out of 3070 diabetic individuals, there were 691 incident cases of CHF (mean age at diagnosis of 70.6±9.8 yrs, 60% males). The adjusted HR of developing CHF for each 1% higher HbA1c was 1.31(95% CI 1.20-1.44, p=1.43×10⁻⁹). In the cases there were subsequently 211 deaths. After adjustment the HR of death for each 1% increase in HbA1c was 1.24 (95% CI 1.09-1.42, p=0.0013).

**Conclusions**

These data suggest that glycaemic control is an independent risk factor for incident CHF in persons with T2DM. In diabetic patients with established CHF, a poor glycaemic control is associated with a worse outcome.
**Introduction**

Diabetes is a metabolic condition characterized by constant hyperglycemia; it is well established as being an independent risk factor for developing cardiovascular events. However, the exact reason for this association remains unclear; and includes association between diabetes and other cardiovascular risk factors, such as dyslipidemia, hypertension, and renal insufficiency. A growing number of epidemiologic studies now implicate chronic hyperglycemia as an important determinant of cardiovascular disease. It is well established that diabetes, a metabolic syndrome that is increasing in prevalence worldwide, is a significant risk factor for developing cardiovascular disease and development of heart failure.

**Epidemiology of Diabetic Heart Failure**

Over the previous 2 decades, the prevalence of diabetes, in particular type 2 diabetes, has significantly risen, and has subsequently caused an increase in the incidence of diabetes-related complications, including heart failure (HF). Investigations involving subgroup analysis of various randomized clinical studies have proven that a significant number of HF patients are also suffering from diabetes. The coexistence of both diabetes and chronic heart failure (CHF) was clearly evident as demonstrated in both the Framingham Study and the UKPDS. They can also in most cases coexist as an inter-relationship such that each condition may impact upon the other in terms of aetiology and outcome. The study also concluded that in the presence of diabetes the risk of CHF increases by 2-8 fold. Studies have proven that for every 1% increase in HbA1c was associated with a 12% increased risk of developing CHF independent of age, BMI, BP and presence of any coronary heart disease. Data analyses from the Framingham study demonstrated that diabetes significantly increases the risk for developing CHF by 1.8 times in men and 3.7 times in women.

**Pathophysiology of Diabetic Heart Failure**

Heart failure development in diabetic patients is associated to abnormal multiple pathophysiologic states. Common comorbidities such as hypertension, renal impairment, dyslipidemia and obesity subsequently lead to both functional and structural abnormalities in the heart; ultimately causing CHF. The United Kingdom Prospective Diabetic Study (UKPDS) showed that hyperglycemia is strongly associated with cardiac abnormalities and dysfunction. The study also concluded that for every 1% rise in HbA1c, the risk of HF was increased by 12%; proving that a significant correlation existed between glycaemic levels and development of HF. Iribarren et al also demonstrated that in diabetic individuals an HbA1c level ≤10 caused an increase of developing HF by 1.56 fold than an HbA1c level of <7.

There has been much debate about the existence and causation of developing diabetic heart failure as the majority of the studies supporting this concept are based on animal studies. Data suggests that myocardial structure is altered by deposition of collagen and increased fibrosis. Di Biello et al were able to prove the presence of early changes of fibrosis in myocardial tissue by using ultrasonic backscatter. Ultrasonic backscatter allows characterization of tissue microstructure using radio
Heart failure in diabetic patients results from complex interaction involving the sympathetic nervous system, renin angiotensin aldosterone system, increased activity of cytokines and increased oxidative stress. Hyperglycemia leads to activation of protein kinase C at cellular levels that subsequently leads to maladaptive changes in the myocardium. Activation of protein kinase C leads to malformations in contractile protein functioning and triggering of synthesis of angiotensin converting enzymes (ACE) genes and nitric oxide synthase activity. An increased production and activity of angiotensin converting enzymes leads to apoptosis, necrosis and interstitial fibrosis of myocytes and endothelial cells. Studies have proven that elevated glycaemic levels lead to glycation of collagen; the final products of glycation lead to stiffening of the myocardium. Also at the molecular level, calcium hemostasis impairment is also evident in myocytes.

Disruption of calcium hemostasis will tend to lead to decreased uptake and release by the sarcoplasmic reticulum. Maladaptations at the receptors are mainly due to the decreased number of sarcolemmal sodium calcium exchanger. Elevated glycaemic levels leads to oxidative stress mainly by production of oxidants from both mitochondrial and non-mitochondrial sources. Oxidative stress causes damage by interacting with mitochondrial uncoupling as well as direct myocyte death. Disruption in mitochondrial function leads to reduced ATP production and reduced myocardial contractions. Alteration in the utilization of substrate is another factor that contributes to cardiomyocyte damage at the molecular level. Diabetic hearts tend to use fatty acids in preference to glucose or lactate; and over a period of time accumulation of lipids leads to cardiomyocyte death. Studies in diabetic individuals have been limited to the use of positron emission tomography which confirms the greater use of fatty acids and decreased glucose oxidation in the heart. Decreasing utilization of fatty acids for oxidation by the heart is an important factor for reduction of cardiomyocyte damage. Therefore evidence demonstrates multiple factors for development of a characteristic diabetic cardiomyopathy independent of other coexisting comorbidities such as hypertension or coronary heart disease. This concept may also explain why diabetic individuals tend to develop heart failure even in the absence of coronary heart disease. Use of ACE inhibitors suppresses levels of serum aldosterone. Aldosterone causes cardiomyocyte fibrosis that subsequently leads to a dysfunction of the left ventricle. Hence these results are evident for blocking of aldosterone release using ACE inhibitors. Clinical studies have also demonstrated that ACE inhibitors reduce the progression of development of diabetic nephropathy in addition to their blood pressure lowering effect. ACE inhibitors are also used in prevention of congestive heart failure and prophylaxis of cardiovascular events.

**Aims of Study**

A potential risk factor that is associated with poor outcomes that is being currently studied is poor glycaemic control. Glycosylated haemoglobin (HbA1c) indicates the ambient plasma glucose concentration over the preceding 2 to 3 months. The HbA1c level is commonly used as an index of average glycaemia and provides a target treatment range in diabetic patients (HbA1c-normal range 6.5%-7%). Raised HbA1c
levels indicate poor metabolic control and eventually lead to both microvascular and neuropathic complications. Lowering of glycaemia levels in diabetic patients delays the onset and progression of diabetic complications.\textsuperscript{35-36} In addition, raised glycaemic levels are also associated with increased risk of cardiovascular events (CV).\textsuperscript{37} Elevated HbA1c levels have also been proven to be associated with increased risk of heart failure in diabetic patients.\textsuperscript{38} In diabetic individuals with no previous heart failure, elevated HbA1c levels have been associated with an increased risk of incident heart failure and mortality.\textsuperscript{39,40} Despite this evidence, studies investigating the relationship between HbA1c levels and outcomes in diabetic patients have been limited and have reported discrepant results.\textsuperscript{41-42} Therefore, our study aimed to investigate if HbA1c levels could predict outcome in patients with diabetic heart failure.

**Methods**

**Data sources**

Our study involved resources from the DARTS (Diabetes Audit and Research in Tayside) and MEMO database (Medicines Monitoring Unit). DARTS is a diabetic population based information system involving patients under the care of NHS Tayside, Scotland (population of approximately 400,000). The DARTS dataset constitutes clinical information for each and every patient being diagnosed with diabetes in Tayside, Scotland since January 1993.\textsuperscript{43} The DARTS database has a 97% sensitivity and is composed of interlinking of patient data sources; record-linking is utilized by way of the patients Community Health Index number (CHI) assigned to each patient at their respective general practice.\textsuperscript{44} Data sources that have been interlinked include date of diagnosis, diabetes type, duration, HbA1c levels, hospital admissions, diabetic medication, diabetic clinic visits, cardiovascular risk factors (BMI, blood pressure, cigarette smoking) and presence of micro or macro vascular complications of diabetes. The database is regularly updated and includes ongoing retrieval and validation of routine data directly from medical records in primary care by a research team of nurses.

The second database used in the study is the MEMO (Medicines Monitoring Unit) database.\textsuperscript{45} MEMO is a University of Dundee based research collaboration that mainly focuses on the effectivity, safety and cost-effective use of drugs and devices on disease. Data primarily involves the Tayside population with linkage to other national datasets also possible.\textsuperscript{46} It contains a detailed list of all prescribed items to patients from community pharmacies. Therefore, for our research purposes we have a detailed record of diabetic medication or insulin prescribed to all diabetic patients within Tayside.

**Study Population**

The Study population involved all the patients diagnosed with Type 2 diabetes during the study period January 1991 to 30 June 2008 in Tayside, Scotland. The sampling pool obtained from the DARTS database were patients who were diagnosed as type 2 diabetes and had suffered an incidence of new congestive heart failure (CHF) during the above mentioned study period. CHF was defined as the presence of a hospital discharge code for CHF or patients who were on prescription for CHF
medication (loop diuretic and an ACE inhibitor). In addition, patients were excluded if they were on loop diuretics such as furosemide for renal disease and were on an angiotensin receptor blocker. The overall cohort for this period included 3,070 patients with diabetes out of which 691 incident cases of CHF were reported.

**Statistical Analysis**

HbA1c values recorded during the study period were used to assess glycaemic control for each patient. Individuals were classified into categories based on quintiles of HbA1c. The levels of HbA1c in each quintile were as follows: Q1: HbA1C ≤6.5%; Q2: 6.5% <HbA1C ≤7.2%; Q3: 7.2% <HbA1C ≤7.9%; Q4: 7.9% <HbA1C ≤8.6%, and Q5: HbA1C >8.6%. All HbA1c values available during the observation period were extracted and averaged.

Development of CHF was modeled using conditional logistic regression using the mean HbA1c during the study period. In statistics, conditional logistic regression is used for the prediction of the probability of occurrence of an event by fitting data to an assigned logistical function. Covariates used in the study were number of HbA1c measures taken, mean arterial pressure and if thiazolidinediones were prescribed as diabetic medication. Thiazolidinediones were added as covariates due to their increased risk of causing heart failure. Clinical data included in the study were: risk factors for vascular disease and co morbidities, hypertension, smoking, dyslipidaemia, blood pressure and body mass index were taken into account.

The primary outcome of the entire program was hospital admission for worsening CHF or death due to cardiovascular causes. Deaths were considered to be cardiovascular unless another cause was attributed. Patients who had suffered from a new incidence of CHF were identified and a date of CHF diagnosis was defined for each patient. Division into quintiles was done to ensure that the groups spanned through a wide range of glycaemic values that were inclusive of the normoglycemic range. Univariate and multivariable Cox proportional hazards models were used to assess the relationship between increasing quintiles (Q1 to Q5) of HbA1c and incidence of CHF and outcome in patients with type 2 diabetes and an established diagnosis of CHF. Hazard ratios are presented as per unit 1% increase in HbA1c, and 95% confidence intervals were calculated for hazard ratios.

**Results**

**Key Findings**

- **CHF Incidence** - The adjusted hazard ratio of developing CHF for each 1% increase in HbA1c was 1.31 (95% CI 1.20-1.44, p=1.43×10⁻⁹).
- **Mortality** - Analyses revealed a linear relationship between mortality and increasing HbA1c quintiles in diabetic patients. After adjustment the hazard ratio of death for each 1% increase in HbA1c increased by 1.24 fold (95% CI 1.09-1.42, p=0.0013).
The study cohort was compromised of 3,070 diabetic individuals of that there were 691 incident cases reported of CHF. The cohort compromised of 60% males (mean age of 60.5 years). The mean age at diagnosis of CHF of the diabetic individuals was 70.6±9.8 years (see Table 1). The mean HbA1c level of the cohort was 8.0 ±1.4%. The results showed that as the HbA1c quintiles progressively increased, there was also a simultaneous increase in the prevalence of complications arising due to diabetes, and subsequently individuals were put on a greater number of diabetic medications for better glycaemic control. Diabetic individuals in the higher quintiles were also on higher doses of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers and on tight control of their cholesterol through statins (data not shown).

Table 1. Clinical Characteristics of patients in analysis

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Case</th>
<th>Control</th>
<th>Case vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>3070</td>
<td>691</td>
<td>2379</td>
<td>-</td>
</tr>
<tr>
<td>Percentage Males(%)</td>
<td>60.3</td>
<td>60.5</td>
<td>60.3</td>
<td>-</td>
</tr>
<tr>
<td>Age at diabetes diagnosis (years)</td>
<td>59.3(12.3)</td>
<td>60.0(12.3)</td>
<td>59.1(12.3)</td>
<td>-</td>
</tr>
<tr>
<td>Age at CHF diagnosis (years)</td>
<td>67.4(11.2)</td>
<td>70.6(9.8)</td>
<td>66.5(11.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>7.7(1.3)</td>
<td>8.0(1.4)</td>
<td>7.6(1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of Hba1c measures</td>
<td>18.7(13.7)</td>
<td>21.4(15.2)</td>
<td>18.0(13.1)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diabetic medication before CHF date:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Insulin</td>
<td>19.5</td>
<td>32.8</td>
<td>15.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>% Metformin</td>
<td>46.0</td>
<td>58.4</td>
<td>42.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Sulphonylurea</td>
<td>27.7</td>
<td>43.6</td>
<td>23.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% TZD</td>
<td>9.1</td>
<td>7.2</td>
<td>9.7</td>
<td>0.0391</td>
</tr>
</tbody>
</table>

Data expressed as mean (±SD) or %

**CHF Incidence** - The incidence of CHF occurring over the 8 years of study increased with subsequent increase in quintiles of HbA1c (see Table 2). On analyses, the adjusted hazard ratio of developing CHF (Q1 used as the reference group) increased progressively with increase in quintiles of HbA1c. On comparison of the quintiles the notable trend was an increase in incidence of CHF as the quintiles increased. The fifth quintile (Q5) had significantly increased incidence of developing CHF (risk adjusted HR: 2.56, 95% CI: 1.78 -3.69, p=3.9×10⁻⁷) and it was 2.5 times higher than in patients with the lowest HbA1c level of 6.5% or less (Q1). The adjusted hazard ratio of developing CHF for each 1% increase in HbA1c was 1.31 (95% CI 1.20-1.44, p=1.43×10⁻⁹).
### Table 2: Independent Effect of HbA1c levels on CHF Incidence

<table>
<thead>
<tr>
<th>HbA1c Quintile</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
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<tbody>
<tr>
<td>Q1 (&lt;6.5)</td>
<td>0.97</td>
<td>0.69-1.36</td>
<td>0.87</td>
</tr>
<tr>
<td>Q2 (6.5-&lt;7.2)</td>
<td>1.60</td>
<td>1.14-2.22</td>
<td>0.01</td>
</tr>
<tr>
<td>Q3 (7.2-&lt;7.9)</td>
<td>1.60</td>
<td>1.14-2.25</td>
<td>0.01</td>
</tr>
<tr>
<td>Q4 (7.9-&lt;8.6)</td>
<td>2.60</td>
<td>1.78-3.70</td>
<td>3.90×10⁻⁷</td>
</tr>
<tr>
<td>Q5 (≥8.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.04</td>
<td>1.03-1.05</td>
<td>2.95×10⁻²³</td>
</tr>
<tr>
<td></td>
<td>1.04</td>
<td>0.87-1.24</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Quintile 1 is the reference group

**Mortality** - Over a period of 8 years of follow-up 211 patients died. The mean HbA1c level of the cohort was 7.9 ±1.4 % (see Table 3). The adjusted hazard ratios for death are shown in Table 4. Using Q1 as the reference the second quintile (Q2) had a significantly low mortality (risk adjusted HR: 0.96, 95% CI: 0.60 -1.52, p=0.86) when compared to the other 4 quintiles (see Table 4). The fourth quintile (Q4) was significantly the highest in mortality (risk adjusted HR: 1.82, 95% CI: 1.13 -2.95, p=0.01). The results clearly demonstrate a linear relationship between mortality and the quintiles of HbA1c levels. After adjustment the hazard ratio of death for each 1% increase in HbA1c increased by 1.24 fold (95% CI 1.09-1.42, p=0.0013).

### Table 3: Clinical Characteristics of patients in analysis

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<tr>
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<th>All</th>
<th>Died</th>
<th>Survived</th>
<th>P(case control)</th>
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<tbody>
<tr>
<td>Number of Patients</td>
<td>613</td>
<td>211</td>
<td>402</td>
<td></td>
</tr>
<tr>
<td>Percentage Males (%)</td>
<td>61.1</td>
<td>57.3</td>
<td>63.2</td>
<td>0.1527</td>
</tr>
<tr>
<td>Age at diabetes diagnosis (years)</td>
<td>59.5(12.2)</td>
<td>61.1(13.0)</td>
<td>58.7(11.6)</td>
<td>0.0210</td>
</tr>
<tr>
<td>Age at CHF diagnosis (years)</td>
<td>69.7(9.6)</td>
<td>71.9(9.9)</td>
<td>68.6(9.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>7.9(1.4)</td>
<td>7.9(1.4)</td>
<td>7.8(1.4)</td>
<td>0.6210</td>
</tr>
<tr>
<td>Number of Hba1c measures</td>
<td>13.9(11.6)</td>
<td>12.6(11.6)</td>
<td>14.6(11.6)</td>
<td>0.0437</td>
</tr>
<tr>
<td>Diabetic medication before CHF date:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Insulin</td>
<td>32.2</td>
<td>33.8</td>
<td>31.3</td>
<td>0.5345</td>
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<tr>
<td>% Metformin</td>
<td>57.4</td>
<td>50.7</td>
<td>61.0</td>
<td>0.0145</td>
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<tr>
<td>% Sulphonylurea</td>
<td>43.6</td>
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<td>0.0095</td>
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<tr>
<td>% TZD</td>
<td>7.5</td>
<td>3.3</td>
<td>9.7</td>
<td>0.0040</td>
</tr>
</tbody>
</table>

Data expressed as mean (± SD) or %
Table 4: Independent Effect of HbA1c levels on mortality

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Mean HbA1c: Q1 (&lt;6.5)</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>Q2 (6.5-&lt;7.2)</td>
<td>0.97</td>
<td>0.69-1.36</td>
<td>0.87</td>
</tr>
<tr>
<td>Q3(7.2-&lt;7.9)</td>
<td>1.60</td>
<td>1.14-2.22</td>
<td>0.01</td>
</tr>
<tr>
<td>Q4(7.9-&lt;8.6)</td>
<td>1.60</td>
<td>1.14-2.25</td>
<td>0.01</td>
</tr>
<tr>
<td>Q5(≥8.6)</td>
<td>2.60</td>
<td>1.78-3.70</td>
<td>3.90×10⁻⁷</td>
</tr>
<tr>
<td>Number of HbA1c measures</td>
<td>1.04</td>
<td>1.03-1.05</td>
<td>2.95×10⁻²³</td>
</tr>
<tr>
<td>HbA1c Standard Deviation</td>
<td>1.04</td>
<td>0.87-1.24</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Quintile 1 is the reference group.

Discussion
Although increased HbA1c levels have been associated with increased incidence of cardiovascular events in the population⁸; the association between elevated HbA1c levels and prognosis in diabetic individuals with established HF has been less analyzed. The analysis of HbA1c data collected in our study during the 8 year period showed that in type 2 diabetic individuals who have a diagnosis of symptomatic CHF, the HbA1c levels are strongly associated as independent risk factors for developing CHF and is also a strong independent risk factor for mortality. In this particular population for every 1% increase in HbA1c the risk of developing CHF was increased by 1.31 fold. In the cohort of patients with established CHF who were on treatment for diabetes, the relationship between mortality and increasing HbA1c quintiles was a linear relationship (See Figure 1). Diabetic individuals in the second quintile (Q2) (6.5 %< HbA1c≤7.2%) had the lowest mortality when compared with the other quintiles. Therefore, in this population, for every 1% increase in the level of HbA1c, the risk of CV death increased by 1.24 fold.
The findings from the study extend those from previous analyses of the association between rising HbA1c levels and CV events. The findings are also consistent with analyses in patients with newly diagnosed diabetes, in individuals with established diabetes, and in diabetic individuals with other associated CV risk factors. A study carried out on 2,412 HF patients (907 with diabetes) involved in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) study revealed that the adjusted risks of CV death, HF hospitalization and mortality increased progressively with rising HbA1c. Of note in this study that in both non diabetic and diabetic individuals with CHF; the HbA1c level is an independent risk factor for HF hospitalization, CV death and total mortality. A similar study examined the association between HbA1c and adverse outcomes in 5,815 diabetic individuals with established heart failure. Association between rising quintiles of HbA1c (Q1-Q5) and risk of CHF and death were studied. Of significant note in this study; the association between HbA1c and mortality in diabetic patients with symptomatic HF appeared U-shaped (Figure 2), with patients with a moderate glucose control at the lowest risk of death. (7.1% < HbA1c ≤7.8%). However, studies that have been carried out have also shown a paradoxical relationship between HbA1c levels and mortality.In a study involving 123 diabetic individuals with systolic HF an inverse relationship between HbA1c and mortality was identified. In this particular study with advanced systolic HF an HbA1c >7% was associated with a lower mortality than an HbA1c level ≤ 7%.

Figure 1. Graph represents the proportion of patients who died at 8 year follow-up by HbA1c quintiles (compared to quintile 1): Error bars indicate the 95% confidence intervals.

Figure 2. Graph represents the proportion of patients who died at 2 year follow-up by quintiles (Q) of HbA1c. The graph demonstrates that the association between HbA1c and mortality in diabetic patients with symptomatic HF appears U-shaped, with patients with moderate glucose control at the lowest risk of death. (7.1% < HbA1c ≤7.8%). Global chi-square p=0.001. Error bars indicate the 95% confidence intervals.
The findings of our study add to the growing body of evidence and confirms the existence of an independent link between increasing glycaemic levels and CV events and supports a complex relationship between HbA1c and mortality in diabetic patients with established HF. Reasons for this relationship however remain unclear.

The increased mortality associated with elevated HbA1c levels is most possibly due to multiple factors and includes both the direct and indirect effects caused by hyperglycemia. Adverse effects of elevated glucose levels include endothelial dysfunction, increased oxidative stress, protein kinase C activation and increased rates of atherosclerosis. Increased glycation end products due to hyperglycemia may also trigger off injurious processes such as myocardial stiffening and activation of cellular receptors for glycation end products that in turn lead to up-regulation of cellular signals subsequently causing cellular dysfunction. Elevated HbA1c levels may also cause an increased resistance to insulin with disturbance in cardiac metabolism, energy utilization in the insulin resistant myocardium and also activation of the sympathetic nervous system. Raised HbA1c levels could also be quite reflective of the individuals poor adherence to medication and in turn associated with poorer outcomes.

Current therapeutic management for HF focus on reduction of neurohumoral activity (e.g., use of ACE inhibitors, angiotensin receptor blockers, Beta blockers and aldosterone antagonists) or by increasing myocardial contractility (digoxin).Our data suggest that for improved clinical management it is worth studying glycaemic control as a method for reducing CHF related morbidity and mortality. However targeting a lower HbA1c level for diabetic patients with established CHF has also its consequences as evident in the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes). Intensive glycaemic control to achieve better HbA1c levels or near normal levels could also be a risk in diabetic individuals with CHF. The ACCORD trial consisted of diabetic patients with established cardiovascular disease being put on an; intensive glycaemic control regime to achieve normal levels of HbA1c (<6%) to reduce the incidence of CV events as opposed to being on the standard therapeutic management (a target range of HbA1c from 7.0% to 7.9%). Results in this trial revealed an unexpected rise in mortality in the cohort assigned to intensive glycaemic control with no significant major reduction in CV events compared to mortality of patients assigned to the standard therapy. Future prospective studies are required to investigate the nature of optimum HbA1c levels in diabetic patients with HF as well as to define ideal treatment goals.

**Limitations**

Firstly the study is a retrospective study with the inherent limitations of this type of study design. Multivariable statistical models were used to adjust for heterogeneity amongst the HbA1c quintiles; however residual unmeasured confounding variables may remain. To assess the relationship between HbA1c and mortality; deaths were assumed to be of cardiovascular cause unless another cause was attributed. The relationship between HbA1c and progression of microvascular disease or
complications of diabetes were not assessed. This should be the focus of further studies. Inspite of these limitations, our data has several strengths. The large cohort size allows stratification of data by HbA1c levels to identify the complex relationship between HbA1c, development of CHF and mortality.

Clinical Implications

Our findings may have important clinical and public health implications. Our results suggest that tight glycaemic control may potentially reduce the incidence of heart failure and might be desirable to achieve levels of glycaemia to the normoglycaemic range as possible (i.e. HbA1c 7%). The potential benefit of tight glycaemic control should be weighed against existing barriers such as fear of hypoglycemia. The study of HbA1c variables is of importance for clinicians as both a prognostic tool and in clinical studies. As a prognostic tool it implies a possibility for intensive diabetic care; however the clinician should be aware of HbA1c values from previous encounters in addition to those measured currently when making the prognosis. The clinician should also be aware of the persistent effect of HbA1c on diabetic complications.

Conclusions

Our data suggests that glycaemic control is an independent risk factor for incident CHF in persons with type 2 diabetes. In diabetic patients with established CHF, poor glycaemic control is associated with significantly impaired survival and poorer CV outcomes. Analyses revealed a linear relationship between mortality and increasing HbA1c quintiles in diabetic patients. Our findings certainly have significant public health implications and future prospective studies should be carried out to investigate glucose lowering therapy and optimal HbA1c levels in HF patients.

References

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Clinical Anatomy Series – Cardiac Anatomy

John Kennedy (5th Year MBChB, BMSc) University of Dundee

Correspondence to: J.Y.Kennedy@dundee.ac.uk

ABSTRACT
The necessity for an appreciation of human anatomy has been integral to medical teaching for hundreds of years. Today, it still remains a crucial component of the undergraduate curriculum, but with opinions being voiced over the adequacy of this teaching 1, and Royal Colleges noting a reduction in the anatomy knowledge base of applicants, this is clearly an area of concern. Indeed, there was a 7-fold increase in the number of medical claims made due to deficiencies in anatomy knowledge between 1995 and 2007. 2 Therefore, not only does a greater understanding of anatomical principles bring advantages to clinical practice, but also, it can make individuals stand out at interview. This series of articles sets out to explore key anatomical structures placed in their clinical context, starting with cardiac anatomy.

Mediastinum and Covering of the Heart

The heart is located in the middle mediastinum i.e. the area inferior to the sternal angle and bounded by the pericardial sac. The pericardium encapsulates the heart and base of the great vessels, and is composed of a fibrous and serous layer with the fibrous layer being outermost. The serous pericardium is further divided into the parietal and visceral (epicardium) layers; the latter is firmly attached to the surface of the heart and the potential space between the two creates the pericardial cavity. 3

Clinical relevance

Somatic sensation to the pericardium is supplied by the phrenic nerves (C3-5) which pass in the fibrous pericardium to innervate the diaphragm. As a result, pericardial pain may be referred to the shoulder. 3

Pericarditis

The aetiology of pericardial inflammation is multifactorial including infection (bacterial, viral, fungal and tuberculosis), post-myocardial infarction, malignancy and autoimmune. Clinical features include sharp central chest pain exacerbated by movement and lying down and relieved by sitting forward. Pain may be referred to the shoulder or neck. Auscultation may reveal a pericardial friction rub, typically at the left lower sternal edge on end expiration with the patient leaning forward. Features of the underlying cause such as pyrexia during infection may also be present. The key investigation is an ECG, which often shows saddle-shaped ST elevation in the early stages. Differentiating this from a myocardial infarction is clearly crucial. Importantly, abnormalities are not normally illustrated on a plain film chest radiograph. 4
**Pericardial effusion**

The potential space between the parietal and visceral layers of the serous pericardium normally contains a small volume of fluid. Excess fluid is termed a pericardial effusion. If the volume is sufficiently large, this can reduce ventricular filling as a consequence of the lack of elasticity of the fibrous pericardium and this is termed cardiac tamponade. In severe cases, this can cause heart failure. Echocardiography is the key investigation for diagnosing this condition, and although most cases resolve spontaneously, a pericardiocentesis (drainage of the excess fluid through insertion of a needle) may be required to alleviate tamponade.  

**The Heart Chambers**

The heart is divided into two atria and two ventricles. Externally, the coronary sulcus separates the atria from the ventricles and contains several vessels including the right coronary artery and circumflex branch of the left coronary artery. Delineating the separation of the left and right ventricles are the anterior and posterior interventricular sulci, which also contain major vessels - anteriorly, the anterior interventricular artery and great cardiac vein and posteriorly, the posterior interventricular artery and middle cardiac vein. Internally, these chambers are separated by the interatrial and interventricular septum.

The right atrium forms the right anterolateral border of the heart. It receives deoxygenated blood from the superior and inferior venae cavae and the coronary sinus, which drains the myocardium. On its interatrial wall is the fossa ovalis – the embryological remnant of the foramen ovale that allowed oxygenated blood to enter the right atrium during foetal life.

The right ventricle forms the majority of the anterior border of the heart. The inflow tract to this chamber is rough in appearance due to the presence of multiple trabeculae carneae, which are muscular strips. Three of these strips attach to the tricuspid valve – which separates the right atrium and ventricle – to prevent eversion of its cusps during ventricular contraction. These are the papillary muscles, and are connected to the tricuspid valve via the thin fibre-like chordae tendineae. The outflow tract, which passes to the pulmonary trunk, is smooth by comparison, and is termed the conus arteriosus. Preventing backflow of blood into the right ventricle is the pulmonary valve, which is also composed of three cusps.

The left atrium forms a large proportion of the posterior aspect of the heart. It receives oxygenated blood from the four pulmonary veins. Again, the fossa ovalis is present on the interatrial septum.

The left ventricle forms the left anterolateral and diaphragmatic surfaces of the heart. Similar to the right ventricle, the inflow tract is rough in comparison to the outflow due to the presence of the trabeculae carneae. In comparison to the right side, only two papillary muscles are present to prevent backflow of blood through the mitral valve; one for each of the valve cusps. The aortic valve is placed posterior to its pulmonary counterpart and serves the same function. The right and left coronary arteries originate from the left and right sinuses, which are the space
between the aorta and the aortic valve. This allows blood to enter the coronary arteries when the valve closes during diastole.

Clinical relevance

Auscultation

The heart sounds heard on auscultation of the precordium relate to valve closure. The first heart sound (“lubb”) represents closure of the atrioventricular valves, the tricuspid and mitral, at the beginning of systole. The second sound (“dubb”) signifies closure of the aortic and pulmonary valves at the end of systole and beginning of diastole. Cardiac arrhythmias and murmurs can be identified and diagnosed when placed in the context of the cardiac cycle.

Valvular heart disease

Valve disease can broadly be split into regurgitation (a backflow of blood secondary to inadequate closure) and stenosis (insufficient valvular opening causing obstruction to flow). Although these pathological features can arise in any valve, the mitral and aortic valves are most commonly affected.

Mitral valve

A combined pattern of stenosis and incompetence is often present, although one may be more prominent clinically. This leads to dysfunctional blood flow which can produce left ventricular hypertrophy, increased pulmonary pressure, pulmonary oedema and left atrial dilatation. Typically, mitral stenosis produces a mid-diastolic murmur, whereas a pansystolic murmur occurs in mitral regurgitation.

Aortic valve

Again, either stenosis or regurgitation can occur, and both can result in heart failure. Aortic stenosis characteristically produces an ejection systolic murmur heard in the aortic area with or without radiation to the neck. Notably, the volume of the murmur does not correlate to disease severity and indeed the murmur may become quieter as heart failure ensues. Symptoms of dizziness, syncope and angina are common, and a slow rising pulse may be apparent in aortic stenosis. Aortic regurgitation produces a diastolic murmur, often associated with a collapsing pulse.

Right sided valve disease

Tricuspid or pulmonary valve disease is often a result of infection, such as rheumatic fever and infective endocarditis (notably in IV drug users), or congenital malformations.

The Coronary Circulation

The right and left coronary arteries arise from the aortic sinuses as discussed above and act to provide oxygenated blood to all of the cardiac tissues.
The right coronary artery passes inferiorly in the coronary sulcus between the right atrium and ventricle. Along its course, it branches to provide the atrial and sinoatrial nodal branch and the right marginal branch. It then terminates as the posterior interventricular branch in the posterior interventricular sulcus. As such, it supplies the right atrium and ventricle, the sinoatrial and atrioventricular nodes, and a proportion of the interatrial and interventricular septum.

The left coronary artery also enters the coronary sulcus, before terminating as the anterior interventricular and circumflex arteries. The former lies in the anterior interventricular sulcus and the latter in the coronary sulcus. This allows the left coronary to supply the left atrium and ventricle and a proportion of the interventricular septum.

Venous drainage of the cardiac tissue is achieved via the great, middle, small and posterior cardiac veins, which all drain into the coronary sinus. This in turn drains into the right atrium. It should be noted that there is a degree of anatomical variation found in the pattern of these vessels.

**Cardiac Conduction System**

Contraction of the cardiac muscle can occur independently as a result of the presence of an internal conduction system which sends electrical impulses to the myocardium. These signals begin at the sinoatrial node, otherwise known as the pacemaker. This is located in the right atrium close to the entrance of the superior vena cava. Impulses from this node result in contraction of the atria. The electrical signal then passes to the atrioventricular node, which is located in the atrioventricular septum near the tricuspid valve. This acts as the starting point for signal transmission to the ventricles. Extending from the atrioventricular node is the atrioventricular bundle. This splits into the right and left bundle branch which both pass in their corresponding side along the interventricular septum, before terminating as the Purkinje fibres. This creates a coordinated spread of excitation along the ventricles with subsequent effective myocardial contraction.

**Clinical relevance**

Coronary artery disease can result in myocardial ischaemia and infarction. The site of artery occlusion determines the area of infarction, and damage to the conduction system in these areas can be assessed by ECG monitoring. Therefore, different ECG readings can point to the affected site. If the resulting ischaemia sufficiently affects the conducting system, fatal arrhythmias and heart failure can occur. The following ECG changes may be seen following a myocardial infarction (MI):

**Anterior MI**

- ST elevation in V1 – V3

**Inferior MI**

- ST elevation in II, III and AVF
Lateral MI

- ST elevation in I, AVL and V5/6

Posterior MI

- ST depression in V1 – V3
- Dominant R wave
- ST elevation in V5/6

Further Reading


References


Implications of Obesity on Anaesthetics - A Case Study

Hannah MacKenzie (4th Year MBChB) University of Dundee

Correspondence to: H.M.B.MacKenzie@dundee.ac.uk

ABSTRACT

As the proportion of obese patients within the general population rapidly increases, more obese patients are requiring anaesthesia. Obesity is associated with anatomical and physiological differences and co-morbidities that impinge on the administration of anaesthesia. A surgical case, which could have been performed under a GA or a spinal anaesthetic is used as a basis of discussion. Various factors affecting airway choice, breathing problems, circulation and other issues are discussed.

Introduction

500 million adults worldwide have a BMI >30kg/m² and are thus classified as obese. With an increasing obese population it is not surprising that the number of obese patients being anaesthetised is also rising. It is well known that obesity is a risk factor for many health conditions such as ischaemic heart disease and respiratory problems. Due to the anatomical and physiological differences and co-morbidities associated with obesity, anaesthetists will need to consider carefully how they anaesthetise and care for these patients.

Case

A 27 year old male with a BMI of 51 (height 1.84m, weight 174kg) required open reduction and internal fixation to treat a left distal fibular fracture. His co-existing co-morbidities consisted of gastro-oesophageal reflux disease (GORD), for which he takes Lansoprazole, and untreated hypertension. He had no known drug allergies.

Normally, the majority of healthy patients of this age would have been offered either the option of a general anaesthetic (GA) or spinal anaesthetic for this procedure. Obesity itself and its associated co-morbidities can increase the risks of GA. This case is used as a basis for discussion of some of these issues and considers whether in fact a GA or spinal anaesthetic is better for this patient.

Airway

Airway maintenance is required during anaesthesia as patients are more prone to airway collapse due to the loss of pharyngeal muscle tone. Airway maintenance can be more difficult in obese patients.

To ensure adequate oxygenation after the induction of anaesthesia and prior to airway device insertion, patients are pre-oxygenated using facemask ventilation. Patients with a higher BMI have bigger, fatter tongues decreasing the size of their upper airway and also have larger quantities of fat in their necks resulting in greater extra-luminal pressures. This combination results in a narrower and less adequately
supported upper airway, which is more prone to collapse and obstruction when unconscious. Airway opening techniques, such as head-tilt-chin-lift and jaw-thrust are often required to overcome this obstruction. However, excessive posterior neck fat pads limiting extension of the atlanto-occipital joint makes ideal positioning less achievable. The lack of an optimal airway makes face mask ventilation more difficult\textsuperscript{2,5} and the use of a “Guedel” airway may be considered.

Two main airway devices are available for the maintenance of airway patency during GA: a laryngeal mask airway (LMA) and an endotracheal (ET) tube. Risk of reflux and subsequent aspiration determines which one is used.\textsuperscript{6+7}

A recumbent position during anaesthesia increases the risk of reflux in all patients.\textsuperscript{8} Loss of consciousness dampens protective airway reflexes making aspiration more likely.\textsuperscript{9} This risk is often potentiated in obese patients as they frequently have co-existing GORD, another risk factor for reflux. There are many reasons thought to contribute to this including reduced lower oesophageal sphincter (LOS) pressure, delayed gastric emptying, high intragastric pressure, hiatus hernia and increased frequency of LOS relaxation.\textsuperscript{10} It is important to protect the trachea to lessen the risk of aspiration and its associated problems.\textsuperscript{8}

An LMA is an airway device inserted without visual aid. It is designed to have a low pressure seal around the laryngeal inlet\textsuperscript{6} with its tip sitting on the upper oesophageal sphincter (Figure 1).\textsuperscript{7} Since this seal is above the entry to the trachea, it does is not adequately protect the trachea from stomach contents in the event of reflux. Furthermore, an inadequate seal increases the likelihood of air escaping into the stomach, which also adds to an already high risk of reflux. Therefore, the use of an LMA is discouraged in those at risk of reflux including obese individuals.\textsuperscript{5}

![Figure 1: The correct positioning of an LMA](image)

An ET tube consists of hollow tubing that is passed through the vocal cords and sits in the trachea. It is inserted into the trachea with the aid of a laryngoscope to ensure correct positioning (Figure 2). A cuff surrounding the distal portion of the tube is inflated once it is in position ensuring a complete seal of the trachea. This protects the trachea from the risk of aspiration\textsuperscript{11,12} and hence is a superior choice for airway maintenance in obese patients and others at risk of reflux.\textsuperscript{5}
It is essential to confirm the correct positioning of an ET tube by listening with a stethoscope to the lungs and over the epigastrium. There should be equal air entry over both lungs and no air entry over the epigastrium. Air entry over the epigastrium indicates that the ET tube is in the oesophagus and not the trachea. If not rectified quickly, ventilation of the stomach will occur which heightens the risk of reflux but more importantly, the lungs are not being ventilated and the patient will de-saturate resulting in hypoxia and death.\textsuperscript{12} It should be remembered that the larger tongues and limited neck extension seen in obese patients makes intubation more difficult.\textsuperscript{5} Patients at risk of reflux during anaesthesia are often prescribed a H\textsubscript{2} agonist or proton pump inhibitor in an attempt to minimise the risk of reflux.\textsuperscript{5}

When using an ET tube for intubation, the risk of reflux and aspiration can be further reduced by using the technique known as rapid sequence induction. This is done as any other intubation but with two differences. Pressure is exerted on the cricoid cartilage during the induction of anaesthesia and compresses the upper airway lessening the chance of aspiration if reflux occurs. Secondly, a fast and short acting muscle relaxant, Suxamethonium, is administered as opposed to a slower longer acting drug. If the intubation fails no further attempts are made. By using a short acting muscle relaxant the patient can promptly take over their airway and breathing in the event of intubation failure.\textsuperscript{13} This is of added value due to the short time to de-saturation in obese patients, discussed below.\textsuperscript{2}

**Breathing**

During GA patients are mechanically ventilated. Obese individuals have a third of the respiratory compliance of normal individuals due to reduced lung and chest wall compliance.\textsuperscript{14}

During inspiration, a larger chest volume is created by the contraction of the diaphragm moving the chest wall upward and the intercostal muscles expanding it outward. The resulting increase in chest volume lowers the air pressure within the lungs facilitating air entry down a pressure gradient.\textsuperscript{5} Obese patients have high proportions of fat within their ribs, chest wall, abdomen and diaphragm reducing chest wall compliance. Consequently, their inspiratory chest expansion is less resulting in a lower inspiratory volume with less oxygen available for diffusion. Thus, obese patients have an increased work of breathing and subsequently require higher pressures of mechanical ventilation.\textsuperscript{15}
It is well known that mechanical ventilation reduces functional residual capacity (FRC) by 20% in non-obese patients. However in the morbidly obese, due to a heavy chest wall and diaphragmatic splinting, which is worse in the supine position, mechanical ventilation results in a 50% reduction in their FRC. A low FRC results in a ventilation perfusion mismatch i.e. the collapsed alveoli are still perfused but not ventilated. Subsequently, obese patients de-saturate more quickly than non-obese individuals. For this reason, an airway must be obtained quickly after cessation of facemask ventilation in order to prevent the patient becoming hypoxic such that time is of the essence.2,14,16,17,18,19

The small time window to perform a potentially difficult intubation in an obese patient can be tackled in a few ways. One method is to position an obese patient at a 25° head-up angle during pre-oxygenation as this can delay the time to desaturation.20 Alternatively, a fibreoptic intubation can be performed in an awake patient. This also has the benefit of avoiding the need for facemask ventilation that is likely to be difficult. During this method the patient remains awake and in control of their airway until successful intubation has taken place. It is easier and more comfortable for the patient if it is done nasally rather than orally. A fibreoptic scope is inserted into the nose with an additional port to apply topical local anaesthetic as required. Once the ET tube is in place and correct positioning confirmed the patient is anaesthetised. Keeping the patient awake and in control of their airway and breathing averts the risk of breathing arrest and subsequent hypoxia from failed intubation.10,21,22

Circulation
Adequate blood pressure (BP) is required to maintain circulation at all times. Anaesthesia, surgery and medications (including anaesthetic agents) all affect BP and thus it is important to monitor BP during anaesthesia. Obese patients are 6 times more likely to suffer from hypertension. BP is a product of cardiac output (CO) and systemic vascular resistance (SVR) SVR is increased in obese patients due to such factors as insulin resistance, endothelial dysfunction and substances released from adipocytes. In addition, excess adipose tissue in obese patient’s results in an increased oxygen demand and thus a compensatory increase in CO. As with any newly diagnosed hypertensive patient, secondary causes must be excluded before attributing it solely to obesity. For example, advanced renal disease is often associated with hypertension and significantly reduces renal excretion of drugs.23,24,25

It is important to realise that BP in uncontrolled hypertensive patients may react differently to that of normotensive patients during anaesthesia as BP sways are not uncommon in the former patient group. This may be an exaggerated hypotensive response to situations such as induction of anaesthesia or an exaggerated hypertensive response to stimuli such as laryngoscopy and intubation. Awareness of this risk helps in the preparation of these cases. In addition, hypertension, especially if poorly controlled, is a risk factor for cardiovascular events occurring during anaesthesia such as myocardial infarction, cerebral haemorrhage and renal failure. These events can lead to further morbidity and mortality. Treating hypertension pre-operatively is vital in an attempt to prevent potential devastating consequences.
Ideally, hypertensive patients should have their blood pressure controlled prior to anaesthesia. A pre-assessment diastolic blood pressure of greater than 110mmHg warrants attempts at reduction with anti-hypertensive medications before elective surgery. However, in some patients it will not always be possible to have their severe pre-operative hypertension brought under control before surgery and it is recognised that these patients are more at risk of peri- and post-operative complications.

Since some anti-hypertensive medications, such as ACE inhibitors, can interact with anaesthetic agents careful planning is necessary to ensure patient safety. It is routine practice that all patients undergoing any type of anaesthesia have intravenous (IV) access. Due to the large amounts of subcutaneous fat found in obese patients IV access is often more challenging.

**Pharmacokinetics**

Morbid obesity can affect the volume of distribution, clearance and half-life of drugs. Thus, caution must be taken with drug dosing (including anaesthetic agents) in obese patients. The main issue is whether total body weight (TBW) or ideal body weight (IBW) should be used to calculate drug dosage. An important point to remember is that obese patients have more adipose tissue but their lean tissue is normally unaltered. Generally speaking hydrophilic drugs are mainly distributed within lean body tissues, i.e. volume of distribution is unaltered in obese patients, with clearance usually unchanged or even decreased. Hence, IBW should be used to calculate the drug dosage of hydrophilic drugs. Conversely, lipophilic drugs are distributed equally in both lean and fat tissues so that there is an increased volume of distribution and clearance in obese patients. Thus TBW should be used to calculate the drug dosage of lipophilic drugs. It is essential to remember that other pharmacodynamic features also play a role and that these rules are not applicable to all drugs. For example, as obese patients are more sensitive to Thiopental a commonly used lipophilic induction agent and the calculated dosage based on TBW should be reduced.

**Other Practical Issues**

Some other practical issues to consider in obese patients undergoing anaesthesia are discussed below.

Patients requiring surgery need to be transferred from their hospital bed to a trolley and then to the theatre table and back again. Due to the greater weight and size of obese patients, these transfers are more difficult than in leaner patients and may predispose to patient or staff injury. One solution would be to anaesthetise such a patient on the operating table enabling them to help with prior transfers. Alternatively, the use of a transfer device could be considered. Another consideration is whether the operating table is able to sustain the patient’s weight and accommodate their width. Furthermore, obese patients are more susceptible than leaner individuals to develop pressure sores if lying in the one position for a long time. This is of particular importance when anaesthetised for a long time. It is thought that pressure sores arise from cell death of inadequately perfused skin with consequent breakdown of the skin to form an open sore. Adipose tissue is poorly
vascularised and obese individuals are therefore at increased risk of this complication. In an attempt to reduce this risk a few practical actions can be done: periodical repositioning of patient, foam wedges, foam mattress and ensuring the patient is lying on a smooth surface.\(^{33}\)

**Case Study Patient Experience**

It was felt that the associated risks with a GA were considerable and that a spinal anaesthetic (spinal) was safer. However, his spinal anaesthetic was still somewhat complicated due to his obesity as this led to difficulties in positioning him for the administration of the spinal anaesthetic. In an attempt to widen the intervertebral space two positions can be utilised. In one, the patient sits up and leans forward with their legs out straight and chin on their chest. In the second, the patient lies on one side bringing their knees towards their chest. Excess fat tissue in obese patients makes locating the posterior midline somewhat difficult in the second position so that a sitting up position was used in this case. Bony landmarks are then used to locate the correct entry site (L3/L4 or L4/L5, below the level of the spinal cord) for the spinal needle. The iliac crests are used as a guide for the level of the L4 vertebral body and the spinous processes as a guide for the intervertebral space. Given the large amounts of subcutaneous fat, the iliac crests and the spinous processes were difficult to palpate making the correct entry site difficult to establish. Nevertheless, this was carried out as best as possible. The introducer was the next potential problem. It is meant to sit in the skin, subcutaneous fat, supraspinous ligament, interspinous ligament and the ligamentum flavum. However, there was concern that the large amounts of subcutaneous fat would prevent the short introducer from reaching as far as the ligamentum flavum. Fortunately its length was adequate. If it had been too short a longer epidural needle would have been used in place of the introducer.\(^{34}\) Dosing alterations must also be considered for spinal anaesthesia in obese patients as this patient group have smaller volumes of cerebral spinal fluid and thus require less anaesthetic agent(s) to achieve the same level of blockade.\(^{35}\)

**Summary**

With an increasing obese population it is important that anaesthetists remain alert to the implications of anatomical and physiological differences and associated co-morbidities on anaesthesia. Where practical the consideration and use of non-GA methods may be the safer and hence preferred option but as in this case, even these are not without their own challenges.

**References**


**Post-Operative Nausea & Vomiting - Use of Anti-Emetic Agents in Anaesthesia**

Catriona Rother (4th Year MBChB, BMSc) University of Dundee

Correspondence to: C.Rother@dundee.ac.uk

**ABSTRACT**

Post-operative nausea and vomiting (PONV) is a recurrent problem in the field of anaesthetics. It is usually defined as nausea, retching or vomiting within 24 hours of surgery and affects 20-30% of patients. Although often considered merely an unpleasant side effect of general anaesthesia or surgery, PONV can result in many unwanted and potentially serious outcomes and increases healthcare expenditure considerably.

**Background**

Post-operative nausea and vomiting (PONV) usually defined as nausea, retching or vomiting within 24 hours of surgery and affects 20-30% of patients. PONV is an important problem and can lead to potentially serious outcomes and an increase healthcare expenditure. Post-operative nausea and vomiting increases recovery room time, requiring expanded levels of nursing care, and delays mobilisation following surgery as movement often exacerbates PONV. As a result, the early discharge of ambulatory surgery patients is frequently delayed, with around 1% requiring overnight admission.

Persistent vomiting can result in dehydration, electrolyte imbalance and metabolic alkalosis. The oral administration of drugs, nutrition and fluids may also be delayed and the level of post-operative analgesia that can be obtained may be limited if effective doses of opiate cannot be administered orally. Vomiting also increases the risk of oesophageal perforation, bleeding and pulmonary aspiration whilst the increased abdominal pressure during emesis may cause tension on suture lines resulting in incisional hernias. An equally important issue surrounding PONV is the high level of patient dissatisfaction and discomfort. Research has shown that nausea and vomiting are feared far more in comparison to post-operative pain, and PONV is ranked as a major concern by the most surgical patients. Thus, it is important to consider the physiology, prevention and treatment of emesis as well as the risk factors that make PONV more common. The following is a short case study included to demonstrate the ways in which a patient’s risk of PONV can be calculated and reduced.
Case Study: Patient A Case Background

Patient A is an 81-year-old gentleman, undergoing a sigmoid colectomy to treat colorectal cancer. He has no history of motion sickness and has had 2 previous anaesthetics without complication. He is otherwise well and takes no regular medications. Patient A stopped smoking over 30 years ago.

The operation is carried out using a midline laparotomy and lasts approximately 4 hours. Total intravenous anaesthesia (TIVA) is used with Propofol administered for both induction and maintenance of anaesthesia. Remifentanil, a short-acting opioid, is administered alongside TIVA and Patient A is also given a thoracic epidural, which should provide extremely effective pain relief for 48-72 hours post-operatively.

Risk Factors for PONV

There are several factors that increase the likelihood of PONV. These factors can generally be separated into patient factors, surgical factors and pharmacological factors.

patient factors increasing the risk of PONV:

• Female gender (especially if menstruating or pregnant)\textsuperscript{3, 4, 11}
• Previous history of PONV\textsuperscript{3, 4}
• Previous history of motion sickness\textsuperscript{3, 4}
• Non-smoking status\textsuperscript{3, 4}
• Age (young children are most at risk of PONV, although this risk decreases with puberty)\textsuperscript{10}

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<th>Case Study: Patient A [Patient Hx]</th>
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<td>Smoking appears to be protective so Patient A’s non-smoking status places him at an increased risk of suffering from PONV.</td>
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Surgical factors increasing the risk of PONV:

• Surgeries associated with increased risk of PONV:
  o Laparoscopy
  o Laparotomy
  o ENT surgery
  o Neurological surgery
  o Breast surgery
  o Gynaecological surgery\textsuperscript{4}

Duration of surgery (the risk of PONV increases with the length of the surgical procedure)\textsuperscript{4}
Case Study: Patient A [Surgery]

The midline laparotomy used in Patient A’s operation stimulates the vagus nerve, which can produce emetogenic effects. The surgery also lasted approximately 4 hours, further increasing the risk of PONV.

**PHARMACOLOGICAL FACTORS INCREASING THE RISK OF PONV:**

- Anaesthetic techniques associated with increased risk of PONV:
  - General anaesthesia (increases the risk of PONV 11-fold compared to regional anaesthesia)\(^4\)
  - Use of volatile anaesthetic agents
  - Use of nitrous oxide
  - Use of reversal agents eg. Neostigmine
  - Use of opioids either intra- or post-operatively\(^8\)

Case Study: Patient A [Pharmacology]

Unfortunately, in the case of Patient A, regional anaesthesia cannot be used. Instead, total intravenous anaesthesia was used with Propofol administered for both induction and maintenance of anaesthesia. Generally, this approach results in a reduced ‘hangover effect’ and less post-operative nausea than maintaining anaesthesia with volatile agents or nitrous oxide.\(^5\)

Patient A was given a single bolus of the muscle relaxant Rocuronium at the beginning of the surgery. As the surgery lasts approximately 4 hours, however, it was decided that no reversal agents were required and so the emetic effect of Neostigmine was avoided.

Pain is a very common cause of emesis.\(^12\) For this reason, effective pain relief is vital in preventing PONV. Narcotic analgesics such as morphine, however, decrease gut motility and often lead to constipation and nausea.\(^7\) The emetic effect of these drugs can be minimised with the use of short-acting opioid drugs\(^6\) such as Remifentanil, used in the case of Patient A. As mentioned previously, Patient A was also given a thoracic epidural to combat post-operative pain.

**OTHER FACTORS INCREASING THE RISK OF PONV:**

- Inexperienced anaesthetic technique\(^9\) e.g. Poor bag and mask ventilation may cause gastric distension and subsequent nausea.
- Poor hydration during or immediately following surgery\(^4\)
- Intra-operative hypotension\(^4\)
- Patient stress/anxiety\(^5\)
### Case Study: Patient A [Other Factors]

Throughout the surgery, Patient A was kept well hydrated with 3 litres of Hartmann’s solution and 500mls of Gelofusine. He was kept well oxygenated which has been shown to reduce from the probability of PONV by 50%. Hypotension was also avoided using Metaraminol and Ephedrine.

It has been suggested that a patient may be less likely to experience PONV if they are calm prior to surgery and well informed regarding what to expect post-operatively. Patient A was not particularly anxious prior to surgery. The operation was explained well and he was aware of the potential complications that could arise in the post-operative period.

### Case Study: Calculating the Risk of PONV for Patient A

It is important to identify any factors that increase the likelihood of PONV in order to attempt to reduce a patient’s baseline risk. There are many different tools that can be used to quantify this risk such as the Apfel scoring system where each additional risk factor increases a patient’s risk of PONV by 20%. The sensitivity and specificity of these scoring systems, however, is generally only around 70% so it remains fairly difficult to predict with any great certainty which patients will be affected. It is useful to determine those at a higher risk of PONV, as this can be used to decide which patients will benefit from prophylaxis and reduces the risk of medication side effects and costs for those that are unlikely to benefit. The relative indication for prophylaxis increases with the number of risk factors.

Patient A was determined as having a mild risk of suffering from PONV. Intraoperatively, Granisetron was administered around 30 minutes prior to the surgical closure of the abdomen. Cyclizine was prescribed for the recovery room and both Cyclizine and Ondansetron were prescribed for the ward to be administered on an ‘as required’ basis.

### Physiology of Nausea and Vomiting

Before the pharmacology of anti-emetic drugs can be considered an understanding of the physiology and aetiology of nausea and vomiting is required. Emesis or vomiting is defined as ‘the reflex action of ejecting the contents of the stomach through the mouth’. It is controlled by a group of closely related nuclei in the brainstem termed the ‘vomiting centre’ that is rich in dopaminergic, histamine, 5-hydroxytryptamine, neurokinin and muscarinic cholinergic receptors. When the vomiting centre is stimulated, a complex series of neural impulses coordinates the simultaneous relaxation of the gastric muscles and contraction of the abdominal muscles and diaphragm, expelling vomit from the stomach. Nausea, often the precursor to vomiting, is triggered by a low level of the same stimuli responsible for the vomiting reflex but the exact mechanism underlying the sensation of nausea is unclear. It is often accompanied by salivation, sweating and pallor.

The ‘vomiting centre’, located in the lateral reticular formation of the medulla and receives input from a wide variety of afferent sources. Input from mechanoreceptors and chemoreceptors in the GI tract is carried via the vagus nerve, involving 5HT and...
dopamine receptors. Other inputs include those from the vestibular system, the cardiovascular system, the pharynx and more complex stimuli from higher cortical centres responding to pain, fear and anxiety.

There is also input from an area known as the ‘chemoreceptor trigger zone’ or CTZ. This is located in the area postrema of the medulla and is very sensitive to emetic stimuli, with abundant 5HT and dopaminergic receptors. It responds to toxins in both the blood and cerebrospinal fluid, and communicates with the vomiting centre.

Many different types of surgery stimulate the vomiting centre as do various perioperative drug types and anaesthetic agents, explaining why nausea and vomiting are such common complaints following surgery. The vomiting centre integrates these various inputs and then coordinates the efferent branches of cranial nerves V, VII, IX and X and organises the muscular contractions and cardiovascular responses used during emesis. Figure 1 demonstrates the afferent inputs to the vomiting centre and the site of action of some anti-emetic drugs.

Figure 1: Adapted from Pleuvry BJ. Physiology and pharmacology of nausea and vomiting.

<table>
<thead>
<tr>
<th>Receptor Types</th>
<th>Arrow Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine 1 (H1)</td>
<td>Small [site of drug action]</td>
</tr>
<tr>
<td>Muscarinic (Ach)</td>
<td>Large [Neuronal Pathway]</td>
</tr>
<tr>
<td>Dopamine 2 (D2)</td>
<td></td>
</tr>
<tr>
<td>Neurokinin (NK-1)</td>
<td></td>
</tr>
<tr>
<td>5-Hydroxytryptamine 3 (5-HT3)</td>
<td></td>
</tr>
</tbody>
</table>

Management of PONV

It is generally an easier task to prevent nausea and vomiting than to treat it. Antiemetics used in anaesthesia can generally be thought of as those prescribed for prophylaxis and those prescribed for ‘rescue’, or to treat PONV.
Prophylactic anti-emetics are usually prescribed following departmental guidelines and protocols, depending on a patient’s risk of sickness following surgery. Prophylactic anti-emetics are rarely warranted in low risk patients. Moderately risk patients may benefit from treatment with a single anti-emetic. If a patient is at high risk of suffering from PONV or if vomiting would be particularly problematic, for example, in patients with raised intracranial pressure or wired jaws, combination therapy is often used. Neurotransmitters implicated in the control of nausea and vomiting include acetylcholine, dopamine and 5-HT. Anti-emetics generally act as antagonists to one or more of these neurotransmitters and many act via more than one mechanism. Using a combination of different anti-emetics that work via different neurotransmitters gives an additive or synergistic effect.

Rescue therapy is indicated for patients in whom prophylaxis has failed and should be administered as soon as signs of nausea or vomiting occur with the prescribed drug being from a different class to the failed prophylactic drug. If there is no improvement in symptoms within 30 minutes, treatment should proceed to the next line of therapy. The commonly used drugs in the management of PONV are indicated in Table 1.

Due to the wide variety of different neurotransmitters involved in emesis, it is difficult to say which class of anti-emetic agents are most effective, as no one anti-emetic will treat PONV for all patients. Most comparative studies have shown very similar efficacies between different anti-emetics, though their side effect profile and cost differ. One trial suggests that Ondansetron, Droperidol and Dexamethasone all reduce the risk of PONV by approximately 26%. 5HT₃ receptor antagonists and Dexamethasone are currently considered the most effective first-line prophylactic agents due to their favourable side effect profile and relative safety.

**Non-Pharmacological treatment options**

Non-pharmacological treatments can also be used in the management of PONV. These methods are required prior to surgery and have been shown to be very effective in some patients. Examples of non-pharmacological treatments include:

- Acupuncture
- Acupressure
- TENS machine treatment
- Hypnosis

It should be noted that in patients with prolonged vomiting or who do not respond to combined rescue therapy, it is important to consider alternative causes of PONV. These could include complications of surgery, hypotension or hypoxaemia or other more sinister underlying problems that are being overlooked, such as intestinal obstruction.
### Table 1- Commonly used drugs in the management of PONV

<table>
<thead>
<tr>
<th>Drug Class examples</th>
<th>Mechanism &amp; Site of Action</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **5HT₃ receptor antagonists**  
Ondansetron, Granisetron | Selectively antagonise 5HT₃ receptors<br>- Centrally at the chemoreceptor trigger zone<br>- Peripherally in the GI tract | Favourable side effect profile.  
Headache.  
Light-headedness.  
Constipation. | Shown to reduce PONV by 26%.<sup>3</sup>  
Target vomiting more specifically than nausea.<sup>6</sup>  
Not associated with extra-pyramidal side effects, excessive sedation or prolonged recovery from anaesthesia and are thus useful for day surgery patients.<sup>3</sup>  
Work best when administered towards the end of surgery.<sup>6,8</sup> |
| **Antihistamines**  
Cyclizine, Promethazine | Block histamine receptors in the vomiting centre.<sup>8</sup>  
Also have anticholinergic properties and block muscarinic receptors.<sup>3</sup> | Dry mouth.  
Sedation.<sup>5</sup> | Cyclizine has been shown to reduce post operative vomiting by 21%.<sup>15</sup>  
Less useful in day surgery patients due to sedative effects.<sup>3</sup> |
| **Butyrophenones**  
Droperidol | Antagonise dopamine and alpha-adrenergic receptors.<sup>5</sup> | Vasodilatation.  
Hypotension.  
Sedation.  
Restlessness.  
Nightmares.<sup>5</sup>  
Prolonged QT interval if given orally.<sup>11</sup> | Droperidol reduces PONV by 24.5%.<sup>4</sup>  
Protects predominantly against nausea (in contrast to 5HT₃ antagonists and often used in combination with these drugs for their additive effect).<sup>4</sup> |
| **Steroids**  
Dexamethasone | Have been shown to be anti-emetic  
Mode of action is unclear.<sup>8</sup> | Favourable side effect profile.  
GI upset.<sup>8</sup> | Reduces risk of PONV by 26.4%.<sup>3</sup>  
Most effective when prescribed prior to induction.<sup>4,8</sup>  
Also effective treatment for nausea and vomiting related to chemotherapy.<sup>2</sup> |
| **Dopamine Antagonists**  
Metoclopramide, Prochlorperazine, Haloperidol | Non-selective antagonism of dopamine receptors (explains poor side effect profile)<sup>11</sup> | Extra-pyramidal motor disturbances.  
Dizziness.  
Xerostomia.  
Sedation.<sup>11</sup> | These older anti-emetics are now used less frequently due to their extra-pyramidal side effects.  
Metoclopramide has been shown to provide no clinically relevant decrease in PONV risk.<sup>16</sup> |
Conclusion

In conclusion, PONV is a continuing problem. Although there are many available antiemetic drugs that can be used to prevent or to treat patients symptoms, no one drug has been proven to be particularly superior to any other, and PONV often persists despite maximal therapy. Simple strategies such as good intravenous hydration, adequate oxygenation and the avoidance of hypotension should not be underestimated and each patient should be considered individually as PONV is notoriously difficult to predict.

Key messages

| • Calculate a patient’s baseline risk of PONV. |
| • Adjust the anaesthetic plan to reduce this risk where possible as this helps avoid unnecessary prescribing and costs. ² |
| • No anti-emetic prophylaxis is recommended for patients at low risk of PONV. |
| • Monotherapy or combination therapy should be used for patients at moderate risk. |
| • Double or triple combination therapy may be needed for patients at high risk. |
| • Rescue therapy drugs should be of a different class to those used for prophylaxis. |

References

Acute Mountain Sickness

Tim Gomersall (2nd Year MBChB) University of Dundee

Correspondence to: T.Gomersall@dundee.ac.uk

ABSTRACT

Acute Mountain Sickness (AMS) is a condition that can affect people ascending to higher altitudes. The aim of this review is to provide a brief overview of AMS to introduce medical students to the highly complex and interesting scenario involving the treatment of a patient at altitude. AMS presents with a number of symptoms including headaches, nausea and disturbed sleep. As the condition progresses it can lead to serious complications including both pulmonary and cerebral oedema and ultimately death. At altitude it can be both dangerous and problematic to treat and evacuation is usually a patient’s best option. As well as addressing the common presentation and treatment of AMS there are a number of ethical considerations created by such a unique environment.

Introduction

Tens of thousands of people are attracted to high altitude environments around the world every year either to experience a unique landscape or to revel in the satisfaction of a successful summit attempt. Doctors working in or around these locations will encounter altitude illness in a variety of forms. Indeed as mountaineering, skiing and rock climbing continue to be popular activities the prevalence of AMS remains at a high level. Maggiorini et al studying climbers in the Swiss Alps found that at 3650m 34% of the climbers presented with three or more symptoms and signs of AMS. Although the focus of this review is AMS, patients in a high altitude and/or mountain environment may require care for various other potentially serious illnesses including hypothermia, frostbite, dehydration, snow blindness and trauma.

High altitude is an environment lacking in oxygen. Although the concentration of oxygen remains constant well beyond the height of Mt. Everest, the partial pressure of oxygen decreases at a rate proportional to the drop in barometric pressure. The barometric pressure at the height of Mt. Everest, 8848m, is a third of that at sea level and consequently the air contains only a third as much oxygen. Too rapid an ascent is very dangerous and is the main cause behind altitude illness. A period of acclimatisation is required to develop physiological adaptations that help the body to cope with a high altitude environment and give us the best chance of preventing altitude illness.
There are acclimatisation limits to the human body and even the best acclimatisers cannot endure the extreme hypoxia of high altitude for long. The loss of appetite at even a modest altitude, the increasing fatigue on ascent and the delirium resulting from lack of oxygenation of the brain tissue all have a debilitating effect on the body. The cumulative effect of oxygen debt means that permanent habitation at extreme altitude is impossible, and climbers refer to areas over 8,000m as the Death Zone for good reason.

The physiological adaptation to high altitude, or acclimatisation, takes place by a number of processes within the body. Although some of these adaptations take place at a biochemical level shortly after the initial exposure to altitude, a number of ‘struggle’ responses, including the hypoxic ventilatory response and an increase in cardiac output, are the most important during early acclimatisation. The hypoxic ventilatory response is an increase in depth and rate of inhalation in response to a decrease in the oxygen saturation of the blood. This is detected by the carotid body and the medulla effects these changes. The increased level of ventilation leads to an increase in blood pH, known as respiratory alkalosis and a reduction in the carbon dioxide content of the blood. The respiratory alkalosis slows the initial hyperventilation as the body does not tolerate the alkalosis. The respiratory alkalosis results in a compensatory increase in renal excretion of bicarbonate and the pH returns towards normal enabling ventilation to further increase. This process that maximises ventilation is referred to as ventilatory acclimatisation and takes between 4 and 7 days at a given altitude. There are a number of other physiological processes involved in acclimatisation including the production of erythropoietin and changes to the pulmonary and cerebral circulations but these are outwith the scope of this article.

**Acute Mountain Sickness (AMS)**

Although it is well known that AMS is caused by hypobaric hypoxia the exact mechanism that results in the illness is unclear although the main risk factor is a rapid rate of ascent. A popular theory is that AMS is a subclinical high altitude cerebral oedema. The brain increases in size in all people ascending to altitude. The increase in cerebral blood flow and resulting increase in blood volume and intracranial pressure could provide explanation for the symptoms of mild AMS. In severe AMS and high altitude cerebral oedema (HACO) there is a leaky barrier between the blood and the brain, a result of increased vascular permeability as a physiological response to the hypoxia. The increased endothelial permeability is secondary to chemical mediators in the blood and allows fluid to move between compartments and accumulate in areas where it should not be. Intracranial pressure increases and presents with progressively worsening neurological symptoms varying in severity from disorientation to loss of memory, hallucinations and finally coma.

The pulmonary form of high altitude sickness (HAPO) arises from regional pressure differences of the vascular bed within the lungs. The areas of vasoconstriction resulting from a maladaptive response to the hypoxia produce areas of high pressure
within the blood vessels\textsuperscript{8}. The high pressure within the capillaries results in a vascular leak into the alveoli and leads to pulmonary oedema.

The two most important risk factors for AMS are a high rate of ascent and a high sleeping altitude. Deficient or excessive physiological adaptations to altitude also predispose the patient to illness. These include excessive pulmonary vasoconstriction or too dramatic an increase in cerebral blood flow. It has been well documented\textsuperscript{7} that age, sex, previous exposure and physical fitness have no significant effect on the likelihood of an individual to develop AMS. However, previous long-term exposure, such as living at an intermediate altitude, bestows the individual with a greater ability to acclimatise to more extreme altitudes.

**Clinical presentation of AMS**

Headaches are the most common feature of AMS. These may or may not present with:

- gastrointestinal upset including nausea, vomiting and loss of appetite
- fatigue
- dizziness
- insomnia

Fluid retention is a classical sign of AMS, as opposed to the usual diuresis associated with acclimatisation, and may present with oliguria as well as peripheral and facial oedema\textsuperscript{2}. As the AMS worsens the patient will suffer from increasingly severe headaches\textsuperscript{6}. Severe AMS is an increase in the severity of the above symptoms along with continuing decline in mental status. This commonly presents as an inability to conduct coordinated movements and loss of mental function\textsuperscript{10}. Cerebral oedema leads to a further decrease in mental function (commonly ataxia, stupor and third and sixth cranial nerve palsies resulting from compression of brain structures because of raised intracranial pressure\textsuperscript{2}) and if left untreated can result in coma. Comatose patients require additional care such as airway management and bladder drainage. Pulmonary oedema commonly presents with several of the following symptoms and signs:

- Shortness of breath at rest
- Productive cough
- Decreased exercise tolerance
- Chest tightness
- Crackles or wheezing
- Central cyanosis
- Tachypnoea
- Tachycardia

Pulse oximetry provides a useful diagnostic tool for HAPO though the normal ranges are highly dependent on altitude and are much lower than the normal range at sea level. However oxygen saturations significantly lower than 75% at altitudes above 5500m are usually diagnostic of HAPO\textsuperscript{10}.
Management of AMS

Prevention is always better than cure in AMS and risk factors must be carefully managed. One of the worst things any climber can do is ascend too rapidly without allowing their body time to acclimatise.

The only real cure for AMS is descent or acclimatisation. Mild AMS is usually self-resolving and the patient should recover given an extra 12 to 36 hours in which to acclimatise whilst ascent is halted. Acetazolamide is known to be effective in speeding acclimatisation and studies have shown it to be useful prophylactically. The drug acts by stimulating ventilatory acclimatisation. A bicarbonate diuresis is induced thereby acidifying the blood and stimulating ventilation. As the patient acclimatises the symptoms will resolve. Peripheral paraesthesia and altered taste are common though benign side effects but resolve when the medication is stopped.

In moderate to severe AMS immediate descent is required along with low flow oxygen if available. Acetazolamide and/or dexamethasone should be given. Dexamethasone is a glucocorticoid, commonly used to combat inflammation and is successful in treating the vasogenic oedema responsible for severe AMS and HACO. The drug acts to stabilise the blood brain barrier and reducing the leakiness of the vessels. The use of acetazolamide to accelerate acclimatisation and a brief course of dexamethasone to treat AMS can be a successful combination. The treatment of HACO is the same as for severe AMS: oxygen, descent and dexamethasone. HACO is a life threatening condition and can result in death within hours if the patient does not descend. A rapid descent can be life saving and delay can result in a slightly confused, ataxic patient becoming comatose and unable to walk at all.

As acetazolamide acts by accelerating acclimatisation there is no risk of masking serious symptoms and as such patients can continue to ascend whilst on the drug after ensuring they are symptom free. It does not prevent worsening illness if the patient continues to ascend while symptoms are present. However dexamethasone treats the pathology and so patients should not continue to climb until they are symptom free off the steroid. Dexamethasone should never be taken during ascent, it does not promote acclimatisation and rebound symptoms can occur when it is discontinued.

In a situation where descent is impossible a hyperbaric bag can be used to simulate descent. This is a portable person sized bag that is pressurised using a foot pump. It simulates the conditions of lower altitude in order to buy time until descent or treatment becomes available. A combination of simulated descent and dexamethasone is the treatment of choice in a situation where the patient cannot be transported to a lower altitude. Immediate descent and oxygen is the optimal treatment in pulmonary oedema at altitude. As for AMS and HACO the hyperbaric bag can be a useful addition when immediate descent is not possible.
Ethical considerations

Denial of symptoms is extremely common among climbers who have invested a large amount of money and time in their pursuit. The possibility of not succeeding is always hard to accept on a once in a lifetime trip to climb any of the big mountains. This can result in other climber’s lives being put at risk and it is the doctor’s responsibility to detect symptoms early and prevent severe illness if possible. However a balance between patient-doctor confidentiality and group safety must be sought. Certainly the climber in question should be consulted before anyone else is notified.

The high altitude environment is not easily accessible to other doctors or medical supplies and many mountain teams are without a doctor. This presents issues in terms of medical resource allocation. A doctor should never refuse to treat someone, but resources must also be used in the most efficient way.

There are a number of ethical pressures exerted upon climbers by the mountaineering community itself. Although the use of bottled oxygen is commonplace at high altitude a core group of climbers would possibly view bottled oxygen as ‘cheating’ and would most definitely think of prophylactic acetazolamide in the same manner. A climber using prophylactic medication would definitely be viewed negatively alongside one who was not.

Conclusion

Acute mountain sickness can be life threatening if not managed carefully. However by ensuring climbers are aware of the risks and consequences and providing treatment when necessary, dangers can be mitigated and climbers protected. Even with the implementation of these measures the high altitude environment is extremely dangerous. The hypoxia, low temperatures and dangerous surroundings all endanger the lives of mountaineers. However climbers continue to expose themselves to these risks. Whether this be for personal achievement, respect or for a host of other reasons known only to the individual, people will always strive to perform at and beyond the limit of their capabilities and doctors will continue to have a place in the provision of care at altitude.

References

The Accuracy of Fine Needle Aspiration at Identifying Thyroid Malignancy in Tayside
Rachael Allan (5th Year MBChB) University of Dundee

Correspondence to: R.E.Allan@dundee.ac.uk

ABSTRACT

Introduction

Thyroid lumps are common with up to 8% of the adult population having a palpable lump and up to 70% having an incidental nodule found on ultrasound. Although most thyroid nodules are benign, a significant number are malignant and therefore need to be investigated thoroughly using fine needle aspiration (FNA) +/- ultrasound.

Methods

This study aims to compare FNA results to histological findings after excision to ascertain the accuracy of FNA diagnosis in NHS Tayside. Included in the study were all patients who had undergone surgery to remove their thyroid nodule in Tayside between 2003 and 2011 after being investigated using FNA (n=273).

Results

119 patients had benign results on FNA with 16 of these found to be malignant on histology after excision. This gives a false negative rate of 13%. 14 patients had malignant results on FNA with all of these found to be malignant on histology after excision, giving a false positive rate of 0%. All other FNA results were either non-diagnostic or borderline. The sensitivity and specificity of FNA was therefore found to be 100% and 30% respectively.

Conclusion

In Tayside, FNA is accurate at predicting malignancy but has a high false negative rate when predicting benign nodules.
Background

Thyroid lumps are common with as much as 8% of the adult population having a palpable lump\(^1\) and up to 70% having an incidental nodule found on ultrasound.\(^2\) In Tayside, all thyroid nodules requiring secondary care are referred to Ninewells Hospital, Dundee and may be seen by an Endocrinologist, General Surgeon or Otolaryngologist (ENT).

Most thyroid nodules are benign with Deandrea et al\(^3\) reporting 33% malignancy for a solitary nodule and 22% for a dominant nodule in a multinodular goitre. Therefore, urgent referral is not required unless there are worrying features present. Worrying features as indicated by the British Thyroid Association\(^4\) include:

- Family history of thyroid cancer
- History of previous irradiation or exposure to high environmental radiation
- Child with a thyroid nodule
- Unexplained hoarseness or stridor associated with goitre
- Painless thyroid mass enlarging rapidly over a few weeks
- Palpable cervical lymphadenopathy
- Insidious or persistent pain lasting for several weeks.

Patients with none of these red flag symptoms should be seen in a specialist thyroid clinic within 4 weeks of referral for assessment, patients with these symptoms should be seen within 2 weeks and patients complaining of stridor should be seen urgently on the same day.\(^3\)

Assessment of a Thyroid Lump

Assessment of a thyroid lump begins with a detailed history and clinical examination which should include the thyroid, surrounding lymph nodes in the neck and a systemic examination.\(^1\) Patients should have their Thyroid Function Tests (TFTs) checked;\(^3,4\) Thyroid Stimulating Hormone (TSH), Thyroxine (T4) and Triiodothyronine (T3). These can be assessed in General Practice. If the results show hyperthyroidism, the patient should be referred to Endocrinology for assessment. All patients with thyroid lumps are then assessed using Ultrasound +/- Fine Needle Aspiration (FNA) to assess the risk of malignancy and determine whether or not surgery is appropriate.\(^1,3,5-7\)

Fine Needle Aspiration [FNA]

FNA may be carried out by a surgeon, cytopathologist, endocrinologist, radiologist or an oncologist provided they have adequate training and experience and have continued to practice their skills.\(^3,8-10\) FNA is performed using a 25 gauge needle which is passed into the nodule under aseptic conditions. The needle is then rotated and fluid aspirated if present. The sample can then be sent to pathology for assessment using either a liquid medium or smeared on glass slides.\(^11\) The results are
reported using the following diagnostic categories as stated in the British Thyroid Association’s Guideline on the Management of Thyroid Cancer:

• **Thy1 – Non Diagnostic**
  Non-diagnostic (inadequate or where technical artefact precludes interpretation; adequate smears usually contain six or more groups of over 10 thyroid follicular cells, but the balance between cellularity and colloid is more important).

• **Thy2 – Non Neoplastic**
  Non-neoplastic (with the descriptive report documenting the features consistent with a colloid nodule or thyroiditis). Cysts may be classified as Thy2 if benign epithelial cells are present.

• **Thy3 – Follicular lesion; suspected follicular neoplasm; worrying features (indeterminate)**
  (i) Follicular lesion/suspected follicular neoplasm. While some of these will be tumours, many will be shown to be hyperplastic nodules on surgical excision. The descriptive text will indicate the level of suspicion of neoplasia.
  (ii) There may be a very small number of other cases where the cytological findings warrant inclusion in this category rather than Thy2 or Thy4 (eg worrying features but cells too scanty to qualify for Thy4, repeat FNAC advised). The text of the report should indicate the worrying findings.

• **Thy4 – Suspicious of Malignancy**
  Suspicious of malignancy (suspicious, but not diagnostic, of papillary, medullary or anaplastic carcinoma, or lymphoma).

• **Thy5 – Diagnostic of Malignancy**
  Diagnostic of malignancy (unequivocal features of papillary, medullary or anaplastic carcinoma, lymphoma or metastatic tumour).

In Tayside, thyroid lumps are investigated and managed using the Nodular Thyroid Disease with normal TSH protocol. This protocol is outlined in Figure 1.

**Aims of Research**

This project compared individual thyroid FNA sub-categories (Thy 1, Thy 2 etc) outcome to histological findings post surgery to ascertain accuracy of FNA diagnosis in NHS Tayside. Results will then be compared with that reported in the literature.

**Methods**

Approval for this project was granted by the NHS Tayside Caldicott guardian and Data Protection. On submission of the Caldicott Guardian Approval the Pathology department at our institute provided a list of patients who had definitive histology.
on thyroid specimens sent between 2003 and 2011. This list contained the name of
the patient, CHI number, date of surgery and histology outcome. All identifiable data
was kept password protected throughout the project. Due to the nature of thyroid
surgery, some patients had more than one surgical procedure and hence there were
multiple entries in the database for those patients. For the purposes of this study
only the first surgical procedure resulting in definitive histological diagnosis was
included for each patient. The information was then used to construct a large
database of thyroid pathology in NHS Tayside using the following headings:

- Name of patient
- CHI number
- Date of Birth
- Ultrasound performed (yes/no)
- Size of single nodule (cm)
- Multinodular goitre present (yes/no)
- Size of dominant nodule in multinodular goitre (cm)
- Ultrasound guided fine needle aspiration (yes/no)
- Result of first FNA
- Result of repeat FNA
- Indication for surgery
- Date of operation
- Operation performed
- Surgeon
- Side of Operation
- Histological result
- Excision (Complete/Incomplete)

In addition to the information provided by pathology, information required to
complete the database was identified using the local Electronic Patient Record (EPR)
system by entering the patient’s CHI number and looking for the corresponding date
of surgery on pathology reports, FNA reports and radiology reports. Once the
database was complete the information was used to complete a study on FNA
results and thyroid malignancy rates in NHS Tayside. Included in this study were all
patients who had thyroid surgery for diagnostic reasons or as a consequence of
clinical requirement, for example acute airway compromise from a large goitre. From
the completed database the preoperative FNA results were identified and compared
to definitive histological diagnosis post surgery. Second FNA results where applicable
were also analysed.

**Results**

There were 598 patient entries on the database provided by the Tayside Pathology
department. After applying the process described in the method section 325
patients were identified. No patients were excluded.

273 of the 325 patients had FNA performed at least once. Table 1 is a summary of
the cytology result of the first FNA performed with percentages calculated (Table 1).
Table 1. Cytology result of first FNA performed with percentages calculated.

<table>
<thead>
<tr>
<th>Cytology result</th>
<th>Thy1</th>
<th>Thy2</th>
<th>Thy3</th>
<th>Thy4</th>
<th>Thy5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>69</td>
<td>119</td>
<td>71</td>
<td>7</td>
<td>7</td>
<td>273</td>
</tr>
<tr>
<td>Percentage of Patients (%)</td>
<td>25%</td>
<td>44%</td>
<td>26%</td>
<td>2.5%</td>
<td>2.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Of this group of patients that had first FNA cytology results of Thy 1, 2 or 3, 36% (n=93) went on to have a further FNA. Table 2 summarises the cytology results for this group.

Table 2. Number of patients who underwent a repeat FNA and corresponding cytology result with percentages calculated.

<table>
<thead>
<tr>
<th>Original FNA result (n=patient number)</th>
<th>Number of patients undergoing a second FNA</th>
<th>Percentage repeated (%)</th>
<th>Percentage (%) of patients with repeat FNA category of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thy1</td>
</tr>
<tr>
<td>Thy1 (n=69)</td>
<td>41</td>
<td>59%</td>
<td>49%</td>
</tr>
<tr>
<td>Thy2 (n=119)</td>
<td>37</td>
<td>31%</td>
<td>11%</td>
</tr>
<tr>
<td>Thy3 (n=71)</td>
<td>15</td>
<td>21%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Of the 325 patients included in the study, 90 were diagnosed with a thyroid malignancy. Of these 90 patients, 58 were female and 32 were male. Therefore, the male: female ratio of patients diagnosed with a thyroid malignancy in Tayside is 1: 2. The age range of patients diagnosed with malignancy was 17-91 and the average age 56. The number of patients diagnosed with each sub-type of thyroid malignancy was also extracted from the database and percentages calculated (Table 3).

Table 3. Percentage of patients diagnosed with each thyroid malignancy sub-type.

<table>
<thead>
<tr>
<th>Type of Thyroid Malignancy</th>
<th>Number of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic Carcinoma</td>
<td>7</td>
<td>8%</td>
</tr>
<tr>
<td>Follicular Carcinoma</td>
<td>12</td>
<td>13%</td>
</tr>
<tr>
<td>Hurthle Cell Carcinoma</td>
<td>4</td>
<td>4.5%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>8</td>
<td>9%</td>
</tr>
<tr>
<td>Medullary Carcinoma</td>
<td>4</td>
<td>4.5%</td>
</tr>
<tr>
<td>Papillary Carcinoma</td>
<td>50</td>
<td>56%</td>
</tr>
<tr>
<td>Poorly/undifferentiated Carcinoma</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 4 correlates the first FNA result with definitive histology post surgery with percentages displayed in the last column. The cytology result and corresponding histology result were used to calculate the following statistical values.

Of patients with an original FNA result of Thy2 the number of false negatives was 16 giving a false negative rate of 13% and a negative predictive value of 86%. Of patients with a FNA result of Thy4/5 the number of false positives was 0 giving a positive predictive value of 100%. Specificity of FNA was calculated as 100% and sensitivity as 30% using the first FNA result.

There were 25 patients with the original FNA outcome of Thy3 and definitive histology of thyroid malignancy. In 14 of these patients the cytopathology report states that the nodule is “probably benign” and in a further 10 that “further investigation is recommended.” Table 5 demonstrates the cytopathologist’s impression of the FNA sample.

Table 4. Cytology result of first FNA and corresponding histology result after excision.

<table>
<thead>
<tr>
<th>Original FNA result</th>
<th>Number of patients</th>
<th>Number malignant</th>
<th>% malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No FNA</td>
<td>52</td>
<td>14</td>
<td>27%</td>
</tr>
<tr>
<td>Thy1</td>
<td>69</td>
<td>21</td>
<td>30.4%</td>
</tr>
<tr>
<td>Thy2</td>
<td>119</td>
<td>16</td>
<td>13.4%</td>
</tr>
<tr>
<td>Thy3</td>
<td>71</td>
<td>25</td>
<td>35.2%</td>
</tr>
<tr>
<td>Thy4</td>
<td>7</td>
<td>7</td>
<td>100%</td>
</tr>
<tr>
<td>Thy5</td>
<td>7</td>
<td>7</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 5. Cytopathologist’s impression (as stated in Pathology report) of FNA Thy3 samples that were histologically found to be malignant (n=25).

<table>
<thead>
<tr>
<th>Cytopathologist’s Impression</th>
<th>Number of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probably Benign</td>
<td>14</td>
<td>56%</td>
</tr>
<tr>
<td>Further investigation</td>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstated</td>
<td>1</td>
<td>4%</td>
</tr>
</tbody>
</table>

Discussion

There were 325 patients included in this study all of whom presented to either Endocrinology or ENT with a thyroid lump that resulted in surgical excision. 273 of these patients were investigated using FNA +/- ultrasound scan - the gold standard for investigating thyroid nodules. 52 patients were not investigated using FNA before theatre due to a variety of reasons including worrying features on presentation such as stridor, metastases suggestive of a primary thyroid malignancy or indeed patient choice. That 14 of 52 (27%) of these patients had malignancy on histology is
concerning but for complete data on the indication for surgery in these patients, the patient notes would have to be retrieved which is outside the scope of this study.

Comparison of the FNA result with the histology result after excision showed 30% of Thy1 results, 13% of Thy2 results, 35% of Thy3 results and 100% of Thy4 and Thy5 results were malignant on histology. These results are interesting as current literature suggests that 9-12% of Thy1 nodules are malignant \(^7,^{12,13}\), in comparison to our study which found 30% of Thy1 results in Tayside to be malignant. This is significantly higher than current literature and may warrant further investigation.

13% of Thy2 results were proven to be malignant lesions on histology which shows there were a number of false negative FNA results. The false negative rate was found to be 13.4% (16 false negatives out of 119 samples), with a negative predictive value of 86%. Literature on this subject varies, with the false negative rate ranging from 4% to 21%.\(^2,^7,^{13,14}\) Ultrasound guided FNA has become common clinical practice in the 10-year period that this study has examined and it is therefore pertinent to assess whether or not this has caused a reduction in the number of false negatives. Thus, further studies examining the issues raised is advisable. The false negatives reported above cannot be commented on fully as these incorporate results from before and after the implementation of ultrasound guided FNA.

The study also shows that 35% of Thy3 nodules were malignant on histology which is in keeping with current literature.\(^7,^{15}\) Interestingly, of the 25 patients who had a FNA of Thy3 and were subsequently diagnosed with malignancy, 14 were stated as being “probably benign” in the cytopathologist’s report.

100% of Thy4 and Thy5 results were malignant on histology showing there were no false positive FNA results and therefore a positive predictive value of 100%. Literature suggests false positive rates of 0-28%.\(^7,^{14,16}\) The sensitivity of FNA in Tayside was shown to be 30% and the specificity was 100%. Literature suggests figures of 79-100% sensitivity\(^1,^{16-18}\) and 67-98.5% specificity\(^16-18\) for FNA.

Therefore, Tayside has a low sensitivity compared to other centres which may need to be looked at in future studies. In total 28% of all thyroid nodules removed were malignant. This is in keeping with current literature which suggests 33%.\(^3\) The most common sub-type of thyroid malignancy in Tayside is papillary carcinoma which accounted for 56% of all thyroid malignancies in this study. Other sub-types were much less common; 13% follicular, 9% lymphoma, 8% anaplastic, 4.5% Hurthle cell, 4.5% Medullary, 3% metastatic and 2% were undifferentiated.

The results also show that the non-diagnostic (Thy1) FNA rate in Tayside to be 25%. Current literature varies on this statistic with Yeung et al\(^1\) stating a non-diagnostic rate of 12% and Sellami et al\(^16\) stating 29-51% non-diagnostic samples between two different operators. Finally, this study showed that in Tayside females are twice as likely to develop a thyroid malignancy than males, with a male to female ratio of 1:2. This supports current consensus that females are more likely to get the malignancy
than males.\textsuperscript{14} The age range of patients in Tayside diagnosed with malignancy was found to be 17-91 with an average age of 56.

\textbf{Conclusion}

In Tayside, FNA is accurate at predicting malignancy in Thy4 and Thy5 sub-categories as all patients in these categories went on to be histologically diagnosed with a thyroid malignancy. The rate of malignancy in the Thy3 sub-category is in keeping with current literature however the rate of malignancy in the Thy2 sub-category is high with a false negative rate of 13\%. The rate of non-diagnostic (Thy1) samples in Tayside is also high (25\%) which needs to be investigated further. Future studies are required to investigate whether or not Tayside’s protocol of assessing thyroid nodules (Fig 1) is accurate enough at predicting which patients are at risk of thyroid malignancy. In order to comment on this, a study will need to be undertaken to look at FNA accuracy before and after ultrasound guidance was introduced as this will give a better picture of current accuracy.

\textbf{References}

4. British Thyroid Association, Royal College of Physicians. British Thyroid Association guidelines for the management of Thyroid Cancer. 2nd Ed.


