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Bloomfield A History 1812–2012

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The Quaker-founded hospital of Bloomfield deserves this celebration. When the founding committee began its deliberations, in 1807, the institutional treatment for those called lunatics was based on fear, and carried out with what looks very like cruelty. Patients were beaten, restrained with chains, heavily dosed with purgatives and emetics, repeatedly dunked in cold water, or pinned for hours with their hands shackled under their knees.

And then in the early 19th century the so-called moral treatment came to Ireland. Based on a model that had been in operation in York since 1792, the moral treatment replaced the assault by fear with an appeal to the patients' self-esteem. The new system eschewed drugs and corporal punishment and used restrain only to a minimum degree. Patients were well fed, entertained and allowed as much freedom as possible.

Bloomfield was an initiative of a group of Irish Quakers who between them subscribed over £3,600, of which £1,520 was used to buy Bloomfield House in Donnybrook from the Emmet family (they had bought it just before Robert's 1803 rebellion). The first patient entered on 16 March 1812. Bloomfield Retreat was never intended to be large—the initial planning envisioned only 12 patients at a time. In the first 50 years of operation some 127 patients were admitted, mostly single and under 40, and from a variety of backgrounds, including farmers, shopkeepers, lawyers and 'lady/gentleman'. In the unsophisticated nosology of the time no cause was assigned to 80 per cent of patients, baring 'mania' or melancholia.

By the end of the 19th century, with the acquisition of nearby Swanbrook the hospital had expanded considerably, and in the fifty years following 1913, a total of over 800 patients were treated. As a sign of the future, patients were getting progressively older.

However it was now clear that the moral treatment failed to cure. Medication began to be used, especially for violent patients. This included drugs such as laudanum, potassium bromide, cannabis, chloral and morphia. By the 1930s and 1940s other treatments such as ECT, insulin coma therapy and malaria treatment for GPI were available.

At the very end of the century it was clear that there was insufficient room to develop the hospital, and it was decided to build a new facility in Stocking Lane, Rathfarnham.

This elegant book is full of fascinating detail about the lives of the patients: what they ate, their entertainments, their jaunts and their crochets. It is based on the ample records of the managing committee of Quakers, and perhaps deals rather too fully with minutiae, but is overall a fine contribution to the field.

T Farmar is the author of 'Patients, Potions and Physicians — a Social History of Irish Medicine'.

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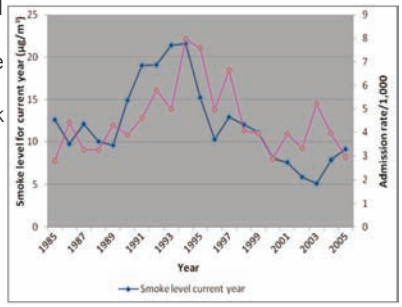
In this Month's IMJ

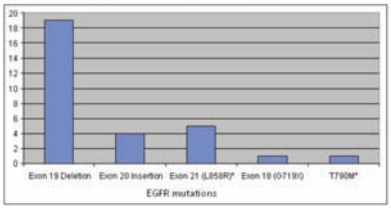
Acute childhood asthma in Galway city from 1985-2005: relationship to air pollution and climate: Loftus et al report on the patterns of hospital admissions for asthma over a 20-year period. The findings demonstrate an association between black smoke levels and hospital admissions. The authors conclude that regulatory changes for coal and diesel emissions have contributed to a reduction in admissions.



Epidermal Growth Factor Receptor (EGFR) mutation testing, from bench to practice: a single institute experience: Shikhrakab et al performed a study screening for EGFR mutations in lung adenocarcinoma patients. They found that 13.8% of patients with metastatic lung adenocarcinoma had an EGFR activating mutation. The authors point out that one of the clinical implications is that the presence of an EGFR mutation predicts a response to tyrosine kinase inhibitors.

Table 2 Breakdown of observed mutation distribution

	Count	% of cohort	Mutation %
Total valid samples (n)	209		
Unmutated	180		
Exon 19 Deletion	19	9.09%	65.52%
Exon 20 Insertion	4	1.91%	13.79%
Exon 21 (L858R)*	5	2.39%	17.24%
Exon 18 (G719X)	1	0.48%	3.45%
T790M*	1		3.45%
Total sensitising mutations	29	13.88%	
Total resisting mutations	1	0.48%	

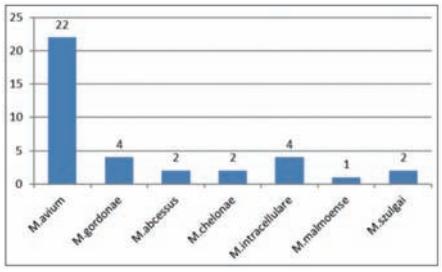


Is the NHS best practice tariff for type 1 diabetes applicable in the Irish context?: O'Brien et al applied the UK 13 key standards of paediatric diabetes care to the cohort of type 1 diabetes children attending Temple Street. Most of the standards were being met but the ones that were unachievable were the annual dietetic review and the 3 monthly OPD appointment. One fifth of the children achieved the HbA1c <7.5% which compares favourably with the corresponding UK figure 15.8%.

Table 4 Comparison of National Health Service best practice standards for paediatric diabetes and current practice in Temple Street

	National Health Service best practice for paediatric diabetes guidelines	Children's University Hospital, Temple Street
1.	Every child cared for by specialist team*	YES
2.	Consultant / specialist with BSPED** training; Paediatric nurse with RCN* diabetes training; Paediatric dietitian with paediatric diabetes training	YES
3.	Newly diagnosed patient should be discussed with team within 24 hours, and seen by senior member of team on next working day	YES
4.	Structured education programme at diagnosis, with follow ups as needed	YES
5.	Four clinic appointments offered annually	Three offered to all patients
6.	HbA1c checked four times annually, with result available at every clinic	Three offered to all patients, available in clinic
7.	Offered dietitian appointment annually	Only offered as required
8.	At least eight additional contacts per year by the team	YES
9.	Annual review as per NICE[9] guidelines	YES
10.	Annual psychological assessment and service access provided as needed	Only offered as required
11.	24 hour advice to emergency management for family and health professionals	YES
12.	Partake in National Paediatric Diabetes Audit; attend local Paediatric Diabetes Network meetings; have a clear policy for transition to adults services	No current national diabetes audit; policies in places; local meetings attended
13.	Clear policy for high HbA1cs and persistant DNAs	No written policy in place

Pulmonary non-tuberculous mycobacteria in a general respiratory population: Chong et al state that the prevalence of non-tuberculous mycobacteria (NTM) appears to be increasing. In this study 37 non-cystic fibrosis patients with NTM were evaluated. The patients had significant underlying pathology, bronchiectasis 34%, COPD 26%, asthma 10%, other 8%, none 16%. Only 16% of the NTM patients required specific therapy.



Can multiple mini interviews work in an Irish setting: a feasibility study: Kelly et al describe the application of the multiple mini interview (MMI) as a selection tool for medical students. The authors describe its use among 109 students. They were tested across 10 stations including communication, teamwork, and ethical reasoning. The students' performances were comparable to that of Dundee applicants.

Table 2 Estimated costs of running the MMI

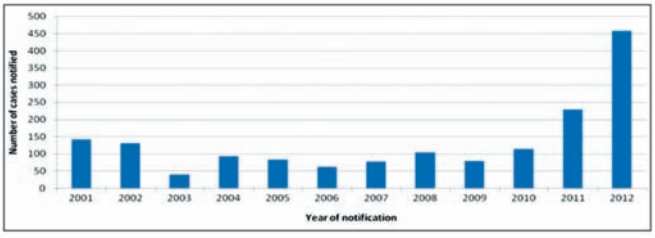
Item	Unit cost	Estimate cost for MMI for 120 applicants
Interviewer expenses (20 interviewers plus 2 backup interviewers =22)	Based on OSCE examiner rates of €500 per full day	11000
Administrative support X4	Based on OSCE administration rates of €250 per full day	1,000
10 actor / role players	Actor training @ €50 per actor	500
	MMI @ €150 per day	1,500
Acting Coach	Sourcing and training actors estimated @ €500	500
	Supervision of acting at MMI @ €150 per day	150
Venue rental	€2,000 per day	2000
Catering for 37 people (lunch/ teas/ coffee)	Estimated @ €15 per person	555
Office supplies / laminating / paper/ photocopying / Various MMI station material props	€200	200
Estimated total cost		**€17405**
Estimated cost per applicant		**€145.04**

Age related influence on screening coverage and satisfaction with cervical check: Fitzpatrick et al sent a questionnaire to 5,000 women attending for a cervical smear. The response rate was 51.6%. The feed-back was positive with the majority stating that they would return again and that they would recommend it to others.

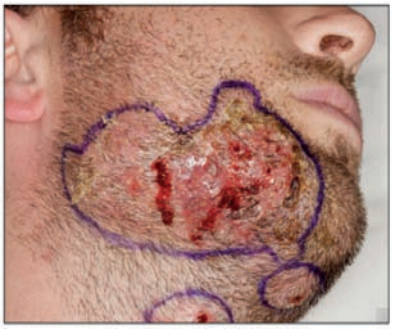
Table 1 Logistic regression: factors associated with (i) 'would recommend CervicalCheck to family and friends', (ii) with 'would return if invited to CervicalCheck' and (iii) associated with knowledge of when next screening due

	Factors associated with 'would recommend CervicalCheck to family and friends'		Factors associated with 'would return if invited to CervicalCheck'		Factors associated with knowledge of when next screening due	
	Univariate OR (95%CI)	Final Model OR (95%CI)	Univariate OR (95%CI)	Final Model OR (95%CI)	Univariate OR (95%CI)	Final Model OR (95%CI)
Age >= 45	0.7 (0.2-2.3)	-	0.1 (0.5-1.9)	-	0.1 (0.5-1.9)	0.5 (0.4-0.7)
Recalls receiving information leaflet	7.6 (1.5-39.2)	-	2.1 (1.0-4.5)	-	n/a	n/a
Contacted by letter from CervicalCheck / contacted CervicalCheck	n/a	n/a	2.3 (1.2-4.5)	2.5 (1.3-5.0)	2.3 (1.2-4.5)	-
Attended own GP for smear	n/a	n/a	1.7 (0.9-3.6)	-	1.7 (0.9-3.6)	-
Knowledge of when next screening due	4.0 (1.2-13.7)	-	3.0 (1.6-5.8)	3.1 (1.6-6.1)	n/a	n/a
Would return to CervicalCheck if invited	19.3 (3.8-96.5)	31 (5.2-183.7)	n/a	n/a	3.0 (1.5-5.8)	3.2 (1.2-8.3)

Pertussis in young infants: clinical presentation, course and prevention: O'Riordan et al report that the rate of pertussis has been rising. Babies present with cough, apnoea or cyanosis. There were 18 cases in Temple Street in 2011. The median duration in hospital was 7 days. Waning immunity among older children appears to be the cause of the increase in cases. Macrolide antibiotics are associated with a reduced duration and severity of symptoms if commenced in the catarrhal stage.



Infection of the beard area . Kerion: a review of 2 cases: Wall et al describe 2 cases of kerion in farmers. Kerion is an inflammatory response to fungal infection. It should be considered when there is a history of exposure to animals. The condition responds to oral antifungals and steroids.



Doctors Working Within Public Health Services

Clare Gerada[1], writing in the BMJ, recently stated that the prevailing culture among NHS staff is one of fear. This negativity may be transmitted to the patient who is already likely to be anxious and scared. There is a sense that humanity has been downsized or removed from hospital systems. In this setting it is difficult for patients to have their emotional needs met. Put simply, if health professionals are to be able to provide best patient care first time and every time, their employers in turn must care for them.

These observations should be a major concern because fear and anxiety leads to under performance in all aspects of human activity including the delivery of health care. It is counterproductive in the care of patients and causes job dissatisfaction in the caregivers. Doctors feel abandoned and unsupported by their political and managerial leaders. Practicing as a doctor is a professional patient-clinician activity. This relationship doesn't sit well with the current industrialization of medicine with its multiple competing agencies, regulatory bodies and frequently unachievable targets. The sense of isolation is compounded by a system that makes it more difficult for the older generation of doctors to provide support to younger colleagues.

Systems that are set up to fail will fail. This needs to be considered when a service configuration is being changed. Frontline clinical staff find it difficult to concentrate on the care of ill patients against a background of organizational uncertainty. Common concerns include whether there will be sufficient staff and resources to care for the patient workload. Caregivers feel squeezed between increasing patient expectations and employers' demands for greater productivity with reduced expenditure. There is a failure in the management of the public's unrealistic expectations. Promises made by politicians in relation to health are frequently unachievable and unsustainable. Some of the points raised by Gerada may strike an accord with doctors working within the Irish health service.

In the UK there are policies designed to name and shame NHS staff who are perceived to have made an error. The Care Quality Commission is the independent regulator of health and social care in England. It was set up in the wake of the Mid-Staffordshire Inquiry. Its remit is to check that hospitals, care home, general practitioners and dentists are meeting national standards. There are concerns that it may create a counterproductive blame culture based on isolated examples of inadequate care. There are also reservations about proposals by Health Secretary Jeremy Hunt to name and shame GPs who fail to spot signs of cancer. Richard Roope[2], clinical lead for cancer RCGP, is critical of this approach. He points out that the average full-time GP encounters 8 cases of cancer annually. Seventy five percent of cancer cases are diagnosed and referred by GPs after only one or two visits. The other 25% of cancers are mostly obscure ones including sarcomas and bone cancers. The placement of undue pressure on GPs will compel them to refer increased numbers of patients with undifferentiated symptoms who ultimately are found not to have cancer. GPs make balanced risk based decisions every 10 minutes. It is important that politicians and the public should have a better understanding of their pivotal role in the provision of health care. Erosion of the GPs effective gatekeeping role could place a further unsustainable burden on hospital services.

A paradox of values has emerged in which staff is expected to care for patients but employers are not expected to care for staff[3]. This is a challenging issue for large, impersonal, public health care systems. The staff is subjected to a constant stream of criticism, cutbacks, and instructions to do better. The failure to attend to the promotion of kinship, and kindness between staff and with patients misses out on a key dimension of what makes people do well for others. There is a clear link between kindness, effectiveness and positive outcomes. This is what some commentators call the patient's experience. Balik et al[4] state that the 5 primary drivers of exceptional patient and family experience are leadership, staff hearts and minds, respectful partnership, reliable care, and evidence based care. Agutter[5] is looking at the healthcare system in a new way through the patient experience project. The project is focused on putting the human element back into patient care. The solutions are relatively simple. They consist of creating a map with information of what to expect in the hospital each step of the way. The ultimate goal is reducing the patient's anxiety.

Politicians and managers would like to believe that that error-free medicine is possible and that a culture of perfectionism can be imposed on doctors and nurses. The designation of 'never events' to clinical complications escalates anxiety and makes good care more unattainable. Initially 'never events' were confined to fundamental issues such as electrocution from medical devices during clinical care. Over time the list has been extended to include more common clinical complications. Frequently, health services give undertakings and promises without ensuring that the required supports including staffing and expenditure are in place. Such utterances are damaging to the doctor-patient relationship. The physician is expected to guarantee what cannot be delivered[6]. If a realistic approach is not adopted, expectations will continue to mount and the public will come to believe that every medical complication is somebody's fault. There is skepticism that this approach will achieve its stated mission of improving medical outcomes. The most likely eventuality is that it will become another measure for the legal profession to employ against doctors during compensation cases.

The doctor-patient relationship was based on care, empathy, understanding and mutual respect. Over time politicians, managers, economists, insurance bodies, and regulatory authorities have entered that relationship. The role of both the patient and the doctor can become confused leading to dissatisfaction for the patient and anxiety for the doctor. The solution is to halt the erosion of professionalism and to re-establish and promote the core values of a doctor, which are good clinical care and patient advocacy.

JFA Murphy
Editor

References

1. Gerada C. Something is profoundly wrong with the NHS today. BMJ 2014;248:3-4.
2. Roope R. RCGP statement on rating GP practices on cancer referrals. 1 July 2014 press@rcgp.org.uk
3. Ballatt J, Campling P. Intelligent kindness: reforming the culture of healthcare. 2011. RCPsych publications.
4. Balik B, Conway J, Zipperer L, Watson J. Achieving an exceptional patient and family experience of inpatient hospital care. 2011 www.IHI.org
5. Agutter J. The patient experience project. www.utah.edu
6. Peters M, Hasan O, Puddester D, Garelick A, Holliday C, Rapanakis T, Ryan AM. Doctors health: taking the lifestyle approach. BMJ 2013;347:f7086.

The National Paediatric Diabetes Register and its Impact on Healthcare

In the field of management it has long been recognised that effective management of any given outcome requires knowledge and control of inputs to the system. This is also true in healthcare particularly in Type 1 diabetes (T1D), a common and severe chronic disease in childhood which is a huge health, social and economic burden[1,2]. In T1D the outcome, in terms of prevention of diabetes related complications, has been clearly shown to be related to resource dependent disease management[3] and more recently the Hvidore Study group demonstrated better glycaemic control in those patients with more clinical contact[4].

Availability of robust reliable data is vital to inform effective resource allocation decisions to optimise health outcomes and ensure effective utilisation of resources, while minimising the opportunity cost of misplaced resources. Particularly critical as in current times when resources are scarce. Indeed one would question how it is possible to appropriately plan services in the absence of such information. Internationally the value of reliable epidemiological data regarding Type 1 diabetes has long been recognised with the establishment of the DIAMOND project by the World Health Organisation in 1990[5] and the Eurodiab collaborations, which have monitored the epidemiology of this important disease since the late 1980s[6,7]. These studies have shown annual increases in incidence of T1D ranging from 0.6 – 9.3% in most European populations, the average increase being 3.9%[6]. Many countries have established national Diabetes Registries to monitor T1D in their populations.

Despite T1D in childhood and adolescence being a readily identifiable disease, as it is rapidly fatal without the administration of insulin, there were limited data available regarding the number affected with this condition in Ireland. In the past Ireland was considered a country with a very low incidence of T1D[8,9] and services configured accordingly. Clinicians however felt this was not the case and to address this data deficiency a baseline incidence study was undertaken in 1997[10] and the process to develop a national Register commenced. The Irish Childhood National Diabetes Register (ICDNR) was established in 2008 with the generous support of the National Childrens Hospital Foundation. It has been designed to comply with all statutory policies regarding data collection, storage and maintenance within the Data Protection Acts and HIQA policies. Its role to define and monitor the epidemiology of T1D in those aged under 15 years in the ROI. The ICDNR is a prospective incident register thus it records in a robust fashion new cases of T1D. It has been strongly supported by children, families and Health Professionals nationally.

As a result of the establishment of the ICDNR for the first time it can be confidently confirmed that Ireland has a high incidence of T1D in the child and adolescent population and that the incidence of this disease has risen substantially since the baseline study of 1997[11]. The increase has been of the order of 5% per annum (although it must be recognised that incidence rates in T1D are not linear over time[7]). Data on almost 1500 children and adolescents with T1D is currently maintained in the Register. The benefits of the ICDNR includes provision of comprehensive and accurate data regarding annual incidence of Type 1 diabetes in children and adolescents in Ireland since 2008. It provides accurate demographic data, allowing identification of areas of higher disease density and evaluation of sub populations with diabetes who require special consideration, e.g. those aged under 5 or adolescent cohorts. These data permit the design of healthcare services to support the National Model of Care. Such data enables reconfiguration of healthcare services to meet specific needs, such as, prioritising the development of transition services in areas where large growth in the adolescent populations with T1D can be forecast. The period of transition from child to adult services for those with diabetes is an area of particular risk where young people may fall out of care and re-engage only with life-threatening crises. The data provided by the ICDNR is the most accurate and robust data regarding childhood diabetes in Ireland and is invaluable to support strategic developments in resource allocation and service provision for childhood diabetes. The ICDNR has already made a significant contribution by providing data and forecasts to inform the HSEs initiative to prioritise Continuous subcutaneous insulin infusion therapy to children under 5, led by Dr Stephen O'Riordan, Clinical Lead for Paediatric Diabetes.

As the Register is maintained over time the annual incidence data will permit accurate determination of the total number of young people (prevalence) under 15 years with T1D in the ROI. Assessing prevalence over time using meticulously collected incidence data is the most robust and reliable method, as in the absence of a unique patient identifier self-reported cross-sectional analysis of centres would be unreliable due to multiple counting of cases (many with diabetes attend more than one centre), uncertainty of diagnosis (increasing numbers of type 2 or monogenic diabetes in this age group)and under-reporting (most paediatric T1D centres do not have a computerised database). The ICDNR enables monitoring of changes in disease epidemiology in the population over time and the pattern and frequency of serious disease complications at diagnosis. A vital function of the ICDNR is that it will enable the assessment of completeness of audit through provision of reliable accurate denominator data, thereby enhancing patient care and improving disease outcomes. In the absence of accurate denominator data it is possible that a significant proportion of the audit population could be missed due to non-attendance etc thus yielding misleading results. As a national disease register the ICDNR participates with the Eurodiab collaboration to aid further insight into the causation of this common complex disease.

The ICDNR is an invaluable resource in Type 1 diabetes which provides a unique insight into the development of this disease in the Irish population and the resources required to appropriately address the needs of this large patient group, thereby optimising service delivery and enhancing patient care.

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References

1. Dabelea, Dana. Mayer-Davis, Elizabeth J. Imperatore, Giuseppina. The value of National Diabetes Registries: Search for Diabetes in Youth Study. Curr Diab Rep (2010) 10:362–369.
2. Catanzariti, L. Faulks, K. Moon, L. Waters, A.-M. Flack, J. and Craig, M. E. Australia's national trends in theincidence of type 1 diabetes in 0-14year olds, 2000-2006. Diabetic Medicine, 26: 596–601.
3. The Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group Effect of Intensive Therapy on the Microvascular Complications of Type 1 Diabetes Mellitus JAMA. 2002 May 15; 287: 2563–9.
4. Cameron FJ, De Beaufort C, Aanstoot HJ, Hoey H, Lange K , Castano L, Mortensen HB, and the Hividore International Study Group.

Lessons from the Hvidore International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach. Paediatric Diabetes 2013: 14;473-480.
5. The DIAMOND Project Group. Incidence and trends of childhood Type 1diabetes worldwide 1990-1999. Diabet. Med. 2006: 23; 857-866.
6. Patterson, Christopher C. Dahlquist, Gisela G. Gyurus, Eva. Green, Anders. Soltész, Gyula and the EURODIAB study group. Incidence trends for childhood type1 diabetes in Europe during 1989 – 2003 and predicted new cases 2005 -2020: a multicentre prospective registration study. Lancet 2009; 373: 2027 -33.
7. Dahlquist G, Soltész G. Trends in childhood Type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. Diabetologia 2012; 8: 2142-7.
8. Bloom A, Hayes T.M., Gamble DR. A register of newly diagnosed diabetic children.BMJ 1975:3:580-3.
9. Metcalfe M, Baum J. Incidence of insulin dependent diabetes in children aged under 15 years in the British Isles during 1988. BMJ. 1991;302:443-7.
10. Roche EF, Menon A, Gill D, Hoey HMCV. Incidence of type 1 Diabetes Mellitus in Children aged under 15 years in the Republic of Ireland. Journal of Paediatric Endocrinology and Metabolism 2002, 15: 1191-4.
11. Roche EF, McKenna A, Ryder K, Brennan A, O'Regan M, Hoey HMCV. The Incidence of Childhood Type 1 Diabetes in Ireland and the National Childhood Diabetes Register. The Irish Medical Journal, 2014 (InPress).

Acute Childhood Asthma in Galway City from 1985-2005: Relationship to Air Pollution and Climate

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Abstract
We examine the relationship of air pollution and climatic variables to asthma admission rates of children in Galway city over a 21 year period. Paediatric asthma admissions were recorded from 1985-2005, and admission rates per thousand calculated for pre-school (1-4 years), school aged (5-14 years) and all children (1-14 years) on a monthly and annual basis. These data were compared to average monthly and annual climatic variables (rainfall, humidity, sunshine, wind speed and temperature) and black smoke levels for the city. Simple correlation and Poisson Generalized Additive Models (GAM) were used. Admission rates each month are significantly correlated with smoke levels (p=0.007). Poisson GAM also shows a relationship between admissions and pollution (p=0.07). Annual smoke levels impact more on admission rates of preschoolers (p=0.04) than school age children (p=0.10). These data suggest that air pollution is an important factor in the epidemiology of acute childhood asthma.

Introduction

The last 40 years have seen an epidemic of childhood asthma through the developed world that is largely unexplained. The prevalence of asthma increased throughout the latter three decades of the twentieth century[1], and more recently has shown evidence of reaching a plateau and beginning to decline[2]. Whilst numerous theories have been advanced, no unifying hypothesis has been agreed[3]. Admission rates for asthma appear to correlate well with the prevalence and severity of asthma[4].

Over the past 20 years in Galway, asthma admission rates increased steadily to a peak in 1995 and thereafter diminished dramatically. The severity of asthma in those admitted appears unchanged, and there is an increased willingness to treat in the community and prescribe prophylactic therapy[5]. A similar series of observations across the UK suggested widespread use of inhaled steroids was responsible for the reduction in asthma admissions[6]. However, it is unlikely that worsening treatment caused the initial rise. A survey in general practice in the UK documented a reduction in consultation rates, not only for asthma, but for all respiratory illnesses across the same timeframe[7]. Could an environmental change be responsible? Paediatric epidemiological studies show that exposure to pollution has a detrimental effect on lung function in children, which is reversed when they move to a cleaner area[8]. In Galway we have a well-defined city population, a single acute paediatric unit, an environment where the major sources of air pollution are vehicular traffic and domestic heating, and 21 years of measurements of asthma admissions, air pollution, and climatic variables. We decided to explore the long-term link, if any, between air pollution, climatic variables, and acute asthma in children.

Methods

Galway is a city on the west coast of Ireland with a population of 72,000, and an area of 22 Km^2. A single hospital provides maternity and paediatric services for the area. The children's unit provides services for a child population of approximately 11,000 who reside in the city, with a further 35,000 in surrounding area. There are no heavy industries in the locality, the prevailing wind is Atlantic south-west to west, and the climate is temperate with relatively heavy rainfall. Domestic heating is provided by coal (81%) and oil-fired central heating. The sale of bituminous coal was banned in 2000. Background urban air pollution was monitored in Galway city on a daily basis from 1983 to 2005. Three sites within 1km of the centre were used. Black smoke (BS) concentrations were measured using the Organization for Economic Cooperation and Development (OECD) method. Black smoke concentration measurements are a measure of small particulate pollution, typically less than 2 microns; well below the respirable threshold. Daily levels of black smoke were obtained from 1985-2005, and converted to monthly and annual averages. Daily records of humidity, wind speed, temperature, rainfall and sunshine for the city were provided by the National Meteorological Service; data were also aggregated to monthly and annual averages. There were few missing data; where readings were missing monthly averages were calculated from available information.

Asthma admissions were retrieved from the paediatric unit register and Hospital Inpatient Enquiry System. Previous comparisons of the unit register and HIPE during studies in 1990, 1997, and 2004 showed good agreement. Given the difficulty of differentiating virus-associated wheeze from asthma in infants, we excluded children under one year of age. Raw numbers of asthma admissions for children with a Galway city address were converted to a rate per 1000 by using census data from 1986, 1996, 2002 and 2006 to define the population. Since the child population is relatively small, admissions (33-90 annually) were aggregated on a monthly and then annual basis for analysis. Relationships between admission rates and climatic and pollution variables were examined by simple correlation. A gamma distribution based Generalised Additive Model (GAM)[9,10] with a

log link function was then employed to explore in detail the association between the monthly admission rates, black smoke concentrations and climatic variables. The study was approved by the hospital ethics committee.

Results

The entire data set, with variables for each month (n=252) of the 21 years, was examined initially by simple correlation. Monthly asthma admissions correlated weakly but significantly with smoke levels (Spearman's rank correlation of r =0.17, p=0.007). There is evidence of a positive association between asthma admissions and black smoke levels for the 1-4 year olds (p=0.04) and a positive trend for 5-14 year olds separately (p=0.10). There appears to be a stronger association between black smoke and admissions rates in ages 1-4, thus explaining the intermediate significance of the combined 1-14 years analysis. Using the GAM no statistically significant climatological effect on the monthly admission rates was found. There was evidence of a positive association between asthma admissions and particulate concentrations for all subjects (1-14 years) (p=0.075). Figure 1 depicts the smooth fitted temporal trend in monthly asthma admission counts after using GAM to account for the effects of

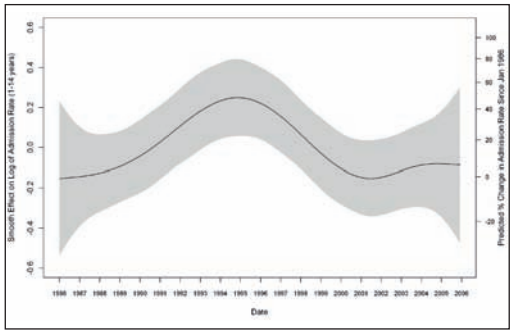

Figure 1

Smooth fitted relationship, after allowing for contribution of pollution and climatic variables, between logarithm of monthly asthma admission rates and time for all children (1-14 years). The right axis indicates the predicted percentage change in admission rates since January 1986. The shaded bar is a pointwise 95% confidence interval for the effect

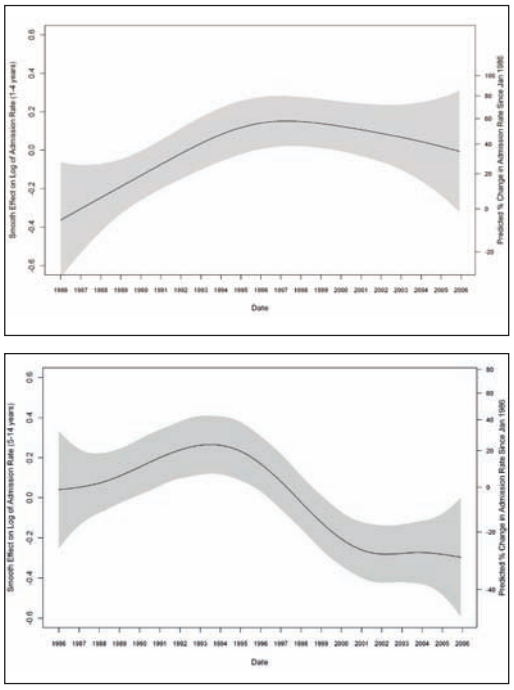

Figure 2

Smooth fitted relationship, after allowing for effects of climate and air pollution, between logarithm of monthly asthma admission rates and time for preschoolers (a) and school-aged children (b). Right axis indicates the implied predicted percentage change in admissions since January 1986. Shaded bar is a pointwise 95% confidence interval for the effect

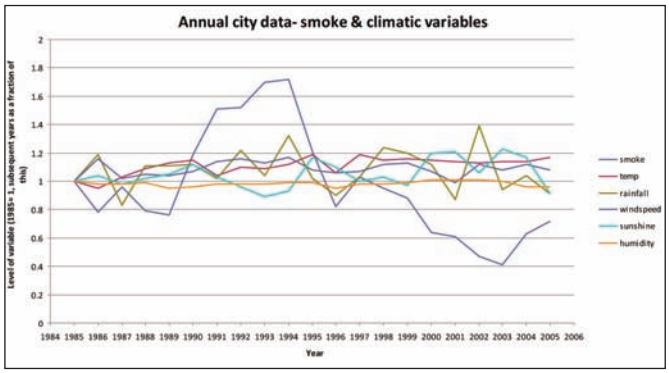

Figure 3 Annual Climatic variables and smoke levels shown as a fraction of baseline (1985) levels

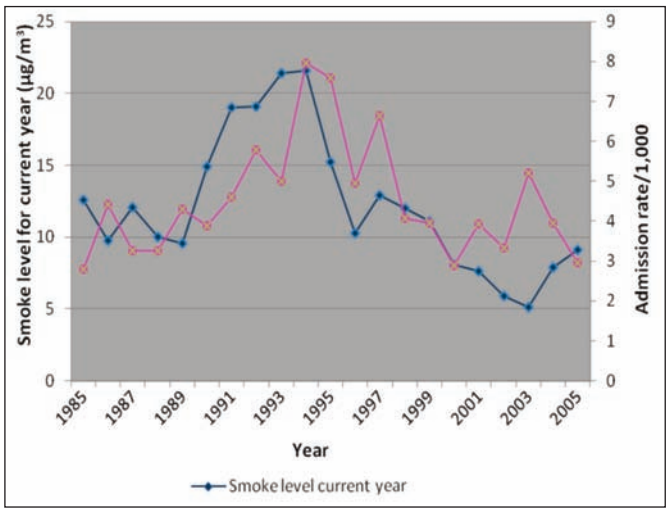

Figure 4 Admission rates and current year's smoke levels 1985-2005. Spearman's rank correlation coefficients for Rate r = 0.27 (p<0.001); and for Count r = 0.29 (p<0.001)

black smoke and seasonal variation. Once these are allowed for there is insufficient evidence for a residual trend.

Looking at the subgroups, however, using GAM, the residual smooth time trend in the admission rates was significant for both preschoolers (p=0.04) and school age children (p<0.001); both exhibiting a peak around 1995 (Figure 2). This implies an impact of factors other than pollution. The time trends for the two age groups differ in terms of estimated behaviour before and after this peak. After allowing for an influence of air pollution, pre-schoolers had an additional 20% rise after 1995 not attributable to pollution, whereas in school age children the rise in admissions to the peak may largely be accounted for by pollution, but the fall was 40% greater than that attributable to it. Data were then aggregated on an annual basis over the 21 year period. There was little year on year variation in climatic variables-temperature, windspeed, rainfall, sunshine, humidity. This is seen in Figure 3. The annual admission rates and black smoke values are shown in Figure 4, which clearly shows an association between black smoke and admission rate.

Discussion

Our data show a strong association between black smoke levels and admission to hospital with childhood asthma. The association between smoke and acute admissions is more evident when plotted annually. Though the hypothesis is biologically plausible, these changes could be coincidental. The reason for the rise and fall in black smoke from the mid-nineties is probably a combination of changes in domestic and vehicular fuel use. Coal sales changed little from 1985 to 1995, suggesting that the rise in black smoke came from other sources. The predominant coal supplier in the area noted a trend to the use of smokeless coal in Galway in the mid 1990s. More stringent emission standards for bituminous coal were implemented in 1995, so coal supplied in Galway after that year had both lower sulphur content and lower smoke emissions. Sale of bituminous coal was banned in 2000, and this was associated with a further small reduction in smoke levels.

Therefore some of the fall in smoke levels from 1995 is due to "cleaner" coal. Short-term (30-minute periods) analysis of particulate matter in Galway show that peaks agree well with peaks in traffic flow, suggesting much of the air pollution is traffic related (unpublished data). The rise in smoke levels up to 1995 coincided with a growth in registered vehicle numbers in the county (from 44,000 to 108,000) and the proportion of diesel-powered vehicles (from 18% to 35%) , indicating that vehicular traffic was a factor in elevating smoke levels. The fall in smoke levels from 1995 occurred despite the further growth in traffic volume and increased proportion of diesel engines, suggesting reduced vehicle emissions were important. We suspect that reduced diesel emissions, consequent on reduced sulphur content and more stringent emission standards implemented in the mid-1990s, were a key factor[11]. We are unable to apportion the relative contributions of domestic and traffic sources to the increased, and then reduced, black smoke levels, as chemical analyses of the black smoke samples over this period are not available. Pollution, viral infection, and allergens all contribute to airway inflammation and narrowing. Analysis of annual data minimises the influence of seasonal climatic allergic and infectious variables. Black carbon can penetrate to alveoli where it is taken up by alveolar macrophages[12]. These irritant particles linger in the lung. They are likely to have a greater detrimental effect in the lungs of children, because of their narrower airway calibre, more rapid respiratory rate, and relatively greater minute volume[13]. Air pollution as an explanation for the epidemic of childhood asthma has been dismissed[14], partly on the basis of comparative studies in areas of high and low pollution[15]. However, the study of "pollution" may not be sufficiently precise; air that looks black and heavily polluted may have little impact on respiratory morbidity if the particles are large or non-irritant. Categorisation of air pollution on the basis of particle size (e.g. PM10, 2.5, 1.0) is crude.

Other factors such as mineral and free radical content, surface area, and number of particles are not "captured" in a simple weight. Black smoke as an indicator of air pollution is imperfect, but is acknowledged as a good marker of diesel pollution[16]. Detrimental effects of black carbon may relate more to particle numbers and total surface area than simple mass[17]. Diesel exhaust particles are more irritant to the lung[18] and more likely to trigger allergic sensitisation[19]. Diesel as a contributor to air pollution in the West increased steadily from the 1960s, assuming a leading role in the 1980s and increasing steadily to the end of the century[20]; the time course of the childhood asthma epidemic. Looking at age group specific effects, air pollution appears to have a greater impact on admission rates for pre-school children than school age children. This is consistent with the physiologic predisposition of smaller children to the detrimental effects of pollution[3]. Prophylactic treatment has probably had little impact on admissions of the pre-school group since inhaled steroids are less effective in this group[4]. The reduction in admissions after the peak is possibly offset by the greater risks of admission noted in pre-school children generally since the introduction of on call co-op services in primary care[5].

We observed an additional decrease in admissions trends in time in school age children in our statistical modelling (in Figures 2) after accounting for the meteorological and black smoke effects. This is consistent with an effect of improved prophylactic therapy in school aged children in the community, co-incident with the dissemination of agreed guidelines[6]. The lack of significance of the residual time trend when the two cohorts are combined is due to these differing behaviours on either side of the peak cancelling each other out. In conclusion, we have shown an association

between a measure of childhood asthma morbidity and black smoke in Galway city. We hypothesise that regulatory changes in the nature of coal and diesel, and more stringent vehicular emission rules have improved air quality and contributed to the reduced incidence of hospital admissions.

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References

1. Manning PJ, Goodman P, O'Sullivan A, Clancy L. Rising Prevalence of Asthma but Declining Wheeze in Teenagers (1995-2003): ISAAC Protocol Ir Med J. 2007 Nov-Dec;100:614-5.
2. Anderson HR. Prevalence of asthma (Editorial) Br Med Jour. 2005; 330: 1037-8.
3. Bauchner H. Has the increase in allergic disease plateaued? Arch Dis Child. 2004; 89: 397.
4. HR Anderson, R Gupta, V Kapetanakis, MI Asher, T Clayton, CF Robertson, DP Strachan and The ISAAC Steering Committee International correlations between indicators of prevalence, hospital admissions and mortality for asthma in children. Int Jour Epid. 2008; 1–10.
5. Shabu A, Carr M, Crushell E, Loftus BG. Patterns of asthma admissions in children. Ir Med J. 2007; 100:407-9.
6. MacFaul R. Trends in asthma hospitalisation: is this related to prevention inhaler usage? Arch Dis Child. 2004; 89:1158-60.
7. Sunderland RS, Fleming DM. Continuing decline in acute asthma episodes in the community. Arch Dis Child. 2004; 89:282-5.
8 Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. The effect of air pollution on lung development from 10 to 18 years of age N Engl J Med. 2004; 351:1057-67.
9. Wood S. Generalised additive models: an introduction using R. London: Chapman and Hall, CRC, 2006.
10. Ruppert D, Wand MP, Carroll RJ. Semiparametric regression. Cambridge University Press, 2003.
11. Wåhlin P, Palmgren F, Van Dingenen R, Raes F. Pronounced decrease of ambient particle number emissions from diesel traffic in Denmark after reduction of the sulphur content in diesel fuel. Atmospheric Environment 2001:35: 3549-52.
12. Kulkarni N, Pierse N, Rushton L, Grigg J. Carbon in airway macrophages and lung function in children. N Engl J Med. 2006; 355:21-30.
13. Schwartz J. Air pollution and children's health, Pediatrics. 2004;113: 1037-1043.
14. Strachan D P The role of environmental factors in asthma British Medical Bulletin 2000;6: 865-882.
15. von Mutius E, Fritzsch C, Weiland SK, Röll G, Magnussen H Prevalence of asthma and allergic disorders among children in united Germany, a descriptive comparison. Br. Med.Jour. 1992; 305:1395-1399.
16. Air Quality Expert Group. Particulate matter in the United Kingdom. London: Defra, 2005.
17. Nygaard UC, Samuelsen M, Aase A and Løvik M The capacity of particles to increase allergic sensitization is predicted by particle number and surface area, not by particle mass Toxicological Sciences 2004 82:515-524.
18. Porter M, Karp M, Killedar S et al Diesel-enriched particulate matter functionally activates human dendritic cells Am J Respir Cell Mol Biol 2007; 37;706-719.
19. Samuelson M, Nygaard UC, Lovik M Allergy adjuvant effect of particles from woodsmoke and road traffic. Toxicology.2008; 246; 124-131.
20. Bond TC, E Bhardwaj, R Dong, R Jogani, S Jung, C Roden, DG Streets, NM Trautmann (2007), Historical emissions of black and organic carbon aerosol from energy-related combustion, 1850–2000, Global Biogeochem. Cycles, 21, GB2018.

Epidermal Growth Factor Receptor (EGFR) Mutation Testing, From Bench to Practice: A Single Institute Experience

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Abstract
Epidermal growth factor receptor (EGFR) gene mutations determine the treatment and prognosis in lung adenocarcinoma. Exon 19 and exon 21 (L858R) deletions represent the most common recognised mutations detected. To date, no figures regarding the prevalence of EGFR mutations in the Irish population have been published. The prevalence of EGFR mutations was retrospectively analysed for all patient samples tested since the introduction of EGFR testing routinely (Mar to Dec 2012) in a single Irish institute. The presence of 41 known treatment linked EGFR mutations in exons 18, 19, 20 and 21 of the EGFR gene was tested in 209 Irish patients. Resection, core biopsy or FNA samples were analysed using a commercially available CE-IVD marked multiplex real-time PCR assay. Samples were included from patients of curative and palliative treatment intent likely to harbour an EGFR mutation.

Introduction

Non-small cell lung cancer (NSCLC) is a heterogeneous disease with vast genomic diversity. Half of all NSCLC tumours harbour somatic mutations in genes like EGFR, HER2, KRAS and BRAF, regardless of smoking status or histological subtype[1,2]. Molecular profiling of tumours is of increasing importance in lung cancer as it plays a critical role in treatment decisions. Recent advances in molecular diagnostics have made tumour profiling a reality in clinical practise. Clinically relevant molecular subtypes of lung adenocarcinoma include tumours that harbour activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). EGFR is a receptor tyrosine kinase that belongs to the EGFR family, which consists of four members: EGFR, ERBB2 (also known as HER2), ERBB3, and ERBB4[3]. Under physiological conditions, EGFR is activated by binding to one of its ligands (like epidermal growth factor). Activated EGFR in turn activates downstream intracellular pathways leading to cellular survival and proliferation. Mutant EGFR in lung cancer is constitutively active, which causes uncontrolled growth and evasion of cell death[3]. The most common mutations of EGFR in NSCLC are exon 21 (L858R) point mutations and exon 19 deletions accounting together for more than 85% of EGFR

CPD available online at www.imj.ie and questions on page 223.

mutations in the disease[3,4]. The presence of EGFR mutations in a tumour predicts response to oral EGFR tyrosine kinase inhibitors (EGFR-TKIs) like gefitinib and erlotinib[4].

The prevalence of EGFR mutations in Asian patients with lung adenocarcinoma is approximately 40% compared to 15% in Caucasian patients[5]. The prevalence of EGFR mutations has not been previously reported in an Irish population. Here, we present the findings of screening for EGFR mutations in lung adenocarcinoma patients treated in the largest lung cancer service in Ireland. At the end of our report we provide a summary of recent advances and the role of first line TKIs in the treatment of advanced NSCLC.

Methods

The prevalence of EGFR mutations was retrospectively analysed for all patient samples tested since the introduction of EGFR testing as a routine service, (Mar to Dec 2012), in a single Irish institute. Formalin fixed paraffin embedded tissue from resection, core biopsy or FNA samples was analysed for 209 Irish patients using the CE-IVD marked Roche Cobas® 4800 EGFR mutation detection assay (Roche Diagnostics Limited, UK). The Roche Cobas® 4800 assay uses a system of three multiplex real-time PCR reactions for the simultaneous detection of 41 treatment linked mutations in exons 18, 19, 20 and 21 of the EGFR gene. Samples were included from patients of curative and palliative treatment intent.

Table 1 Clinical characteristics of patients with an EGFR mutation

Characteristic	
Mean age	63
Sex	
Male	10 (34.5%)
Female	19 (65.5%)
Smoking history	
Never smoked	18 (62%)
Previous smoker	7 (24%)
Current smoker	2 (7%)
Unknown	2 (7%)
Clinical stage at time of testing	
Stage IIIb	4 (13.8%)
Stage IV	25 (86.2%)

Results

During the study period 209 patients were tested for an EGFR mutation. Of those tested 51.2% were male (n=107) and 48.8% (n=102) female. The mean age at testing was 67 years. Patients tested had either stage IV disease (88%, n=180) or stage IIIb disease (12%, n=25). Of the study cohort, 29 patients had an EGFR mutation (13.8%, 95% CI 8.4-17.6%). Clinical characteristics of these patients are outlined in Table 1. One patient had two EGFR mutations making the total number of mutations detected 30 in 29 patients. Among the mutations detected relative frequency was as follows: exon 19 deletion 63.3% (n=19, 95% CI 46.1-80.6%), exon 21 (p.L858R) 16.7% (n=5, 95% CI 3.3-30.0%), exon 20 insertions 13.3% (n=4, 95% CI 1.2-25.5%) and exon 18 (p.G719X) and exon 20 (p.T790M) both at 3.3% (n=1, 95% CI 0-9.8%) (Figure 1, Table 2).

Table 2 Breakdown of observed mutation distribution

	Count	% of cohort	Mutation %
Total valid samples (n)	209		
Unmutated	180		
Exon 19 Deletion	19	9.09%	65.52%
Exon 20 Insertion	4	1.91%	13.79%
Exon 21 (L858R)*	5	2.39%	17.24%
Exon 18 (G719X)	1	0.48%	3.45%
T790M*	1		3.45%
Total sensitising mutations	29	13.88%	
Total resisting mutations	1	0.48%	

* One patient expressed both the L858R and T790M mutations.

The incidence of mutations was higher in females than in males; 63.3% of those with an EGFR mutation were female (n=19, 95% CI 46.1-80.6%). Reciprocally, 36.7% of the EGFR mutations were detected in males (n=11, 95% CI 19.4-53.9). All samples tested were formalin fixed paraffin embedded tissue or cell preparations. Turn around time (TAT) for EGFR mutation processing substantially improved over ten month period, from over five weeks to less than four working days (Figure 2).

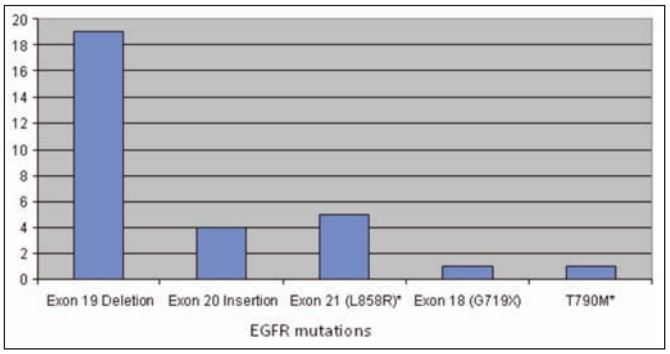

Figure 1 Breakdown of observed mutation distribution

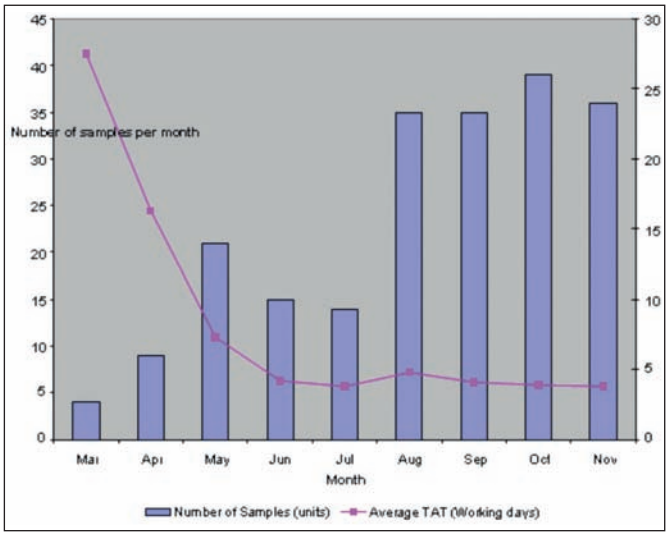

Figure 2 Turn Around Time versusmonthly sample numbers

Discussion

Lung cancer is the most common cause of cancer related death in Ireland[6]. It is estimated that lung cancer rates will continue to increase over the next 10 years, especially in females due to rising numbers of smoking females[6]. Prior to the discovery of EGFR mutations, platinum based chemotherapy was the standard of care in metastatic NSCLC, with modest improvements in overall survival, but at the expense of significant toxicities. Treatment of lung cancer continues to be a major health concern, requiring more research and novel therapeutic approaches.

Clinical features that suggest the presence of an EGFR mutation include adenocarcinoma histology, Asian ethnicity, female sex, never and light smokers[1,5]. Our findings are by large consistent with these clinical features. Of the patients who harbour an EGFR mutation, 19 (65.5%) were females. We found that 62% (n=18) of patients with mutant EGFR never smoked. Although clinical criteria may be useful in patients selection for screening, international guidelines recommend routine screening for EGFR mutations in all metastatic lung adenocarcinomas, as this will have important therapeutic implications. Routine screening is not recommended in pure squamous histology[7,8]. In our institute we do screen all patients with metastatic lung adenocarcinoma for EGFR activating mutations regardless of their clinical characteristics. However, in some cases screening is not possible due to the small volume of diagnostic samples, in these instances we recommend repeating the biopsy only if patient's clinical features are suggestive of an EGFR mutation disease and if their clinical status allows them to undergo a second biopsy. Our data shows that the frequency of EGFR mutations in patients with metastatic lung adenocarcinoma treated in our centre is 13.8%. This rate is comparable to the rate of 15% reported in other Caucasian populations[5]. There are no reported studies of the prevalence of EGFR mutations in an Irish population. One

potential source of bias in our study is the fact that data were collected from a single institute. The number of samples tested in our centre between August 2012 and November 2012 was in the range of 35 to 39 samples per month. Prior to August 2012 we tested less than 20 samples per month. That does not reflect implementation of selection criteria as much as it reflects that the service became well established and fully funded only after August 2012 in our centre.

Presence of an EGFR mutation predicts response to tyrosine kinase inhibitors (TKIs). There are two classes of oral EGFR TKIs in clinical use; reversible EGFR TKIs like geftinib and erlotinib, and irreversible TKIs like afatinib. Six phase III clinical trials have compared first line platinum based chemotherapy with gefitinib or erlotinib in patients with EGFR mutant lung adenocarcinoma[9-14]. All these trials have consistently demonstrated superiority of EGFR TKIs in achieving longer progression free survival and greater response rates. In the four trials where mature overall survival data is available, there was no significant difference between EGFR TKIs and chemotherapy[9-12]. This is likely because cross over was allowed between the control arm and the experimental arm. Quality of life which is crucial in the palliative setting was assessed in four of these trials using various assessment tools, with results showing that patients who received EGFR TKIs had a better quality of life than patients who received platinum based chemotherapy[9-11,13]. This in part can be explained by the lower toxicity profile of EGFR TKIs, with the commonest side effect being acne-like skin rash. The rates of grade 3 or 4 neutropenia were as low as 0.54%[15]. Based on this compelling evidence we treat all patients with mutant EGFR stage IV lung adenocarcinoma with a TKI. The role of oral TKIs in mutant EGFR NSCLC in the neoadjuvant and adjuvant settings is currently under investigation in a number of clinical trials[16-19].

Similarly, phase III data on the irreversible TKI, afatinib, has shown a longer progression free survival in an EGFR mutant population when compared to standard chemotherapy[20]. A phase IIb trial comparing first line afatinib to gefitinib in patients with mutant EGFR lung adenocarcinoma is recruiting patients at present. Another phase III trial comparing first line afatinib to erlotinib is also in the process of recruiting patients[21]. Lapatinib, a HER2/EGFR TKI, used commonly in the treatment of breast cancer, and dacomitinib, a pan HER TKI, are currently being evaluated in phase III clinical trials[22]. Unfortunately, 30% of patients with EGFR mutant lung adenocarcinoma do not respond to TKIs, and the vast majority of those who do respond eventually go on to develop resistance[23]. Several mechanisms have been described to illustrate this phenomenon. Second-site EGFR mutations is the most common resistance mechanism, with T790M mutation being the most reported. The T790M mutation blocks the binding of TKIs to the ATP pocket in the EGFR kinase domain. Activating downstream mutations in the EGFR pathway such as PIK3CA, BRAF and ERK, are also known to cause resistance to TKIs. Met overexpression has been reported in up to 10% of resistant cases. Finally, 5% of patients show histological transformation to small cell lung cancer with resultant resistance to TKIs. Several drugs have been developed to overcome this resistance. Second generation TKIs like neratinib and pelitinib are being tested in phase II clinical trials[23]. It is important to note that no treatment has yet been approved for resistant disease.

The role of TKIs is not limited to EGFR mutant NSCLC. Two phase III clinical trials have demonstrated the superiority of TKIs over best supportive care in patients with heavily pre-treated metastatic wild-type EGFR NSCLC[5,8]. ISEL and BR.21 showed that treatment with a TKI led to an increase in the progression free survival and a better quality of life. A survival benefit was shown in BR.21 but not ISEL. However, the data available is less clear when it comes to comparing TKIs with chemotherapy. INTEREST and TITAN are two trials that compared gefitinib and erlotinib, respectively, with conventional chemotherapy in patients with metastatic, EGFR wild-type NSCLC, who were previously treated with platinum-based chemotherapy. The authors of both trials reported that TKIs were not inferior to conventional chemotherapy. In contrast to these findings, the TAILOR study found that conventional chemotherapy produced a better response rate and a longer progression free survival when compared to erlotinib in a similar patient population. Finally, the SATURN trial examined the benefit of maintenance TKIs following treatment with platinum based chemotherapy in patients with EGFR wild-type NSCLC. Results showed a prolongation in the progression free survival[8]. The success of TKIs in producing clinically significant results in patients with mutant EGFR lung cancer has generated an accelerated interest in identifying additional molecular targets. ALK gene rearrangements in lung cancer were discovered in 2007. Subsequently, crizotinib, an ALK inhibitor, received accelerated approval by the US Food and Drug Administration (FDA) in 2012 for ALK positive patients[24]. Insertion mutations in HER2 are seen in 2% to 4% of NSCLC patients. Studies are ongoing to assess the role of TKIs (afatinib and neratinib) in the treatment of this subtype[25].

In conclusion, we have shown the results of screening for EGFR mutations in patients with lung adenocarcinoma in a tertiary institute in Ireland. Our practice, in accordance with international guidelines, is to screen all patients with metastatic lung adenocarcinoma for EGFR mutations. We found that 13.8% of patients with metastatic lung adenocarcinoma treated at our centre have an EGFR activating mutation. A rate that is similar to that reported in international trials in Caucasian patients. NSCLC patients with EGFR mutations represent only a small percentage of lung adenocarcinomas overall. The war on lung cancer is far from over. Basing treatment options on the molecular profile of individual tumours, in other words personalized medicine, is an invaluable weapon in this war.

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References

1. Ding L et al Somatic mutations affect key pathways in lung adenocarcinoma Nature. 2008 Oct 23; 455:1069-75.
2. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, Nardone J, Lee K, Reeves C, Li Y, Hu Y, Tan Z, Stokes M, Sullivan L, Mitchell J, Wetzel R, Macneill J, Ren JM, Yuan J, Bakalarski CE, Villen J, Kornhauser JM, Smith B, Li D, Zhou X, Gygi SP, Gu TL, Polakiewicz RD, Rush J, Comb MJ.. Global survey of phosphotyrosine signalling identifies oncogenic kinases in lung cancer. Cell. 2007 Dec 14; 131:1190-203.
3. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer. 2006;118:257–62.
4. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA.. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004 May 20; 350:2129-39.
5. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, Majem M, Lopez-Vivanco G, Isla D, Provencio M, Insa A, Massuti B, Gonzalez-Larriba JL, Paz-Ares L, Bover I, Garcia-Campelo R, Moreno MA, Catot S, Rolfo C, Reguart N, Palmero R, Sánchez JM, Bastus R, Mayo C, Bertran-Alamillo J, Molina MA, Sanchez JJ, Taron M; Spanish Lung Cancer Group.. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009 Sep 3; 361:958-67.
6. Cancer in Ireland 2011: Annual report of the National Cancer Registry.
7. Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.Ann Oncol. 2012 Oct; 23 Suppl 7:vii56-64.
8. Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, McShane LM, Milton DT, Strawn JR, Wakelee HA, Giaccone G.. American Society of Clinical Oncology provisional clinical opinion:

epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol. 2011 May 20;29:2121-7.
9. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, : Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957, 2009.
10. Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT, Ahn MJ, Yun T, Ahn JS, Suh C, Lee JS, Yoon SJ, Han JH, Lee JW, Jo SJ, Lee JS.: First-SIGNAL: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 30:1122-1128, 2012.
11. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T; North-East Japan Study Group: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380-2388, 2010.
12. Mitsudomi T1, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukuoka M; West Japan Oncology Group.: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11:121-128, 2010.
13. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L, You C. : Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735-742, 2011.
14. Rosell R et al; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. : Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13:239-246, 2012.
15. E. Bria, M Milella, F Cuppone,S Novello, A Ceribelli,V Vaccaro,I Sperduti, A Gelibter, GV Scagliotti, F Cognetti, D Giannarelli. Outcome of advanced NSCLC patients harbouring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis. Ann Oncol. 2011 Oct; 22:2277-85.
16. Intergroupe Francophone de Cancerologie Thoracique.Tailored Post-Surgical Therapy in Early Stage NSCLC (TASTE). http://clinicaltrials.gov/show/NCT00775385. Accessed 1 March 2013.
17. Astellas Pharma Inc. A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Single-agent Tarceva® (Erlotinib) Following Complete Tumor Resection With or Without Adjuvant Chemotherapy in Patients With Stage IB-IIIA Non-small Cell Lung Carcinoma Who Have EGFR-positive Tumors. http://clinicaltrials.gov/ct2/show/NCT00373425. Accessed 1 March 2013.
18. Chinese Lung Cancer Surgical Group. Erlotinib versus Vinorelbine/Cisplatin as Adjuvant Treatment in Stage IIIA NSCLC Patients with EGFR Mutations. http://clinicaltrials.gov/ct2/show/NCT01410214. Accessed 1 March 2013.
19. Erlotinib Versus Gemcitabine/Cisplatin as (Neo) Adjuvant Treatment in Non-small Cell Lung Cancer (EMERGING). http://clinicaltrials.gov/ct2/show/NCT01407822.
20. James Chih-Hsin Yang et al. Sequist. LUX-Lung 3: A randomized, open-label, phase III study of afatinib vs. pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung g harbouring EGFR-activating mutations. J Oncol 30:480s, 2012.
21. Nelson V, Ziehr J, Agulnik M, Johnson M. Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. Onco Targets Ther. 2013; 6:135-43.
22. ARCHER 1009: A Study Of PF-00299804 (Dacomitinib) Vs. Erlotinib In The Treatment Of Advanced Non-Small Cell Lung Cancer. http://clinicaltrials.gov/ct2/show/NCT01360554.
23. Ohashi K, Maruvka YE, Michor F, Pao W. Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. J Clin Oncol. 2013 Mar 10; 31:1070-80.
24. Shaw AT, Engelman JA. ALK in lung cancer: past, present, and future. J Clin Oncol. 2013 Mar 10; 31:1105-11.
25. Oxnard GR, Binder A, Jänne PA. New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol. 2013 Mar 10; 31:1097-104.

Is the NHS Best Practice Tariff for Type 1 Diabetes Applicable in the Irish Context?

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Abstract
The National Health Service in the UK has identified thirteen key standards of paediatric diabetes care. Funding depends on services meeting these standards. The aim of this study was to determine if these standards are applicable in an Irish setting. All patients attending the diabetes service during 2012 were included. Patient charts, electronic appointments, nursing notes and computerised results were used to ascertain relevant information for comparison with the NHS standards. Patients attended a mean 2.97 (SD 0.7) medical and 2.2 (SD 2.9) nursing appointments per year, with a median additional contacts of 8 nurse phone calls (range 0 – 125). Most standards were met by this service. In comparing our service to the NHS standard, we have identified a number of areas for improving our service provision. Limited resources and staff shortages make a number of these standards unachievable, namely annual dietetic review and three monthly outpatient appointments.

Introduction

Over 95% of paediatric diabetes diagnoses in Europe are type 1[1]. The Diabetes Control and Complications Trial showed definitively that intensive therapy in type 1 diabetes mellitus improves glycaemic control, reducing the risk of long-term microvascular and macrovascular complications[2,3]. Achieving tight metabolic control is difficult and requires multidisciplinary input[4]. Best practice guidelines from the National Institute of Health and Clinical Excellence (NICE)[5] and the International Society for Pediatric and Adolescent Diabetes (ISPAD)[6] recommend that newly diagnosed children with type 1 diabetes should receive standardized care. This should include immediate referral to a multidisciplinary paediatric diabetes team; entry onto a national register; adequate diabetes education updates; 24 hour access to diabetic emergency management advice; screening for coeliac disease and thyroid dysfunction at diagnosis; routine assessment

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for retinopathy, microalbuminuria and hypertension from age 12, along with ongoing psychosocial support[5,6]. Recent audit of UK practice showed that diabetes control in childhood is sub optimal[7]. The National Diabetes Audit 2009-10[8] found that only 14.5% of children achieved the target glycosylated haemoglobin (HbA1c) of under 7.5% (58 mmol/mol), and this improved to 15.8% the following year [9]. 30.7% of children had HbA1c greater than 9.5% (80 mmol/mol) in 2009-10 and this improved slightly to 28.7% the next year[8,9]. To address this, the National Health Service developed thirteen key standards of paediatric diabetes care to be implemented from April 2012. If standards are not met, services have one year to improve, otherwise funding (£3,189 per child per annum) will be withdrawn[10].

These standards also address the structure and training of the diabetes team. Newly diagnosed patients must be discussed with the specialist team within 24 hours, and seen by the team on the next working day. A structured education programme must be provided at diagnosis with updates and 24 hour access to advice on emergency management should be available. Patients must be offered four clinic appointments and HbA1c checks per year, with annual review as per the NICE guidelines. Patients should also have annual dietetic and psychological assessment. The diabetes team should partake in local meetings and national audit, and formal written policies must be in place for transition, poor glycaemic control, and non-attendances[10].

Although a detailed national audit in Ireland has not been performed, it is likely that current practices are reflective of those in the UK. There are limited data available on the demographics of the Irish paediatric diabetes population. In 2006, twenty-nine consultants provided care for two thousand and forty patients with type 1 diabetes in nineteen centres across the Republic of Ireland, with only 50% of these consultants having a special interest in diabetes[11]. The average caseload per diabetes nurse specialist was 162, and per dietitian was 416. 70% of patients had no access to psychology services. No data on HbA1c levels was reported in this study[11]. A national paediatric diabetes audit group has recently been set up in Ireland. This aims to describe the services currently provided for children in Ireland with Type 1 diabetes, and the short-term outcomes in this population. As a pilot study for this national audit, we audited our service to determine if the UK tariff guidelines could identify areas for improvement in an Irish context.

Table 1 Clinic overview

	0-5.99 yrs	6-11.99 yrs	12-15.99 yrs	>16 yrs	All Patients
Total Patient Number Jan 2013	41	99	129	45	314
Newly Diagnosed Jan-Dec 2012	10	21	18	0	49
Shared care	5	8	6	0	19

Methods

All children with type 1 diabetes attending the Children's University Hospital, Temple Street, were included in this retrospective chart review, which covered a period from January to December 2012. Patient charts, electronic appointments, diabetes nursing notes and computerised blood results were used to compile the relevant information. This service provision was compared with the NHS standards. This was subsequently analysed using Statistical Product and Service Solutions version version 20.0 (IBM, New York, USA).

Table 2 Demographics

	0-5.99 yrs	6-11.99 yrs	12-15.99 yrs	>16 yrs	All Patients
Analysis 12 month follow up	23	74	110	39	246
Mean (SD) Diabetes Duration (after 1 year of diagnosis)	2.5 (2.3)	4.2 (2.2)	6 (3.1)	7.7 (3.7)	
Male	12 (52%)	34 (45%)	50 (44%)	25 (65.6%)	121 (49%)
Insulin pumps	8 (34%)	44 (59%)	46 (41%)	12 (32%)	110 (45%)
HbAic % {mmol/mol} (mean (SD))	8.2 {66}(0.9)	8.1 {65}(0.7)	8.5 {69} (1.2)	8.7 {71} (1.5)	8.4 {68}
HbAic < 7.5% (58 mmol/mol)	8 (35%)	10 (13.5%)	21 (19%)	11 (28%)	50(20.33%)
<8 (64 mmol/mol)	9 (39%)	36 (48%)	18(16%)	10 (25%)	73 (29.67%)
>9 (75 mmol/mol)	3 (13%)	6 (.08%)	5 (.03%)	11 (28%)	25 (10.16%)

Table 3 Comparison of our service from Jan 2012 – December 2012 with the NHS standards (Mean and SD in italics)

Tariff	NHS Standards	0-4yrs	5-11yrs	12-16yrs	>16yrs	All Patients
Number of patients included in analysis		12	68	106	36	222
OPD Appointments	≥4					
5 appointments		0	4	2	1	7
4 appointments		1	4	6	1	12
3 appointments		10	54	85	28	177
2 appointments		0	6	7	4	17 (shared care)
1 appointment		0	0	3	1	4
0 appointments		*1	0	*3	*1	*5
DNS Apt		Mean 3.42 (2.94)	Mean 2.32 (0.46)	Mean 1.9 (2.7)	Mean 2.3 (3.42)	Mean 2.2 (2.9)
		Median 2.5 (0.5-5.75)	Median 1 (0-4)	Median 1 (0-2)	Median 1 (0-3)	Median 1 (0-3)
		Range 0-8	Range 0-17	Range 0-17	Range 0-18	Range 0-18
No of HbA1c checks	≥4	3.55 (1)	3.29 (0.6)	3.45 (1) 3.26 (1.2)	Mean=3.38 (0.93)	
Additional Contacts Phone call from nurse	≥8	Median = 8 (IQR 3.75-11.75, Range 0-19)	Median = 2 (IQR 1-5, Range 0-112)	Median = 3 (IQR 1-5, Range 0-17	Median = 4 (IQR 1-7, Range 0-16)	Median =3 (IQR 1-6, Range 0-112)
Phone call to nurse		Median = 9.5 (IQR 3.5-35.5. Range 0-125)	Median = 7 (IQR 2.5-23. Range 0-94)	Median = 5 (IQR 1-13.5. Range 0-31)	Median = 3 (IQR 1-6. Range 0-47)	Median =5 (IQR 2-16. Range 0-125)
TFT	1	10 (83.3%)	63 (92%)	99 (93.4%)	35 (97.2%)	207 (93%)
Coeliac Screen	1	6 (50%)	61 (89.7%)	98 (92.5%)	34 (94.4%)	199 (89.6%)
Lipid Profile	1	1 (8.3%)	13 (19.1%)	65 (61.3%)	26 (72.2%)	105 (47%)
Microalbuminuria	1 (12yrs)	10 (83.3%)	61 (89.7%)	94 (88.7%)	33 (91.7%)	198 (89%)
Dietitian Apt	1	1 (8.3%)	12 (17.6%)	25 (23.6%)	5 (13.9%)	43 (19.4%)
Ophthalmology	1 (12yrs)	8 (66.7%)	58 (85.3%)	104 (98.1%)	29 (80.6%)	199 (90%)
Psychosocial Apt	As required	2 (16.7%)	64 (22%)	24 (22%)	7 (19.4%)	97 (43%)

* Of the 9 patients with one or less appointments, 1 was based in another country for a year, 2 were seen as inpatients when attending with other comorbidities and 6 have care shared with other centres. One is a true non-attender, which was addressed.

Results

314 patients were attending the diabetes service on 31st December 2012, of whom 49 were diagnosed in 2012. Nineteen (of 314) had care shared with another centre. Demographics of these patients are shown in Tables 1 and 2. Service provision for all patients who had been followed up for at least 12 months in comparison to the NHS standards is shown in Tables 3 and 4.

The diabetes team at Children's University Hospital, Temple Street comprised 0.6 working time equivalent (WTE) consultant, 1 WTE specialist registrar, 1 WTE intern, 0.3 WTE Senior Health Officer, 2.2 WTE diabetes nurses, 0.5 WTE social worker, 0.3 WTE dietitian, 0.5 WTE psychologist, and 0.1 WTE psychiatrist. The consultant, specialist registrar, intern and senior house officer workload was split between diabetes and endocrinology. In this service, outpatient appointment frequency was reduced to four monthly in 2010 to allow more time per consultation as patient numbers increased. Where necessary, additional outpatient appointments or diabetes nurse appointments were offered. The mean number of outpatients appointments attended were 2.97 (SD 0.7) and diabetes nurse appointments were 2.2 (SD 2.9). The median number of additional contacts provided was 8 nurse phone calls (range 0-125).

Table 4 Comparison of National Health Service best practice standards for paediatric diabetes and current practice in Temple Street

	National Health Service best practice for paediatric diabetes guidelines	Children's University Hospital, Temple Street
1.	Every child cared for by specialist team*	YES
2.	Consultant / specialist with BSPED** training; Paediatric nurse with RCN× diabetes training; Paediatric dietitian with paediatric diabetes training	YES
3.	Newly diagnosed patient should be discussed with team within 24 hours, and seen by senior member of team on next working day	YES
4.	Structured education programme at diagnosis, with follow ups as needed	YES
5.	Four clinic appointments offered annually	Three offered to all patients
6.	HbA1c checked four times annually, with result available at every clinic	Three offered to all patients, available in clinic
7.	Offered dietitian appointment annually	Only offered as required
8.	At least eight additional contacts per year by the team	YES
9.	Annual review as per NICE¤ guidelines	YES
10.	Annual psychological assessment and service access provided as needed	Only offered as required
11.	24 hour advice to emergency management for family and health professionals	YES
12.	Partake in National Paediatric Diabetes Audit; attend local Paediatric Diabetes Network meetings; have a clear policy for transition to adults services	No current national diabetes audit; policies in places; local meetings attended
13.	Clear policy for high HbA1cs and persistant DNAs	No written policy in place

* Consisting of a doctor, nurse and dietitian, as a minimum, with specific training in paediatric diabetes
** British Society for Paediatric Endocrinology and Diabetes
¤ National Institute of Health and Clinical Excellence
× Royal College of Nursing

Such as phone calls, emails, school visits
Δ Non-attendance

20.3 % of patients achieve the target HbA1c of <7.5%. Almost 30% of our patients had a HbA1c below 8%, and only 10% had a HbA1c of greater than 9%. 19.4% had a dietetic review, 43% a psychology review, and 90% had an ophthalmology review during the study period. While 246 patients attended the service in Temple Street in 2012 and were diagnosed with diabetes for > 1 year, complete 2012 data was not available for all as some patients transitioned to newly established services locally and to young adult services during the study period. Complete data on service provision was available for 222 patients, as seen in Table 3.

Discussion

Auditing our practice against the NHS tariff has been a useful exercise for our department. Despite our suboptimal resources, we are mostly compliant with the NHS standards. These include the diabetes team composition, structured education programme, number of contacts per year and psychosocial assessment as required. However, we are not meeting all criteria. This is reflective of UK practice, where a recent study of 21 paediatric diabetes services revealed that no centre met all NICE guidelines regarding resource recommendations[12]. Increasing patient numbers and limited resources have necessitated modifications in our practice. In order to maximize the benefit of each outpatient encounter, and avoid the overbooking of clinics, we have reduced outpatient frequency to four monthly. Patients identified to be having difficulties are offered focused extra medical or nursing appointments. We feel that this has been a successful intervention, but it has reduced our average outpatient appointments attended to 2.97 per patient per year. Diabetes Specialist Nurse appointments and frequent phone calls bring our average number of contacts per patient per year far above the guideline number of 8.

While our clinic average HbA1c remains sub optimal, and this remains a constant focus area for improvement, 20.33% of our patients achieve HbA1c <7.5% (56 mmol/mol), compared to only 15.8% of UK patients in the 2010-11 audit[9]. Our patient population includes a relatively large proportion of socially disadvantaged patients, where achieving optimal control is more challenging[12]. Adolescents in our service are less successful at maintaining good control and on reviewing the data from this audit, we are planning to see teenagers every 3 months rather than the clinic standard of 4 monthly. Our patients aged over 16 have a significantly higher HbA1c (mean 8.7 % (71 mmol/mol)), and this is largely affected by selection bias. Patients are generally transitioned to the adult services at 16 years of age, but patients with poor glycaemic control are often held for a further year to optimize their control in advance of transition. A specific area for improvement identified by this audit is the streamlining of annual assessment investigations. Full lipid profiles are not performed in all patients over 12 years of age, despite most having annual blood tests done. Depending on correct form completion, the biochemistry laboratory will perform either a full lipid profile or a single cholesterol test. The magnitude of this discrepancy was not previously identified and will be addressed. Furthermore, international guidelines suggest checking for microalbuminuria in children >5 years from diagnosis and annually from puberty but in our service urinary microalbumin/creatinine ratio is tested unnecessarily in most patients under 12 years. Ophthalmology assessment is also performed when not indicated in children under 12 years.

Dietitian availability for children with type 1 diabetes in Ireland is a significant issue, with only 19.4% receiving dietetic review during the study period. Despite our large patient numbers, we have just 0.3 WTE dietitian but this very committed and efficient individual has facilitated newly diagnosed education and carbohydrate counting for pump initiation for a large group of patients during this study period. It is not possible to offer an appointment to each patient annually in this context, and patients who have acquired full carbohydrate counting skills may not want or require an annual dietitian review. Regarding psychological review, we are compliant with the standards, whereby patients are asked at annual review if they would like to access psychological services. While our service had informal policies in place to address poor diabetes control and recurrent non attendance, after this audit identified deficiencies, we have put formal policies in place.

In order to identify these potential areas for improving our service, patient charts and blood results were meticulously analysed. This process was extremely time consuming and limited by a reliance on accurate documentation. It is likely that all appointments and contacts are an underestimation of the true number as they depended on manual data entry. This issue is not confined to our service and was a common problem in the National Paediatric Diabetes Audit 2009-10 whereby the accuracy of the paper records was questioned[8,9]. This audit shows the benefit that a service can accrue from systematic evaluation. An automated national computerised system would allow the prospective collection and audit of performance indicators. However, the implementation of such a system that integrated with clinical practice, would require significant financial investment. We found that auditing our service against the NHS standards has reassured us in the quality of care that we provide, and also identified a number of potential areas for improvement. Little is known about the provision of care for children with type 1 diabetes in Ireland, and a national audit is currently in progress.

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References

1. Edge J, Ackland FM, Payne S, McAuley A, Hind E, Burren C, Burditt J, Sims D. Inpatient care for children with diabetes: are standards being met? Arch Dis Child. 2012;97 :599-603.
2. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329:977-986.
3. Raskin P. The DCCT—Finally! Trends in Endocrinology and Metabolism. 1993;4 :279-280.
4. Pihoker C, Forsander G, Wolfsdorf J, Klingensmith GJ. The delivery of ambulatory diabetes care to children and adolescents with diabetes. Pediatric Diabetes. 2009;10:58-70.
5. NICE. CG015. Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. National Institute for Clinical Excellence. 2009.
6. IDF. Global IDF/ISPAD guideline for Diabetes in Childhood and Adolescence 2011 [November 24, 2012]. Available from: http://www.ispad.org/NewsFiles/IDF-ISPAD_Diabetes_in_Childhood_and%20Adolescence_Guidelines_2011.pdf.
7. Gosden C, Edge JA, Holt RI, James J, Turner B, Winocour P, Walton C, Nagi D, Williams R, Matyka, K. The fifth UK paediatric diabetes services survey: meeting guidelines and recommendations? Arch Dis Child. 2010;95 :837-840.
8. NHS. National Diabetes Paediatric Audit Report 2009-2010. 2011.
9. NHS. National Diabetes Paediatric Audit 2010-2011. 2012.
10. NHS. Paediatric Network Best Practice Tariff for Paediatric Diabetes 2012 [July 18, 2012]. Available from: http://www.diabetes.nhs.uk/networks/paediatric_network/best_practice_tariff_for_paediatric_diabetes/.
11. Savage T, Clarke A, Costigan C, Loftus BG, Cody D. Services for children with diabetes. Ir Med J. 2008;101:15-17.
12. Harron KL, McKinney PA, Feltbower RG, Holland P, Campbell FM, Parslow RC. Resource and outcome in paediatric diabetes services. Arch Dis Child. 2012;97:526-528.

Pulmonary Non-Tuberculous Mycobacteria in a General Respiratory Population

To receive CPD credits, you must complete the questions online at www.imj.ie.

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Abstract
The prevalence of non-tuberculous mycobacterium (NTM) appears to be increasing. Much of the experience in the literature about this emerging organism comes from specialised units or populations such as cystic fibrosis patients. We, therefore, aim to evaluate the experience in a general respiratory population of dealing with patients with positive culture of NTM. We did a retrospective review of medical notes of general respiratory patients from whom NTM were isolated from January 2007 to July 2012. Cystic fibrosis patients were excluded. We reviewed 37 patients' (19 males, 18 females) medical records. A total of 73 positive cultures were reviewed. 28 isolates were from sputum samples alone, 34 isolates were from bronchoalveolar lavage alone and 11 isolates were from a combination of sputum and bronchoalveor lavage (11 isolates). We found that Mycobacterium avium was the most frequently isolated Mycobacterium in our laboratory with 22 (60%) patients had Mycobacterium avium in their pulmonary cultures. Interestingly, Mycobacterium gordonae and mycobacterium intracellulare were the second commonest mycobacterium (4, 11%) cultured. We noted 2 (5%), cases of Mycobacterium szulgai, 2 (5%) cases of Mycobacterium chelonae and 2 (5%) cases of Mycobacterium abscessus. There was 1(3%) case of Mycobacterium malmoense. There is prevalence of NTM in male COPD patients (7, 89%) and female bronchiectasis (10, 77%) patients. Of our 8 COPD patients, 6 (75%) were on inhaled corticosteroids while 2 (25%) were not. 9 (24%) patients were smokers, 11 (30%) were ex-smokers, 14 (38%) were non-smokers and the smoking status of the remaining 3 (8%) was unknown. Of the 37 patients, only 6 (16%) received treatment. However, 2 patients stopped their treatment due to treatment toxicity. We concluded that the isolation of NTM is not uncommon. Defining NTM disease is difficult and deciding which patient to be treated needs careful evaluation as treatment can potentially be very toxic.

Introduction

The past twenty years have seen an increased recognition of the role of non-tuberculous mycobacteria (NTM) in respiratory disease. This growing awareness may be attributed both to increasing prevalence of infection and a more widespread acknowledgement of a pathogenic role for NTM. Studies from Europe and North America have demonstrated that isolation of NTM is not uncommon[1-3]. Some of this increase in the number of NTM isolates may be due to improvement in the microbiological culture methods, increasing awareness of NTM infections, aging and increasing numbers of immunosuppressed populations[4]. There are conflicting data between North American and European studies on incidence and other epidemiological features with variations in the prevalence of specific mycobacteria even within countries[5], the presence of underlying disease and differences in gender prevalence in patients with the disease[2,6]. Whilst some NTMs may not be pathogenic, they have been associated with a wide variety of lung diseases including cavitary disease, bronchiectasis and hypersensitivity pneumonitis. Because environmental NTMs are capable of contaminating clinical specimens or acting merely as commensals, correlation with clinical and radiological findings is required to define the presence of the disease.

Published criteria include the presence of pulmonary symptoms, together with radiographic opacities on plain radiographs or computed tomography (CT) scans[7]. These findings need to be combined with positive culture results from patients' specimens. Despite increasing awareness of the role of NTMs in respiratory disease, most published data comes from individual case reports, epidemiological studies, or reports from specialised institutions or specific populations such as cystic fibrosis patients. The implication of these studies for the individual practicing clinician is not clear. We therefore reviewed the cases of all non- cystic fibrosis patients who had positive respiratory cultures for NTM over a five year period in our institution, a tertiary care university teaching hospital, examining the relationship of NTM culture and disease with underlying demographic and clinical variables.

Methods

The laboratory records in the department of Microbiology were used to identify all isolates of NTM from January 2007 to July 2012. The medical records of patients from whom NTM were

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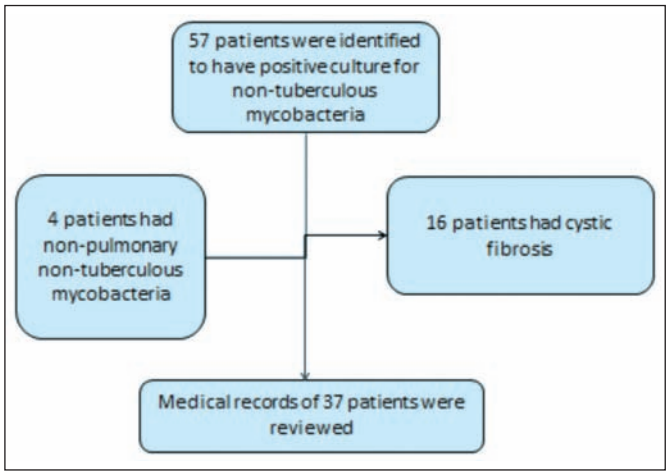

Figure 1 Flow chart of study

isolated were reviewed and patients with cystic fibrosis or non-pulmonary isolates were excluded.

Results

A total of 57 patients from whom NTM were isolated were identified. Of these, 20 were excluded from further analysis as 16 patients had cystic fibrosis and 4 had non-pulmonary isolates of non-tuberculous mycobacteria (Figure 1). The medical records of 37 patients (19 male and 18 female) with a total of 73 positive cultures were reviewed. The 73 respiratory tract isolates were from sputum samples alone (28 isolates), bronchoalveolar lavage alone (34 isolates) and combinations of sputum and bronchoalveor lavage (11 isolates). The NTM most frequently isolated in our institution was Mycobacterium avium (n=22) (Figure 2).

Mycobacterium gordonae and Mycobacterium intracellulare were each isolated from 4 patients. 2 patients had Mycobacterium

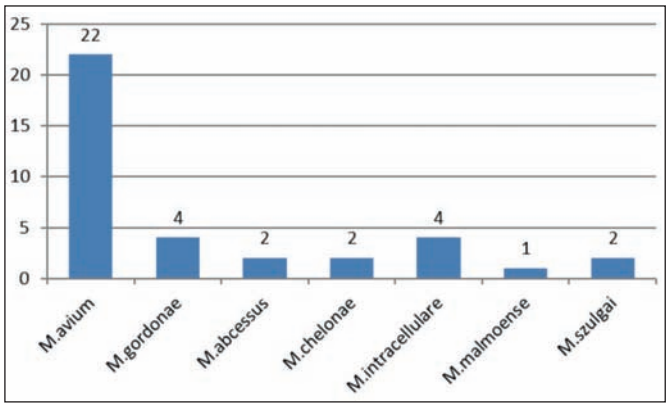

Figure 2 Distribution of non-tuberculous mycobacteria in 37 patients

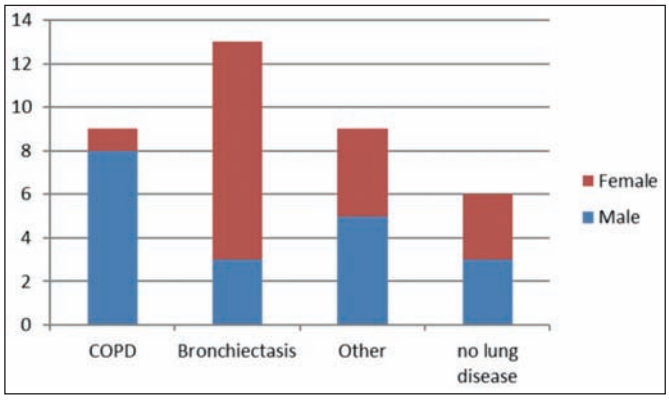

Figure 3: The distribution of underlying lung disease in our patients

szulgai, 2 had Mycobacterium chelonae and 2 had Mycobacterium abscessus. 1 patient had Mycobacterium malmoense. Our study population consisted of 19 male and 18 female patients. The mean age of our patients was 64.8±14.6 years. All except 6 patients had underlying respiratory disease; the most common were bronchiectasis (14, 37%) and COPD (8, 24%). Our patients' characteristics are shown in Table 1. There was a significant female predominance among subjects with bronchiectasis (77%), while those with underlying chronic obstructive pulmonary disease (COPD) were more likely to be male (89 %) (figure 3). Of our COPD patients, 6 were on inhaled corticosteroids at the time of diagnosis while 2 were not. 2 patients were on inhaled corticosteroids for their bronchiectasis or asthma. Symptoms such as fever, weight loss, night sweats and loss of appetite occurred in 7 patients in our population.

Table 1 The characteristics of our patients

Number	37
Age	64.8 ± 14.6
Male: Female	19:18
Underlying Lung Disease	
Bronchiectasis	34%
COPD	26%
Asthma	10%
Interstitial Lung Disease	5%
Other	8%
None	16%
Smoking Status	
Non-smoker	26%
Smoker	29%
Ex-smoker	37%
Unknown	8%
Percentage of Patients using Inhaled Corticosteroids	
COPD	60%
Bronchiectasis/ asthma	12%

Seven patients presented with recurrent lower respiratory tract infections, 3 presented with persistent productive cough and 3 had a history of haemoptysis. Two patients were asymptomatic at diagnosis but had chest x-ray changes that were consistent with mycobacterial infections. 9 (24%) patients were smokers, 11 (30%) were ex-smokers, 14 (38%) were non-smokers and the smoking status of the remaining 3 (8%) were unknown. Most of our patients remained well despite having NTM positive cultures. We utilised the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines in defining disease for our population and considering treatment. We found that 6 patients fulfilled the diagnostic criteria for NTM disease and were put on treatment. However, only 4 patients completed the full course of treatment, with 2 stopping treatment prematurely due to intolerance of the medications due to nausea. One of the 2 patients who stopped treatment died due to pulmonary NTM disease.

Discussion

This case series confirms that NTM is commonly cultured from laboratory specimens in a general respiratory practice but that the clinical significance in many cases is unclear. The American Thoracic Society (ATS/IDSA) have published guidelines for the identification and management of patients with NTM[7]. These guidelines suggest that patients suspected of having NTM disease must have persistent symptoms compatible with NTM infection, radiologic changes and the finding of at least two sputum samples or one bronchial wash or lavage positive for NTM[7]. Follow-up of patients whose pulmonary specimens have grown NTM but do not meet the criteria for treatment is suggested until the diagnosis is firmly established or excluded. The authors point out that the making of the diagnosis does not, per se, necessitate commencing treatment.

Our data confirm the findings of Winthrop et al. that men with NTM were more likely to have COPD and women were more likely to have bronchiectasis[1]. The reason for this is unknown. An association of pulmonary NTM with pectus excavatum and scoliosis was confirmed by Kartalija et al, who also found lower levels of whole-blood IFN-g after ex vivo stimulation, and altered serum adipokine levels normalized for body fat[8]. Thus this phenotype may be associated with an underlying immunological or mucocilary clearance defect. The severity of any immune dysfunction has also been postulated to contribute both to the severity of the structural lung disease and NTM disease[9]. Inhaled corticosteroids may impair local respiratory defences and

predispose to respiratory infections in COPD. NTM appears to have a predilection for patients with COPD who use inhaled corticosteroids, with an adjusted odds ratio of 29.1 in a recent study[10]. In our study, 60% of COPD patients had been on inhaled steroids. The precise mechanism underlying an increased risk of NTM infection in patients on inhaled corticosteroids remains unclear[10]. As expected, the majority of the NTM cultured in our laboratory were Mycobacterium avium complex, in keeping with the majority of previous studies[1-3]. Interestingly, Mycobacterium gordonae, a mycobacterium with very low pathogenicity, was the second commonest organism found, in 10% of samples in our series. This is in contrast to the study done by Kennedy et al on the incidence of NTM in southwestern Ireland from 1987 to 2000 who found that the commonest NTM isolated in decreasing order are MAC, malmoense, marinum and kansaii[11]. Although low in pathogenicity, Mycobacterium gordonae has been reported to cause disease even in immunocompetent patients requiring treatment[12]. In our series there were also two cases of Mycobacterium Szulgai, which is rare occurrence in most international series [13]. A previous case report by Sanchez-Alarcos stated that there had only been 35 cases previously in the English language literature[13]. However a single case has recently been reported by another institution in Ireland[14].

These differences in findings probably reflect geographical variation in the prevalence of NTM species between and within countries and emphasize the need to be aware of the occurrence of unusual NTM locally. As smoking is a risk factor for underlying lung disease, it might be assumed that the prevalence of smoking in patients with NTM would be very high. However, only 29% of our patients, who had an extensive amount of background lung disease, had a current smoking habit. It can be argued that the effect of cigarette smoking depends on ethnicity, sex and duration of the smoking habit. Another possible hypothesis is that smoking produces significant levels of oxygen radicals that destroy NTM and thus helps to protect against NTM disease. As our results show, not all patients will benefit from treatment for NTM disease. 33% of the treated patients in our population did not tolerate the medications well. Treatment guidelines for NTM disease[7] issued by ATS were followed in the management of these cases. Treatment consisted of a multidrug regimen, which may be complicated by potential toxicity, interactions with other concomitant medications and a prolonged requirement for treatment[15]. The multidrug regimen prescribed to patients with NTM disease depends on the particular NTM species isolated. Susceptibility testing is recommended to guide therapy and close liaison with a local clinical microbiologist is advised. Expertise from an experienced respiratory physician in NTM disease should be sought and patients diagnosed with NTM disease need to be regularly monitored for clinical improvement and toxicity. It is important to note that failure rates are high, treatment might be prolonged, nearly always in excess of twelve months and relapses despite initial successful therapy can occur[15].

In conclusion, this series suggests that the isolation of NTM is not uncommon in a general respiratory practice. Clinicians should be aware of any unusual local epidemiology of NTMs. A diagnosis of NTM disease can be difficult to make and not all patients with positive NTM respiratory culture required treatment. Treatment should be tailored individually as treatment is often poorly tolerated.

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References

1. Winthrop KL, McNelley E, Kendall B, Marshall-Olson A, Morris C, Cassidy M, Saulson A, Hedberg K Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. Am J Respir Crit Care Med. 2010 Oct 1;182:977-82.
2. Andréjak C, Thomsen VØ, Johansen IS, Riis A, Benfield TL, Duhaut P, Sørensen HT, Lescure FX, Thomsen RW Nontuberculous pulmonary mycobacteriosis in Denmark: incidence and prognostic factors. Am J Respir Crit Care Med. 2010 Mar 1;181:514-21.
3. Marras TK, Chedore P, Ying AM, Jamieson F, Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997-2003Thorax. 2007 Aug;62:661-6.
4. CL Daley, DE Griffith, Pulmonary non-tuberculous mycobacterial infections Int J Tuberculosis Lung Disease 2010 Jun;14:665-71.
5. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR, Prevalence of Nontuberculous Mycobacterial Lung Disease in U.S. Medicare Beneficiaries. Am J Respir Crit Care Med 2012;185:881–886.
6. Al-Houqani M, Jamieson F, Mehta M, Chedore P, May K, Marras TK, Aging, COPD, and other risk factors do not explain the increased prevalence of pulmonary Mycobacterium avium complex in Ontario. Chest. 2012 Jan;141:190-7.
7. Griffith DE, Aksamit T, BrownElliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K, ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment,and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007 Feb 15;175:367-416.
8. Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, Strand MJ, Bai X, Ramamoorthy P, Rothman MS, Nagabhushanam V, McDermott M, Levin AR, Frazer-Abel A, Giclas PC, Korner J, Iseman MD, Shapiro L, Chan ED, Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. Am J Respir Crit Care Med. 2013 Jan 15;187:197-205.
9. Melia E, Freeman AF, Shea YR, Hsu AP, Holland SM, Olivier KN, Pulmonary nontuberculous mycobacterial infections in hyper-IgE syndrome, J Allergy Clin Immunol. 2009 Sep;124:617-8.
10. Andréjak C, Nielsen R, Thomsen VØ, Duhaut P, Sørensen HT, Thomsen RW, Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis.Thorax. 2013 Mar;68:256-62.
11. Kennedy MP, O'Connor TM, Ryan C, Sheehan S, Cryan B, Bredin C, Nontuberculous mycobacteria: incidence in Southwest Ireland from 1987 to 2000. Respir Med. 2003 Mar;97:257-63.
12. Fujita Y, Matsumoto H, Fujikane T, Nakao S, Sasaki N, Takahashi M et al, Pulmonary infection caused by Mycobacterium gordonae in immunocompetent patient, Kekkaku. 2000 Apr;75:369-74.
13. Sánchez-Alarcos JM, De Miguel-Díez J, Bonilla I, Sicilia JJ, Alvarez-Sala JL, Pulmonary infection due to Mycobacterium szulgai. Respiration. 2003;70:533-6.
14. McSweeney FG, O'Brien ME, Sheehan S, Pulmonary Mycobacterium szulgai infection. Ir Med J. 2012 Sep;105:275-7.
15. Arend SM, van Soolingen D, Ottenhoff TH, Diagnosis and treatment of lung infection with nontuberculous mycobacteria. Curr Opin Pulm Med. 2009 May;15:201-8.

Can Multiple Mini Interviews Work in an Irish Setting? A Feasibility Study

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Abstract
Multiple Mini Interview (MMI) is a new selection tool for medical school applicants. Developed at McMaster University in 2004 it comprises a series of interview stations designed to measure performance across a range of competencies including communication skills, team work, and ethical reasoning. In September 2012, 109 First Year Medical students underwent the MMI. It consisted of 10 stations. The median total score, out of 150, was 100 (min 63, max 129). Cronbach Alphas for the 10 individual stations range from 0.74 to 0.80.Overall Cronbach Alpha of MMI items was 0.78. Staff and student feedback was positive. The outline cost per student was estimated at €145. This study demonstrates that it is feasible to hold a MMI with acceptable levels of reliability and stakeholder approval in an Irish setting. Further work is ongoing to establish the concurrent and predictive validity of MMI in this cohort of medical students.

Introduction

Medicine is a highly sought after career choice amongst Irish school leavers. In 2010, for example there were 3,292 applicants for 434 medical schoolplaces[1]. An ideal selection tool would reliably rank applicants in accordance with valid criteria enabling predictions that they would make good doctors[2]. However there are many facets to being a good doctor[3]. Designing a selection tool that measures across these facets in a reliable and valid way is challenging. One newer tool that is gaining popularity is the Multiple Mini Interview (MMI)[4]. First developed at Mc Master University in 2004 it comprises a series of interview stations, each designed to measure performance on a different non cognitive competency such as communication skills, team work, moral reasoning and ethical decision making. It takes place in a timed circuit, similar to an OSCE. MMI is emerging as a promising selection tool with respect to its ability to predict student performance in undergraduate tests.[5,6] A recent systematic review has indicated that MMI is growing in popularity across Canada, UK, Australia and USA. It has been applied in both undergraduate and graduate Medical Schools as well as higher professional training. Its use has spread to dental, health sciences, pharmacy and veterinary programmes. The average number of stations is 10, each lasting 8 minutes and generally with one interviewer per station[5]. The aim of this study was to establish the feasibility of running a MMI in an Irish setting.

Methods

All students enrolled, for the first time, in First Year Medicine, NUI Galway, September 2012 were eligible. Ethical approval was granted by NUI Galway Research Ethics Committee. Participation was voluntary. Volunteers were entered in to a draw for an iPad. Funding was granted by WestREN (http://westren.nuigalway.ie/). Interviewers and administrators were recruited from the School of Medicine, Nursing and Health Sciences and Western Training Programme in General Practice. Role-players were selected from the Simulated Patients Group. A small number of senior cycle medical students assisted with role playing and administration. One of the authors (MK) and an acting coach trained the role players. MMI interviewers received written information in advance while interviewer briefing on station content and marking grids was conducted immediately before the MMI (by MK). Interviewers underwent online training to use OMIS software to electronically mark the MMI[7]. This software enables live psychometric analysis of station and interviewer performance.

The MMI circuit consisted of ten, seven minute stations, with one interviewer per station. Material for the stations was provided by Dundee Medical School and blueprinted against the Irish Medical Council's eight domains of professional practice[8]. Minor station modifications were made to ensure authenticity in an Irish setting. Five stations involved an interviewer, a role-player and the candidate. The other five stations were interview based (one interviewer: one candidate). Each station was scored across three domains and one global rating scale. Domain scores ranged from 0-5 (0= poor; 5 =excellent) with detailed written descriptors of excellent and poor performances. Global score were on a five point scale ranging from unacceptable to excellent performance. The MMI circuit ran over two days. Post MMI students received a debriefing lecture. In addition students obtained individual written feedback on their performance. Post MMI student and interviewer evaluation was collected anonymously by electronic questionnaire, entered into SPSS and analysed.

Results

There were 241 eligible students. Of these, 109 students (45% of class) completed the MMI comprising 41 males, 68 females. There were 64 (58.7%) EU nationals and 45 (41%) were Non-EU which is reflective of class norms. There were 49 interviewers, nine role-players, nine senior-cycle medical students and three administrators. An MMI cycle consisted of two parallel circuits. The MMI cycle was repeated 6 times to accommodate up to 120 students. Each station was scored out of a total of 15. The median total score, out of 150, was 100 (min 63, max 129). Cronbach Alphas for the 10 individual stations range from 0.74 to 0.80. Overall Cronbach Alpha of MMI items was 0.78. Feedback was returned by 71 students (65% response rate). Ninety per cent either agreed or strongly agreed that the content of the MMI was relevant to their understanding of the practice of medicine (see Figure 1). To put that in context of the students who had undergone a traditional selection interview (n=30) only 60% thought that the issues raised during the interview were relevant,

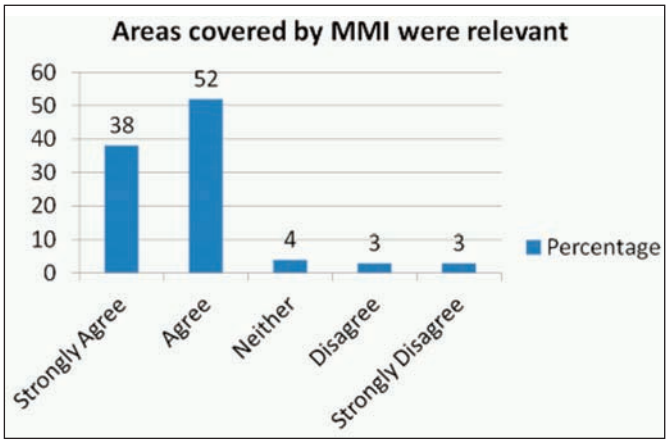

Figure 1 Student Feedback on the relevance of the MMI

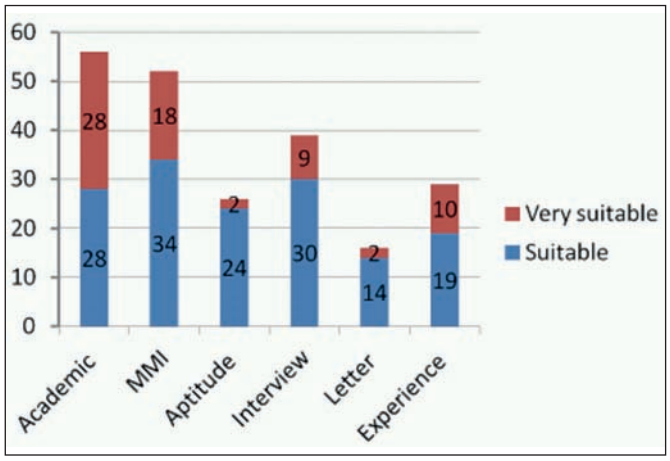

Figure 2 Student Feedback on the suitability of a variety of selection tools

Table 1 Interviewer Feedback on the MMI

Question Stem	Agree or Strongly agree	Neither agree nor disagree	Disagree or strongly disagree
The areas covered by the MMI were relevant to the practice of medicine.	75% (n=18)	8.33% (n=2)	16.67% (n=4)
The MMI stations were constructed in a manner that tested the candidates' ability to a reasonable degree	79.17% (n=19)	12.50% (n=3)	8.33% (n=2)
The issues raised by the MMI stations were sufficiently important to the practice of medicine to warrant inclusion in a selection test	62.5% (n=15)	25% (n=6)	12.5% (n=3)
MMI would be a useful addition to medical student selection in Ireland	70.83% (n=17)	8.33% (n=2)	20.83% (n=5)

correspondingly only 38% (n=47) of students who had taken an admission test (such as the HPAT) (n= 47) thought the issues covered in the test was relevant. There was no significant difference in these opinions based on student gender or nationality.

Interviewers felt that the main advantage of MMI was its ability to "*assess candidates' actual performance objectively and consistently in tasks that are relevant to performing as a clinician*" (n=4). A second advantage was that it was a "*good assessment of non-cognitive and inter-subjective skills*" (n=4). As one interviewer put it "*The MMI seems to provide a 'best of all' option in terms of selection methods by striking a balance between objectivity, aptitude, and 'the human factor.*" However MMI was considered "*Expensive in terms of personnel, time and resources*" (n=3); with the "*Potential for enhanced inequity in student selection due to potential for preparation at 'grind schools'*" (n=4) and the potential exists for quieter or international students to underperform "*The MMI can struggle to allow for cultural and language differences*" (n=6). An analysis of the cost involved in the running an MMI was conducted, based on an assumption that hosting the MMI would be external to core academic activity and hence would incur additional costs. As interviewers and administrators who took part in this study received no payment, we estimated costs based on typical OSCE rates for licencing exams (see Table 2). The total cost excludes the cost of investing in software support and station development. The cost per applicant, based on 120 applicants, is estimated at €145 per person.

Table 2 Estimated costs of running the MMI

Item	Unit cost	Estimate cost for MMI for 120 applicants
Interviewer expenses (20 interviewers plus 2 backup interviewers =22)	Based on OSCE examiner rates of €500 per full day	11000
Administrative support X4	Based on OSCE administration rates of €250 per full day	1,000
10 actor / role players	Actor training @ €50 per actor	500
	MMI @ €150 per day	1,500
Acting Coach	Sourcing and training actors estimated @ €500	500
	Supervision of acting at MMI @ €150 per day	150
Venue rental	€2,000 per day	2000
Catering for 37 people (lunch/ teas/ coffee)	Estimated @ €15 per person	555
Office supplies / laminating / paper/ photocopying / Various MMI station material props	€200	200
Estimated total cost		**€17405**
Estimated cost per applicant		**€145.04**

Discussion

Medical student selection is a complex and emotive issue. At its heart is a sense of social responsibility to select, from amongst hundreds of very able applicants, those best placed to become good doctors. This study demonstrated that it is feasible to hold a MMI in an Irish setting. Due to the level of expertise with OSCE examinations, the move to MMI proved both practicable and achievable. Student performance was comparable to that of Dundee applicants[9], as was the station item Cronbach alphas which demonstrated a satisfactory level of reliability. Station material was blueprinted against the eight domains of professional practice, thus ensuring both face and content validity. Feedback from students indicated that the test achieved an acceptable level of approval amongst this stakeholder group. Interviewers were overall supportive of MMI as a selection tool. This is in keeping with reports from MMI feasibility studies internationally which also note stakeholder approval[10,11].

Economics are an important aspect of feasibility as MMIs are labour intensive and potentially costly. Our estimated costs assume that no cost is absorbed by the respective medical schools which would not necessarily be the case. Redistributing these costs to applicants risks giving rise to socioeconomic bias and due consideration needs to be taken to avoid this. In Canada and UK faculty involvement in selection is seen as core academic activity. Evidence from international experience is that MMIs are a more economical use of faculty time than traditional interviews. Costs can also be kept to a minimum by utilising senior cycle medical students as trained role players and venue rental costs could be avoided if MMIs become core institutional activity[12]. The study did have some important limitations. Participants were already selected to medical school, therefore the range of scores achieved is unlikely to represent the spectrum from an applicant pool. Secondly the students who volunteered for the study may differ from their class mates in some important respects. This paper reports on the feasibility and face validity of the process of MMI as opposed to establishing its concurrent or predictive validity. Further work is required and is currently underway to determine these in an Irish setting as well as establishing the impact of age, gender and nationality on performance.

The real question is whether MMI would be implementable on a national level. The main determinant of this is the numbers of places available in medical school, coupled with the ratio of applicants called to MMI for places offered. For example with approximately 450 undergraduate places a ratio of 3:1 would imply 1,350 applicants are called to MMI. Such numbers would be best accommodated via a central process. It may be possible to shortlist applicants by rank ordering them either on Leaving Certificate or Leaving Certificate/HPAT combined scores. The timing of release of Leaving Certificate results would necessitate hosting the MMI in late August. Scheduled MMI dates could be announced by the CAO at the time of application to medicine, with advice for all applicants to keep these dates available. Invites to MMI could be made via the CAO system, once Leaving Certificate/ HPAT results were available. The use of OMIS software in the marking of MMI would facilitate a quick turnaround of final offers to medicine. MMIs require time, effort and commitment on the part of medical schools. One may ask is it

worth it? Reforms to entry and selection to medical school in Ireland have provoked debate and are under review[13,14]. Attrition in medical schools in Ireland is low and therefore those enrolled are highly likely to graduate[15]. Therefore is it not a necessity to employ the best available tools to ensure we enrol, educate and graduate the most suitable candidates? We contend that the use of MMIs is worthy of further consideration in the Irish context.

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References

1. O'Flynn S, Fitzgerald T, Mills A. "Modelling the impact of old and new mechanisms of entry and selection to medical school in Ireland: who gets in?" Irish Journal of Medical Science (2013): 1-7.
2. Patterson F, Ferguson E "Selection for medical education and training" in T. Swanwick Understanding Medical Education: Evidence, Theory and Practice. Oxford, UK, Wiley-Blackwell 2010, Chp 24.
3. Albanese MA, Snow MH, Skochelak SE, Huggett KN, Farrell PM. (2003). "Assessing personal qualities in medical school admissions". Academic Medicine,2003: 78, 313-321.
4. Eva KW, Rosenfeld J, et al. "An admissions OSCE: The multiple mini-interview." Medical Education 2004; 38: 314-326.
5. Pau A, Jeevaratnam K, Chen YS, Fall AA, Khoo C, Nadarajah VD. The Multiple Mini-Interview (MMI) for student selection in health professions training-A systematic review. Medical Teacher 2013 35, 1027-1041.
6. Husbands A, Dowell J. "Predicitive validity of the Dundee multiple mini interview". Medical Education 2013: 47:717-725.
7. Kropmans TJB, O'Donovan BGG, Cunningham D, Murphy AW, Flaherty G, Nestel D, Dunne FP "An Online Management Information System for Objective Structured Clinical Examinations". Computer and Information Science 2012; 5; 1.
8. Medical Council. Eight Domains of Good Professional Practice as devised by Medical Council 2012. http://www.medicalcouncil.ie/Information-for-Doctors/Good-Professional-Practice/ accessed 22/04/2012.
9. Dowell J, Lynch B, Till H, Kumwenda B, Husbands A. (2012). "The multiple mini-interview in the UK context: 3 years of experience at Dundee". Medical Teacher.2012; 34, 297-304.
10. Brownell K, Lockyer J, Collin T, Lemay JF. "Introduction of the multiple mini interview into the admissions process at the University of Calgary: acceptability and feasibility".Medical Teacher 2007; 29; 4: 394-396.
11. Razack S, Faremo S, Drolet F, Snell L, Wiseman J, Pickering J. "Multiple mini-interviews versus traditional interviews: stakeholder acceptability comparison". Medical Education 2009 43:993-1000.
12. Rosenfeld JM, Reiter HI, Trinh K, Eva KW. "A cost efficiency comparison between the multiple mini-interview and traditional admissions interviews". Advances in Health Sciences Education 2008; 13: 1: 43-58.
13. O Flynn S, Mills A, Fitzgerald T. "Interim Report School Leaver Entrants – National Research Group Evaluating Revised Entry and Selection Mechanisms to Medicine 2012". http://www.medicine.tcd.ie/assets/pdf/HPAT-report-July2012-HEA-final.pdf accessed 22/04/2012.
14. ME Kelly, D Regan, F Dunne, P Henn, J Newell, S O'Flynn. "To what extent does the Health Professions Admission Test-Ireland predict performance in early undergraduate tests of communication and clinical skills? An observational cohort study" BMC Medical Education 2013, 13:68 (10 May 2013).
15. Maher BM, Hynes H, Sweeney C, Khashan AS, O'Rourke M, Doran K, et al. "Medical school attrition-beyond the statistics a ten year retrospective study". BMC Medical Education. 2013;13:13.

Juxta-Articular Myxoma: An Unusual Benign Mesenchymal Lesion, Readily Mistaken for Malignancy

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Abstract
Myxomas are benign tumours of mesenchymal origin. We describe the first reported case of paraspinal juxta-articular myxoma. Juxta-articular myxomas show increased cellularity and distinction from cellular myxoma is required. The differential also includes malignant myxofibrosarcoma. For patient prognosis and management it is essential to separate these entities. Complete surgical excision is the mainstay of treatment as local recurrences may occur.

Introduction

We describe a paraspinal juxta-articular myxoma. Myxomas are uncommon benign tumours of mesenchymal origin, mostly intramuscular in location. Juxta-articular myxoma, a variant of myxoma occurring around large joints, especially the knee (88%), is consideredbenign[1,2]. Reported sites include shoulder, elbow, ankle and hip joints[2]. To date, no case involving paraspinal joints has been reported. The main histological differentials are cellular myxoma and low grade myxofibrosacroma.

Case Report

A 55 year old female presented with a palpable, otherwise asymptomatic neck mass. It was present for 4 years, enlarging slowly over that time. There was no history of trauma. MRI of the cervical spine revealed an ovoid, loculated, partially cystic lesion at the level of C5 to C8, intimately associated with the transverse processes of the vertebral bodies and lying between the vertebral bodies and the sternocleidomastoid muscle. Intraoperatively, a 4 cm non-encapsulated mass was identified deep to cervical fascia adjacent to cervical vertebrae posterior to the upper end of the left sternocleidomastoid muscle. This did not appear radiologically or intra-operatively to arise from muscle. This mass was excised with clear margins. Multiple pieces of soft tissue were received in the laboratory. Microscopic sections revealed a poorly circumscribed cellular lesion in-between skeletal muscle (Figure 1). The tumour was composed of ovoid and spindle cells within a myxoid stroma. Myxoma describes any bland hypocellular gelatinous neoplasm[3]. When intramuscular, one expects a paucicellular lesion with round/stellate cells intermixed with myxoid extracellular stroma containing sparse capillary sized blood vessels[4]. Nuclear pleomorphism or mitoses are absent. Juxta-articular myxoma, is more cellular with increased vascularity[1]. Distinction from a cellular myxoma is based on location adjacent to large joints and the lack of a GNAS1 mutation[5]. Distinguishing

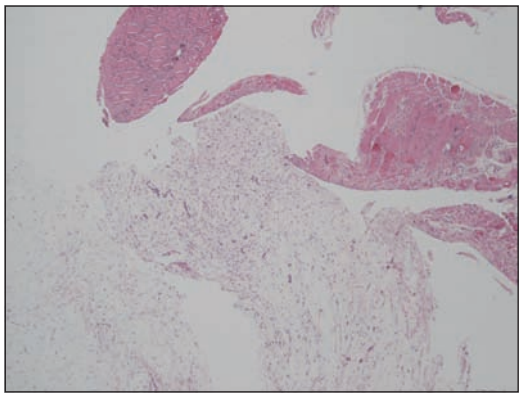

Figure 1

Haematoxylin and eosin stained image showing the poorly circumscribed cellular myxoid tumour, intermixed with fragments of skeletal muscle. Magnification x 200

between juxta-articular myxoma and low grade myxofibrosarcoma requires assessment of nuclear pleomorphism, hyperchromasia, and the presence of mitoses or necrosis[3].

Given the absence of mitoses, necrosis, hyperchromasia or nuclear pleomorphism in this case (Figure 2), low grade myxofibrosarcoma was excluded. This myxoma was cellular with admixed vessels and, given the radiologic and intraoperative confirmation of a lesion arising from the cervical vertebrae,a diagnosis of juxta-articular myxoma was made. The degree of cellularity, whilst unusual in a myxoma, is well described in juxta-articular myxoma[5]. This case was referred to Professor Christopher Fletcher, a world expert on soft tissue pathology, who confirmed the diagnosis.

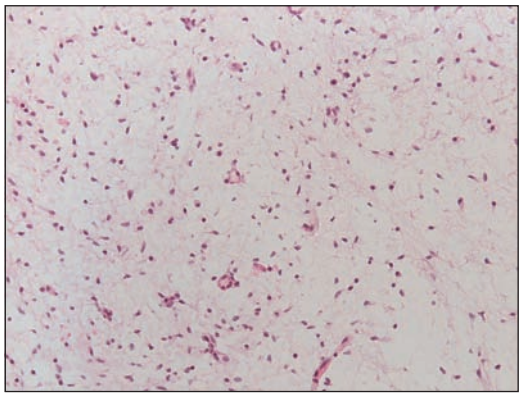

Figure 2

Haematoxylin and eosin stained image of an area of increased cellularity. No necrosis or cellular atypia is seen. Mitoses are not identified. Magnification x 400

Discussion

Myxomas most commonly occur between the ages of 40 and 60 years, with a female predilection[6]. They originate from primitive mesenchymal stem cells with differentiation towards altered fibroblasts that have lost the ability to produce collagen. Instead they produce hyaluronic acid and immature collagen[7]. They occur in many locations including heart, bones, genitourinary tract, skin, retroperitoneum, intestine, joints and most commonly skeletal muscles[3]. Myxomas are non-encapsulated, and may infiltrate surrounding tissues, however they do not metastasize[8]. Myxomas are slow growing tumours presenting as a painless mass or compression of surrounding structures[9]. Plain films are often normal or show a non-specific soft tissue mass. Ultrasound reveals a hypoechoic mass containing fluid filled clefts or cysts. CT shows a homogeneous low density mass. MRI shows a low intensity mass on T1 weighted images and high signal intensity on T2[7]. The imaging characteristics in both intramuscular myxoma and juxta-articular myxoma will be similar, except for the relationship to adjacent structures such as muscle and joints[6]. In cases of myxofibrosacroma, a more infiltrative growth pattern is seen on CT[8].

Most tumours are ovoid/globular with a glistening grey white appearance[9]. Microscopically, myxoma is hypocellular composed of undifferentiated stellate cells with an irregular meshwork of reticulum fibres in a matrix of hyaluronicacid-containing mucoid[10]. Cellular myxoma is more cellular with increased vascularity[4]. Juxta-articular myxomas are similar tocellular myxoma but lack a GNAS1 mutation[5], and are associated with large joints. Distinction from low grade myxofibrosacroma requires exclusion of nuclear pleomorphism, hyperchromasia, mitoses and necrosis[3]. These changes can be focal, and lead to difficulty, on small biopsy specimens. Full surgical excision is the treatment with core biopsy inappropriate. Myxomas do not metastasize however local recurrence is described in cases with incompleteresection[8]. Juxta-articular myxomas are more prone to recur[1].

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References

1. Meis JM, Enzinger FM. Juxta-articular myxoma: a clinical and pathologic study of 65 cases. Hum Pathol. 1992;23:639–646.
2. Van Roggen, J.F., Mc Menamin, M.E., Fletcher, C.D. Cellular myxoma of soft tissue: a clinicopathological study of 38 cases confirming indolent clinical behavior. Histopathology. 2001 Sep;39:287-97.
3. Fletcher C. Diagnostic histopathology of tumours. 3rd edition. P 1570-1571.
4. Fletcher C. D.M., Bridge, J.A., Hogendoorn, P., Mertens, F. WHO Classification of Tumours of Soft Tissue and Bone. Fourth edition. P 186.
5. Okamoto S, Hisaoka M, Meis-Kinfblom J M, Hashimoto M. Juxta-articular myxoma and intramuscular myxoma are two distinct entities. Activating Gs(alpha) mutation at Arg 201 codon does not occur in juxta-articular myxoma. Virchows Arch 2002: 440:12-15.
6. RJP Körver, PHMH Theunissen, WT van de Kreeke, MJA van der Linde, IC Heyligers. Juxta-articular myxoma of the knee in a 5-year-old boy: a case report and review of the literature (2009:12b). Eur Radiol. 2010 March; 20: 764–768.
7. Caro P, Dubrana F, Le Nen D. Myxome untramusculaire. Rev Chir Orthop 1991: 77:568-570.
8. Waters B, Panicek DM, Lefkowitz RA, Antonescu RA, Healey JH, Athanasian EA, Brennan MF. Low-Grade Myxofibrosarcoma: CT and MRI Patterns in Recurrent Disease. AJR February 2007 vol. 188.
9. Ozbek N, danaci M. Okumus B, Gursel B, Cakir S, Dabak N, Karagoz F. Recurrent intramuscular myxoma: review of the literature , diagnosis and treatment options. Turk J Cancer 2006:36:75.
10. Purdy Stout A. Myxoma, the tumour of primitive mesenchyme. Ann Surge 1948: 127:706-719.

Two Hit Hypothesis: An Unusual Complication Following Supra-Pubic Catheter Insertion

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Abstract
Osteomyelitis is an inflammation of the bone caused by an infection. Though bone is normally resistant to bacterial infection, events including trauma, presence of foreign bodies including prosthesis can act as a nidus for infection. Osteomyelitis is a rare but recognised complication of radiotherapy[1]. Osteomyelitis of the pubis has scarcely been reported as a complication following urological procedures- prostatectomy[2], sling surgery[3] and catheterisation[4,5]. We report a rare complication of a gentleman post radiotherapy presenting with delayed osteomyelitis of the pubis following supra-pubic catheterisation.

Case Report

A 66 year old man presented to clinic for routine follow up regarding prostate cancer. He was diagnosed with Gleason 4+3 adenocarcinoma of the prostate six years ago, his initial PSA was 12.0 ng/mL. He underwent an open radical retropubic prostatectomy. His PSA nadir was <0.03ng/mL. Following biochemical recurrence he underwent external beam radiotherapy. He developed dense urethral strictures and was intermittently catheterising after multiple dilatations. A supra-pubic catheter was inserted. He started complaining of severe supra-pubic pain and decreasing mobility within a few weeks of supra-pubic catheterisation. His abdominal and neurological examinations were normal. His PSA was 0.03 ng/mL. A diagnosis of bone metastasis was presumed. Radionuclide whole body bone scan showed no evidence of bone metastases. Computerised Tomography (CT) brain showed no evidence of intracranial mass. MRI pelvis revealed high signal changes around the pubic rami and pubic symphysis with surrounding inflammatory soft tissue changes suggestive of osteomyelitis. He subsequently had CT guided aspiration of the inflammatory collection (Figure 1). Cultures confirmed Multi-Resistant Staphylococcus Aureus (MRSA) and Enterococcus Faecalis and was commenced on a four week course of intra-venous Vancomycin. He was subsequently follow-up at out-patients at a 6-week interval with significant resolution of symptoms.

Discussion

Our case demonstrates the unusual complication of osteomyelitis of the pubis following pelvic surgery and salvage radiotherapy. The presentation however was mitigated following supra-pubic catheterisation. Osteomyelitis of the pubis has numerous of risk factors, of which our patient had a previous radical prostatectomy and pelvic radiotherapy. Despite these, his symptoms only developed after supra-pubic catheterisation. Furthermore a CT Abdomen/Pelvis prior to catheter insertion showed no evidence of infection. Osteomyelitis is a recognised rare complication of radiotherapy in many surgical specialties[1]. The timing of onset is variable. Patients with osteomyelitis of the pubis usually present with pelvic pain and poor mobility due to pubic symphysis destruction.

Osteomyelitis of the pubis has previously been described in urological literature. Stern et al reported a case of osteomyelitis of the pubis in a 40 year old woman ensuing from a chronic indwelling urinary catheter requiring open debridement. They hypothesise that catheter erosions allow direct spread of vaginal flora into the symphysis[4]. Vaidyanathan et al., report the case of osteomyelitis of the pubis in a 20 year old tetraplegic woman postulated to be secondary to chronic leakage along the supra-pubic track[5]. Moore et al., in a case quite similar to ours, report osteomyelitis of the pubis in a 57 year old man, two years post robotic assisted laparoscopic prostatectomy and salvage radiotherapy presenting with recurrent urinary tract infections and intermittent pelvic pain[6]. They postulated that pelvic radiotherapy following pelvis surgery was the causative aetiology. As was the case with our patient, conventional imaging are difficult to interpret useless there is significant periosteal thickening, elevation or sclerosis. Magnetic Resonance Imaging (MRI) is a very sensitive imaging modality in detecting osteomyelitis, usually demonstrating high signal abnormalities in the pubic rami consistent with marrow oedema. Bone biopsy with histopathological examination and culture is the gold standard for the microbiological diagnosis of osteomyelitis. Osteitis pubis and osteomyelitis of the pubis are recognised complications of sling insertion for the treatment of urinary incontinence whether inserted trans-abdominal[7] or transvaginal[8].

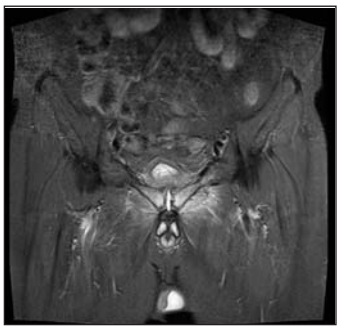

Figure 1

Coronal MRI STIR sequence T2 demonstrating high signal within the pubic rami bilaterally with associated hyperintensity in the surrounding soft tissues suggestive of osteomyelitis

We report a rare complication that to the best of our knowledge is only the third case of osteomyelitis of the pubis following indwelling urinary catheter. This case report serves to highlight the significant consideration and informed consent is necessary prior to supra-pubic catheterisation especially in patients with previous pelvic surgery and radiation. The aetiology of osteomyelitis in this case is likely due to a number of mitigating factors- pelvic surgery, pelvic radiotherapy and subsequent supra-pubic catheterisation.

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References

1. Wignall TA, Carrington BM, Logue JP. Post radiotherapy osteomyelitis of the symphysis pubis: computed tomographic features. Clin Radiol. 1998 Feb;53:126-30.
2. Kaplon DM, Iannotti H. Prostatic capsular perforation with extravasation resulting in pubic osteomyelitis: a rare complication of KTP laser prostatectomy. J Endourol. 2008 Dec;22:2705-6.
3. Graham CW, Dmochowski RR, Faerber GJ, Clemens JQ, Westney OL. Pubic osteomyelitis following bladder neck surgery using bone anchors: a report of 9 cases. J Urol. 2002 Nov;168:2055-7.
4. Stern JA, Clemens JQ. Osteomyelitis of the pubis: a complication of chronic indwelling catheter. Urology. 2003 Feb;61:462.
5. Vaidyanathan S, Soni B, Hughes P, Singh G, Oo T. Preventable long-term complications of suprapubic cystostomy after spinal cord injury: Root cause analysis in a representative case report. Patient Saf Surg. 2011 Oct 27;5:27.
6. Moore DC, Keegan KA, Resnick MJ, Eisenberg R, Holt GE, Cookson MS. A 57-year-old man with a history of prostatectomy and pelvic irradiation presents with recurrent urinary tract infections, hematuria, and pelvic pain. Urology. 2013 Feb;81:221-5.

7. Goldberg RP, Tchetgen MB, Sand PK, Koduri S, Rackley R, Appell R, Culligan PJ. Incidence of pubic osteomyelitis after bladder neck suspension using bone anchors. Urology 63: 704–708, 2004.

8. Fialkow MF, Lentz GM, Miller EA, Miller JL. Complications from transvaginal pubovaginal slings using bone anchor fixation. Urology. 2004 Dec;64:1127-32.

Vismodegib in the Treatment of Advanced BCC

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Abstract
Basal-cell carcinoma (BCC) is the most commonly diagnosed malignancy, comprising over 80%of non-melanoma skin cancers. Surgical excision is adequate treatment for most BCC's. Options are however limited for the minority of patients presenting with locally advanced inoperable or metastatic BCC. The Hedgehog signalling pathway is a critical driver in the pathogenesis of both sporadic and hereditary BCC. On 31st January 2012, based on a phase II clinical trial the US Food and Drug Administration approved Vismodegib (Erivedge®, Roche) a first-in-class, small-molecule oral Hedgehog-inhibitor for the treatment of locally advanced inoperable and metastatic BCC. We present our experience treating the first Irish patient with this agent.

Case Report

A fifty two year old man was referred with a 14-year history of a slowly enlarging interscapular lesion, (Figure 1). The patient's past history included peptic ulcer disease and a 30-pack year history of cigarette smoking. A biopsy of the lesion revealed an invasive, ulcerated basosquamous cell carcinoma. Given the extensive nature of the tumour site an MRI scan was performed showing a lesion extending from the skin involving spinal muscles bilaterally and abutting the spinous processes from C7-T2. Complete staging with CT thorax, abdomen and pelvis documented no metastatic disease. The multidisciplinary team outcome concluded that down-staging with vismodegib would be appropriate given disease extent. A successful application was made for compassionate use of the drug. The patient received the approved daily dose of 150mg. Within two weeks there was dramatic improvement. At 16 weeks multiple scouting biopsies revealed florid inflammatory and giant cell reactivity but no evidence of malignancy. During treatment he reported muscle spasms, dysguesia, alopecia and anorexia consistent with the known adverse effects of this agent. An MRI at 22weeks showed healing at the level of the deep fascial planes. The area of ulceration had almost completely healed at week 26 of vismodegib, at which point he developed two nodules within the boundaries of his original tumour (Figure 2). Biopsies revealed nodular BCC. The patient is now being assessed for surgical excision.

Discussion

Most BCC's are cured by surgery alone. Patients who present with locally advanced or metastatic disease at diagnosis represent a minority and have limited treatment options. Overall survival estimates for patients with metastatic disease are poor ranging from 8 months to 3.6 years.[1] The pathogenesis of BCC is well understood and most cases of both sporadic BCC[2,3] and Basal Cell Naevus Syndrome[4,5] involve activated and aberrant Hedgehog pathway signalling. This pathway is fundamental in the development of embryonic cells and is important in the maintenance of adult cell homeostasis.[6] Irregular activation results in a number of signals and modifications of secreted ligands, culminating in the deactivation of Smoothened (SMO), which normally acts as an inhibitor of downstream Gli–proteins. Persistent stimulation of these proteins upregulate target genes important in cell differentiation and survival.[7] Vismodegib inhibits SMO and demonstrated efficacy in phase II trials[8,9] with response rates of 43% and 30% reported in patients with locally advanced and metastatic disease, respectively. Consistent with other targeted agents e.g. vemurafenib in the treatment of BRAF-mutated melanoma, acquired resistance to vismodegib appears rapidly with a median duration of response of 7.6 months. Indeed, our patient developed resistance at 6 months. The mechanism of vismodegib resistance remains unclear but may involve alternate pathway activation or acquired mutations. The histology of recurrent BCC in our patient differed from original biopsies and such histological variation has beenreported.[10] This concept will be important in future research to aid understanding of acquired resistance.

In the phase II study over 40% of patients with locally advanced BCC discontinued treatment before progression of disease.[8] The reasons for discontinuation were not collected, however adverse effects specifically muscle cramps and dysguesia as experienced by our patient have been implicated. The underlying pathogenesis and optimal treatments of toxicities are unknown. The clinical impact and position of vismodegib in treating metastatic/inoperable BCC and down-staging borderline inoperable BCC continues to evolve. Our patient experienced

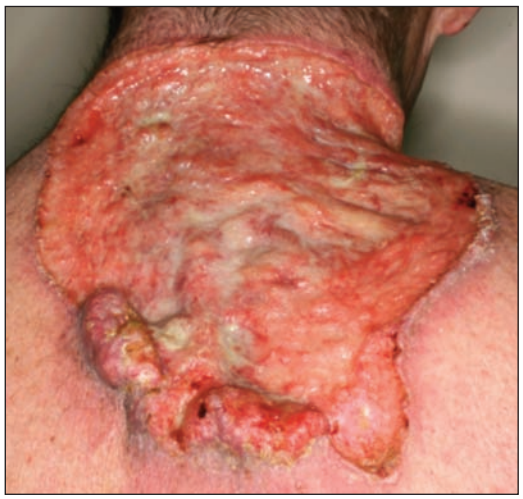

Figure 1
Baseline image showing extensive, ulcerated basosquamous carcinoma

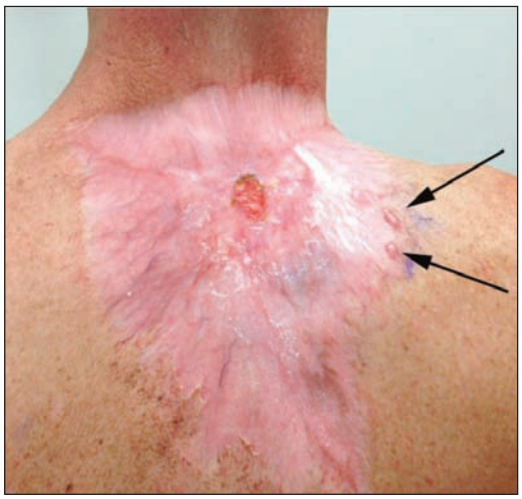

Figure 2
Lesion post 26 weeks of Vismodegib with 2 new nodules evident within boundary of original tumour

moderate toxicity from this agent and will now proceed to surgery with potentially improved surgical outcome.

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References

1. Walling HW, Fosko SW, Geraminejad PA, Whitaker DC, Arpey CJ. Aggressive basal cell carcinoma: presentation, pathogenesis, and management. Cancer Metastasis Rev. 2004;23:389–402.
2. Aszterbaum M, Rothman A, Johnson RL, Fisher M, Xie J, Bonifas JM, Zhang X, Scott MP, Epstein EH. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. J Invest Dermatol. 1998;110:885–888.
3. Reifenberger J, Wolter M, Knobbe CB, Köhler B, Schönicke A, Scharwächter C, Kumar K, Blaschke B, Ruzicka T, Reifenberger. Somatic mutations in the PTCH, SMOH, SUFUH and TP53 genes in sporadic basal cell carcinomas. Br J Dermatol. 2005;152:43–51.
4. Caro I, Low JA. The role of the Hedgehog signaling pathway in the development of basal cell carcinoma and opportunities for treatment. Clin Cancer Res.2010;16:3335–3339.
5. Ng JM, Curran T. The Hedgehog's tale: developing strategies for targeting cancer. Nat Rev Cancer.2011;11:493–501.
6. Tang JY, So PL, Epstein EH Jr. Novel Hedgehog pathway targets against basal cell carcinoma. Toxicol Appl Pharmacol.2007;224:257–264.
7. Hui CC, Angers S. Gliproteins in development and disease. Annu Rev Cell Dev Biol. 2011;27:513–537.
8. Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, Solomon JA, Yoo S, Arron ST, Friedlander PA, Marmur E, Rudin CM, Chang AL, Low JA, Mackey HM, Yauch RL, Graham RA, Reddy JC, Hauschild A. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med. 2012;366: 2171–2179.
9. Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, Coppola C, Chanana AM, Marji J, Bickers DR, Epstein EH. Inhibiting the Hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med. 2012;366:2180–2188.
10. Chang AL, Oro AE. Initial assessment of tumor regrowth after vismodegib in advanced Basal cell carcinoma. Arch Dermatol. 2012;148:1324–1325.

Age Related Influence on Screening Coverage and Satisfaction with CervicalCheck

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Abstract
The aim of this study was to evaluate levels of satisfaction of women attending the CervicalCheck programme and reasons for the age differential in screening uptake. A questionnaire was sent to 5,000 randomly selected attenders with a normal smear test (3,500 aged 25-44, 1,500 aged 45-60). Almost all in both age groups said they would return to CervicalCheck if invited (98.5%;98.5%) and recommend the service to family/friend (99.6%;99.5%). The single independent predictor of 'would recommend to family/friend' was willingness to return to CervicalCheck (OR=31 (5.2-183.7)). Predictors of 'would return if invited' were knowledge of when due to return (OR=2.5 (1.3-5.0)) and having contacted or having received a letter of invitation from CervicalCheck (OR=3.1 (1.6-6.1)). Independent predictors of 'knowledge of when due to return' were older age group (OR=0.5 (0.4-0.7)) and willingness to return to CervicalCheck (OR=3.2 (1.2-6.3)). The GP is particularly important in informing older women and encouraging attendance.

Introduction

CervicalCheck is the nationwide cervical cancer screening service for Ireland, provided by the National Cancer Screening Programme in conjunction with GPs, other primary care providers and hospitals[1]. In the first round of screening, it was observed that screening coverage was significantly higher in the younger population age under 45[2]. The aim of this study was to evaluate levels of satisfaction experienced by women who had a smear test under the CervicalCheck programme, with a normal smear test result, and to explore the reasons for the age differential in screening uptake.

Methods

A questionnaire was sent to 5,000 randomly selected attenders at screening from two age groups (3,500 to women aged 25-44 years, 1500 to women aged 45-60 years, reflecting the total population of screened women) who had a normal smear test result. A reminder was sent to all women one month post initial survey. SAS version 9.1 was used for data analysis. Chi-square tests were used to compare responses rates between the younger and older age groups. Backward stepwise logistic regression was used to determine independent positive predictors(s) of (i) "would recommend CervicalCheck to family or friend" (ii) "would return if reinvited to CervicalCheck" and (iii) knowledge of when due to return to CervicalCheck.

Results

The response rate overall was 51.6 per cent (age 25-44, 45.7%; age 45-60, 63.9%). Under half (45.1%) of those responding indicated they had received an invitation letter; the remainder indicated they had been registered with the programme by their GP at a visit (35.3%), had contacted the programme directly (17.4%) or did not recall (1.8%). Younger women (<45 years) were more likely than older women (45-60 years) to have become aware of CervicalCheck via their GP (43.7% vs. 38.8%; $p<0.05$) and family (17.9% vs. 10.9%; $p<0.01$). 1753 women sought more information following invitation, 53.5% from their GP, 28.4% from the internet, including the CervicalCheck website; among these, a greater proportion of younger women used the internet (25.6% vs. 9.7%; $p<0.0001$). Younger women were better informed regarding when to return for routine smear; 74.6% of younger women ticked in 3 years/when invited by CervicalCheck compared to 60.1% of older women; $p<0.0001$. Almost all in both age groups said they would return to CervicalCheck if invited (98.5%; 98.5%) and recommend the service to family/friend (99.6%; 99.5%). After backward stepwise logistic regression the single independent positive predictor of 'would recommend to family/friend' was willingness to return to CervicalCheck. Independent positive predictors of 'would return if invited' were knowledge of when next screening due and having contacted/having received a letter of invitation from CervicalCheck. Independent positive predictors of 'knowledge of

Table 1 Logistic regression: factors associated with (i) 'would recommend CervicalCheck to family and friends', (ii) with 'would return if invited to CervicalCheck' and (iii) associated with knowledge of when next screening due

	Factors associated with 'would recommend CervicalCheck to family and friends'		Factors associated with 'would return if invited to CervicalCheck'		Factors associated with knowledge of when when next screening due	
	Univariate OR (95%CI)	Final Model OR (95%CI)	Univariate OR (95%CI)	Final Model OR (95%CI)	Univariate OR (95%CI)	Final Model OR (95%CI)
Age >= 45	0.7 . (0.2-2.3)	-	0.1 . (0.5-1.9)	-	0.1 . (0.5-1.9)	0.5 . (0.4-0.7)
Recalls receiving information leaflet	7.6 . (1.5-39.2)	-	2.1 . (1.0-4.5)	-	n/a	n/a
Contacted by letter from CervicalCheck / contacted CervicalCheck	n/a	n/a	2.3 . (1.2-4.5)	2.5 . (1.3-5.0)	2.3 . (1.2-4.5)	-
Attended own GP for smear	n/a	n/a	1.7 . (0.9-3.6)	-	1.7 . (0.9-3.6)	-
Knowledge of when next screening due	4.0 . (1.2-13.7)	-	3.0 (1.6-5.8)	3.1 . (1.6-6.1)	n/a	n/a
Would return to CervicalCheck if invited	19.3 . (3.8-96.5)	31 . (5.2-183.7)	n/a	n/a	3.0 . (1.5-5.8)	3.2 . (1.2-6.3)

when due to return' were younger age group and willingness to return (Table 1).

Discussion

There is a high level of satisfaction overall among women attending CervicalCheck. It is suggested that individual preferences exist among women in respect of both the treatment they receive and the amount of information they require, and that concordance with these preferences leads to increased satisfaction[3]. The level of understanding regarding optimal frequency of screening is poor, particularly among older women. The website does not appear to be used greatly by older women to access information, with just 9.8 per cent of those needing additional information looking at the CervicalCheck website. Knowledge of when to return for screening was associated with a willingness to return. Those who were happy to return were also happy to recommend to family and friends, which should assist with improving coverage into the future. The response was less than in other studies conducted by the NCSS of attenders to BreastCheck[4], reflecting the lower response in younger women.

While this study does not address reasons for non-attendance specifically this study does highlight different routes for informing older and younger women about CervicalCheck and may inform initiatives aimed at improving coverage among older women. The GP and Practice Nurse are of particular importance in informing older women about CervicalCheck and encouraging attendance. Use of the internet by the current cohort of older women attending CervicalCheck for information about CervicalCheck or cervical screening is limited.

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References

1. National Cancer Screening Service. http://www.cancerscreening.ie/about/index.html [cited 2013].
2. National Cancer Screening Service. CervicalCheck Progamme Report 2010-2011. Dublin: National Cancer Screening Service, 2012.
3. Fylan F. Screening for cervical cancer: a review of women's attitudes, knowledge, and behaviour. Br J Gen Pract. 1998;48:1509-14.
4. Fitzpatrick P, Winston A, Mooney T. Radiographer gender and breast-screening uptake. British Journal of Cancer. 2008;98:1759-61.

Pertussis in Young Infants: Clinical Presentation, Course and Prevention

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Abstract
Pertussis is a highly contagious disease caused by the Gram negative aerobic coccobacillus, Bordetella pertussis. It may present with severe symptoms and complications in infants and can pose a diagnostic challenge. This is a vaccine preventable illness covered by the Irish Childhood Immunisation Schedule. In 2011, a retrospective review was conducted of the records of infants, under six months, with a confirmed diagnosis of pertussis, presenting to Temple Street Children's University Hospital (TSCUH). A summery of notifications of pertussis nationally, from 2001 to 2012, was also examined as part of the study. This found that the rate of reported cases of pertussis has been increasing in Ireland. This national increase corresponds with a rising number of cases identified at TSCUH. Patients commonly presented severely ill with cyanosis and apnoea, on a background of prolonged cough. We found that pertussis was diagnosed rapidly in most cases however in all cases there was a delay to commencement of appropriate macrolide therapy.

Introduction

There has been a recent increase in the number of reported cases of pertussis in Ireland. Pertussis is a vaccine-preventable, highly contagious disease caused by Bordatella pertussis. Pertussis in young infants is a severe illness, often requiring prolonged hospitalisation. Not only is there considerable economic expense but there are also costs in parental time, loss of earnings and stress on the extended family[1-3]. The Irish Childhood Immunisation Schedule vaccinates against pertussis (acellular pertussis vaccine) at 2, 4, and 6 months, 4-5 years and 11-14 years[4]. According to the Health Prevention Surveillance Centre (HPSC) data for the first quarter of 2013 shows that 91% of infants in Ireland have received three doses of pertussis vaccine during the first year of life. The introduction of this vaccination in the United States, in the 1940's, reduced the incidence of pertussis by 80%[5]. However there has been widely reported increasing incidence of pertussis in developed countries despite high vaccine uptake [6]. While increased reporting, due to improved diagnostic tests, may account for some of the increase, there is strong evidence to suggest that waning immunity amongst older children and adults is a key factor[7,8]. New measures to control the spread of pertussis include vaccinating health care workers and

vaccination boosters for pregnant women and adolescents. Reducing transmission from known infected patients still plays a vital role in controlling the spread of disease.

Given the increase in numbers of patients presenting with pertussis we reviewed admissions to Temple Street Children's University Hospital (TSCUH), in order to profile the presentations of pertussis in the infant population where diagnosis is often more challenging and complications are more severe[5]. This review also addresses measures to control the spread of disease from known infected patients.

Methods

A retrospective review was carried out of all infants under six months of age, admitted to TSCUH during 2011, with a confirmed diagnosis of pertussis. A confirmed diagnosis was a clinical diagnosis of pertussis in addition to laboratory detection of B. pertussis by either culture or polymerase chain reaction (PCR). Demographic data on all children admitted with pertussis was reviewed, including: age, number of siblings, sick contacts, duration and nature of symptoms, indicators of severity of illness (length of stay in hospital and whether high dependency or intensive care were required), and factors which affected potential transmission (institution of isolation precautions and time to commencement of macrolide antibiotic therapy). Pertussis is a statutory notifiable disease in Ireland. Data on the annual number of cases notified in Ireland was obtained from the national Computerised Infectious Disease Reporting (CIDR) system, maintained at the HPSC. Data on hospital costs was obtained from the Department of Health, and data on hospital-acquired cases and institution of isolation precautions was obtained from the TSCUH Infection Prevention and Control Department.

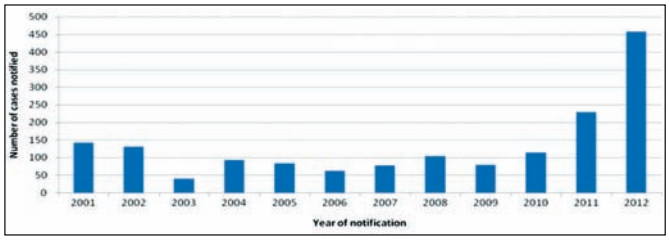

Figure 1 Incidence of pertussis in Ireland from 2001 to 2012 (data courtesy of HPSC)

Results

The number of cases of pertussis notified in Ireland decreased in the early 2000s. Between 2003 and 2008, 40 to 104 cases of pertussis were notified annually[9], with infants suffering the highest incidence of morbidity and mortality[10]. The HPSC have recorded a marked increase in the number of confirmed pertussis cases, notified year on year, since 2010 (Figure 1). Figures doubled from 2010 to 2011 and doubled again from 2011 to 2012. There were eighteen laboratory confirmed cases of pertussis diagnosed at TSCUH in 2011. Fifteen of these were under 6 months of age and therefore were included in this study. A complete data set was available on all patients, with the exception of two patients transferred with a pre-existing diagnosis of pertussis and one other patient who was not admitted to hospital. All patients acquired pertussis in the community and there was no recorded case of infection acquired in hospital.

The infants with pertussis had a median age of 44 days (range 36 to 96 days). Ten patients had siblings living in the home. In only one case the siblings were reported to be unvaccinated. Ten patients had documented exposure to a sick contact in the home. This was most commonly the child's mother or older siblings with similar respiratory symptoms, often with prolonged cough. All patients had a history of cough (median 14 days of symptoms prior to presentation, range 3 to 17 days). There was a history of concurrent vomiting in four of the cases. One patient was reported to have apnoeic episodes for a number of days before presentation. Patients presented to the hospital as a result of increased severity of symptoms – for example with the development of apnoea and cyanosis (Table 1).

Table 1 Patient demographic and clinical profile of children age less than six months with pertussis

Patient	Age (days)	Sex	Presentation	Sick Contacts	Macrolide	Diagnosis	LOS (PICU)	Complications
1	41	F	Cough	Brother – No vaccines	Clarithromycin	PCR & Culture	11 (4)	PICU, Respiratory Arrest, Bradycardia
2	38	M	Aponea	Nil	Erythromycin	PCR	8 (3)	PICU, Intunation, Bradycardia
3	42	F	Cough	Mother	Clarithromycin	PCR	13 (8)	PICU, Cardiorespiratory Arrest, Ventilatior
4	73	F	Cyanosis	Brother	Clarithromycin	PCR	9	HDU, NGT
5	50	M	Vomiting	Nil	Clarithromycin	PCR & Culture	5	NGT, Cardiology consult (ASD)
6	43	F	Cyanosis	Nil	Clarithromycin	PCR & Culture	7	NGT
7	36	M	Aponea	Brother	Clarithromycin	PCR & Culture	7	NGT
8	96	M	Aponea	Nil	Clarithromycin	PCR & Culture	4	Nil
9	68	F	Fever	Brother	Clarithromycin	PCR & Culture	6	Nil
10	76	M	Cyanosis	Mother	Clarithromycin	PCR & Culture	4	Nil
11	65	M	Aponea	Nil	Erythromycin	PCR & Culture	8	Nil
12	40	M	Cough	Brother x 2	Erythromycin	PCR & Culture	7	Nil
13	36	M	Aponea, Cyanosis	Mother	Nil	PCR & Culture	0	Nil
14	44	F	Aponea	Uncle	Clarithromycin	PCR	4	Nil
15	71	M	Cyanosis	Nil	Clarithromycin	Culture	5	Nil

Female (F), Male (M), Polymerase Chain Reaction (PCR), Paediatric Intensive Care Unit (PICU), High Dependency Unit (HDU), Nasogastric Tube (NGT), Atrial Septal Defect (ASD)

One infant was discharged home directly from the Emergency Department (ED). Two were transferred from another hospital directly to the Paediatric Intensive Care Unit (PICU). All others were admitted through the ED to the wards. Of those admitted to the wards, one required admission to the PICU, making a total of three PICU admissions. Another child was admitted from a ward to the High Dependence Unit (HDU). PICU admissions had a median length of stay of 4 days (range 3 to 8 days). The overall median duration of hospital admission was 7 days (range 4 to 13 days). Calculating for a cost of €800 for a night on a general ward and €1600 for a night in intensive care the total cost of admissions to the hospital was in excess of €90,000, with an average cost of €6,450 per patient.

As per hospital policy all patients under investigation for pertussis were isolated with droplet precautions. Isolation facilities were not available in the ED and so patients were isolated upon entry to the ward. For pertussis nasopharyngeal aspirates are the preferred sample, otherwise a pernasal swab is acceptable[11]. Of the admitted patients, four did not have a record of when pertussis swabs were taken, and two had swabs taken after leaving the ED. All other patients were under investigation at time of entry to the ward and were therefore isolated from this time. The two patients swabbed after leaving the ED were isolated 7-9 hours after entry to the ward. In all admitted cases, appropriate antibiotics were prescribed but there was a lag between presentation and initiation of first line macrolide antibiotics. Specific antimicrobial therapy was not initiated in the ED, despite a high clinical suspicion of pertussis. Macrolide antibiotics were commenced between 4.5 hours and 24 hours after presentation, with a median time to commencement of 15 hours.

Discussion

Despite a high uptake of the acellular pertussis vaccine, pertussis has been increasing both internationally and in Ireland. This increase has been reflected in the rising number of cases

identified at TSCUH. The increasing incidence has a particular impact on infants under the age of 6 months, where symptoms may be subtle but complications can be life threatening. Prior to the onset of more severe symptoms, the patients in this study had symptoms similar to those of a viral upper respiratory tract infection. The diagnosis of early pertussis is difficult and requires a high index of suspicion amongst parents and primary health care providers to identify infants before the onset of complications. A prolonged duration of cough was the most common symptom prior to presentation. Many infants presented to TSCUH with dramatic symptoms – three quarters experiencing apnoea, cyanosis or both. The significance of pertussis in infants is reflected in the prolonged duration of stay and the high number of admissions to PICU and HDU care among the study sample. This protracted hospital course with challenging complications requires substantial resources. The resurgence in pertussis has resulted in considerable impact, on hospital finances and parental resources.

A laboratory diagnosis requires the timely collection of samples and results may not be available for a number of days after samples are sent. Until rapid detection testing such as PCR become more widely available and with shortened turnaround time the diagnosis remains a clinical one. Macrolide antibiotic therapy is associated with reduced duration and severity of symptoms only if started in the catarrhal stage of the illness. However, once the paroxysmal phase has begun, prompt use of antibiotics and isolation reduces the time during which the patient is contagious. While many cases are correctly identified and appropriately treated, this opportunity to reduce infectivity by the introduction of early antibiotic therapy is often overlooked. Addressing the lag in commencing therapy is likely to yield a decrease in transmission rates. High levels of vaccination have not eliminated the spread of pertussis. Awareness amongst parents and physicians will aid early detection but to see the true benefit of this early isolation and commencement of macrolide therapy are essential.

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References

1. deGreeff SC, Lugnér AK, van den Heuvel DM, Mooi FR, de Melker HE, Economic analysis of pertussis illness in the Dutch population: implications for current and future vaccination strategies, Vaccine, 2009 27:1932-7.
2. O'Brien JA, Caro JJ. Hospitalization for pertussis: profiles and case costs by age, BMC Infectious Disease, 2005 Jul.
3. Lee LH, Pichichero ME. Costs of illness due to Bordatella pertussis in families, Archives of Family Medicine, 2000 Nov-Dec.
4. Childhood Immunisation Schedule, Health Service Executive, 2012 March.
5. Beckenhaupt, et al. Epidemiology and Prevention of Vaccine-Preventable Diseases, The Pink Book: Course Textbook – 12th Edition, Centers for Disease Control and Prevention, May 2012.
6. Cherry JD. Epidemic Pertussis in 2012 — The Resurgence of a Vaccine-Preventable Disease, New England Journal of Medicine, 2012; 367:785-787.
7. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning Protection after Fifth Dose of Acellular Pertussis Vaccine in Children, New England Journal of Medicine, 2012; 367:1012-1019.
8. Kmietowicz Z, Pertussis cases rise 10-fold among older children and adults in England and Wales, British Medical Journal, 2012;345:e5008.
9. Health Protection Surveillance Centre, Pertussis, Epidemiological Data.
10. National Immunisation Advisory Committee – Royal College of Physicians of Ireland, Immunisation Guidelines for Ireland – Chapter 11. 2008 Edition, (updated December 2012).
11. Guidelines for the Public Health Management of Pertussis, Health Service Executive, October 2013.

Infection of the Beard Area. Kerion: A Review of 2 Cases

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Abstract
Folliculitis barbae is a common condition of both infective and non-infectious aetiology. It most frequently presents as a superficial folliculitis, with fine pustules appearing at the opening of hair follicles in the beard area, often associated with shaving; known as Bockhart impetigo and usually due to infection caused by *Staphylococcus aureus*. If untreated, the infection and inflammation can progress, leading to a more deeply seated infection known as sycosis barbae. Perifollicular nodules, termed furuncles, may appear and when these are multiple and coalesce, a deep-seated, communicating, pustulating plaque called a carbuncle develops, often with associated systemic upset. Such an appearance, which can prompt incision and drainage, should not, however, be assumed to be solely due to staphylococcal infection. Particularly in the context of a history of close animal contact or a lack of response to antibiotic treatment, a diagnosis of tinea barbae should be considered and investigated. Prompt treatment with antifungal agents and often systemic steroids is required once the diagnosis is made. This will help reduce an exacerbation of the pronounced destruction that results from the immune response to the fungal infection, known as a kerion, which would be compounded by surgical intervention. In this article, we review two such cases and review the investigation and management of the disease.

Case 1
The Dermatology service was consulted by the maxillofacial surgery team to review a 34 year old cattle dealer who had first noticed a "ring-like" lesion on the right jaw 16 days previously. It had gradually spread, become itchy and the site became purulent, markedly tender and swollen. He attended his general practitioner who prescribed oral itraconazole and flucloxacillin. The pain, however, intensified and further suppurative areas discharged prompting admission to a local hospital. A diagnosis of bacterial cellulitis was made and the mass on the right jaw line was incised and drained. In addition, intravenous flucloxacillin, benzylpenicillin and metronidazole were commenced and itraconazole discontinued. There was no improvement 2 days later, prompting a change in antibiotic regimen to intravenous piperacillin/tazobactam and metronidazole and admission to the National Maxillofacial Unit in St. James's Hospital. Wound swabs and blood cultures were negative, there was a neutrophil leucocytosis (neutrophils11.52 x 109/L) and CRP was raised (111.4mg/L). Antibiotic treatment with intravenous metronidazole and amoxicillin with clavulanic acid was altered on the advice of Microbiology to flucloxacillin, benzylpenicillin and metronidazole.

Examination revealed a large, indurated, erythematous, boggy mass on the right jaw line and there was purulent discharge exuding from multiple sites with prominent cervical lymphadenopathy. A clinical diagnosis of tinea barbae with kerion

Table 1 The infective causes of folliculitis of the beard area and guidance for investigation and treatment

		Folliculitis of the Beard Area	
		Bacterial	**Fungal**
Frequency		Common	Rare
Risk Factors		Direct exposure to animals Shaving/chronic irritation, diabetes, topical steroids, systemic immunosuppression, trauma, occlusion	
Symptoms		Often itchy More pain with deeper infection, although pain may be absent with kerion formation	
Complications		Furuncle: An infection of the pilosebaceous unit Carbuncle: A collection of furuncles	Kerion: An inflammatory response to fungal infection
Scarring		Infrequent	Frequent with kerion in absence of rapid treatment
Investigation	Swab (most frequently isolated organism)	*Frequently positive (Staphylococcus aureus)*	*Often negative (Trichophyton verrucosum, Microsporum canis, Trichophyton mentagrophytes)*
	Biopsy	Consider where index of suspicion of tinea barbae raised by: • History of direct exposure to animals • Unresponsive to antibiotics • Alopecia of the beard area • indurated, erythematous, purulent mass	Procedure: • Two samples • One in formaldehyde for histopathology • One in universal container for microbiology culture & sensitivity (± polymerase chain reaction) • Highlight that fungal infection is suspected
Treatment		Should be guided by microbiological investigation ± microbiology team advice Flucloxacillin	Itraconazale/terbinafine (1st line) Griseofulvin (2nd line) oral prednisolone may be required in the instance of kerion, with treatment course duration depending on degree of inflammation.

formation was suggested. Areas of the indurated, purulent mass were biopsied and specimens sent for histopathology and tissue culture. Fungal spores were identified on direct microscopy following preparation of the tissue sample with a calcofluor white stain. Fungal culture at 37°C resulted in sub-agar growth of chlamydospore and broad and irregular hyphae characteristic of *Trichophyton verrucosum*. Processing of a second biopsy sample allowed extraction and purification of chromosomal DNA followed by amplification of the18s rRNA gene. The product was sequenced and an online Basic Local Alignment Search Tool (BLAST) search verified the fungal genome. Treatment with oral terbinafine 250mg daily was commenced, however 2 days subsequently pronounced pain and tenderness persisted. Oral prednisolone at a dose of 30mg daily was therefore added to the regimen. The patient was reviewed in the dermatology outpatient clinic one week later, and a significant improvement noted. Oral prednisolone was weaned over the subsequent 2 months, but oral antifungal treatment was continued for a further 2 months. Seven months later, only mild scarring was evident on the right jawline.

Case 2

The Ear, Nose and Throat (ENT) team requested Dermatology input for a 54 year old farmer and butcher who had developed a thumb-sized pustular mass within the beard area on the right side of the neck. Six weeks previously the patient had aggravated a newly developed "pimple" within the beard area while shaving. A rash subsequently developed and his GP commenced a course of oral flucloxacillin and benzylpenicillin. A week later the area had enlarged and was oozing a clear fluid. Bacterial swabs on two occasions were negative. The patient was referred to ENT where the lesion was incised, drained and biopsied. A course of metronidazole and amoxicillin with clavulanic acid was commenced. After two weeks, the area involved had increased in size with marked purulence. Histopathology demonstrated a fungal folliculitis, prompting referral to the Dermatology service.

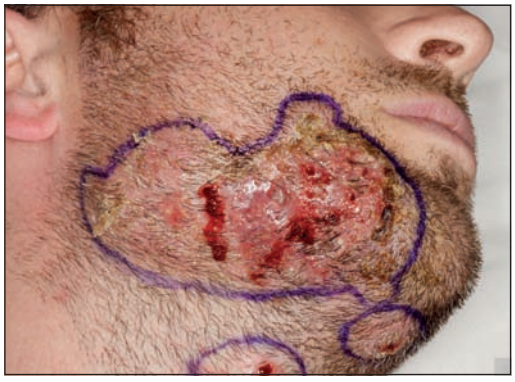

Figure 1

An erythematous, boggy mass on the right jaw line with purulent discharge exuding from multiple sites

Examination revealed an indurated, pustular mass on the anterior aspect of the right side of the neck with multiple smaller pustules and scarring posterolaterally. Further bacterial and fungal swabs were taken and itraconazole 200mg twice daily was commenced. After a week without improvement, a reducing dose of prednisolone 20mg daily was added and itraconazole continued. A significant improvement occurred over the following three weeks that lessened on steroid withdrawal. Examination revealed a small number of persisting pustules. Itraconazole was prescribed for a further six weeks, and oral prednisolone for a month, followed by clobetasol propionate BP 0.05% w/w (super potent topical steroid) ointment daily for two weeks. Ten weeks after commencement of itraconazole, new pustules continued to erupt within the beard area. A swab was taken and griseofulvin 1g daily was commenced. Six weeks later, only scarring and patchy alopecia were noted on examination. The patient, however, reported intermittent yellow spots occurring within the previously affected area. Swabs were negative but an intermittent bacterial folliculitis was suspected. A two month course of tetracycline 300mg daily resulted in no further episodes and complete clearance of the area.

Discussion

Dermatophytes are fungi that are capable of causing skin infections, known as dermatophytoses and belong to three related genera, *Microsporum spp.*, *Trichophyton spp.* and *Epidermophyton spp.* Tinea barbae is an uncommon dermatophyte infection of the bearded areas of the face and neck, in adult males. It was more common prior to the invention of disposable razors when contaminated barbershop blades resulted in infection known as "barber's itch"[1,2]. *Trichophyton verrucosum* and *Trichophyton mentagrophytes* are now the most commonly isolated species, while *Microsporum canis* is less commonly isolated[3]. These are zoophilic dermatophytoses resulting from direct contact with animals in those who are occupationally exposed. They demonstrate an ectothrix pattern of invasion whereby arthroconidia (asexual spores) are present on the exterior of the hair shaft resulting in fluorescence under Wood's lamp. Invasion also occurs within the hair shaft resulting in destruction of the hair cuticle that results in an inflammatory reaction. Perifollicular, exudative pustules form and because of the large numbers of terminal hairs in bearded areas, the result is often a vigorous inflammatory reaction known as a kerion. Unfortunately, incision and drainage are likely to worsen the short and long-term outcome, resulting in additional scarring. Oral prednisolone has

been advocated to suppress the inflammatory reaction and thus limit the scarring, although the evidence is largely anecdotal.

Our two cases demonstrate the importance of establishing a clinical diagnosis with special attention given to occupational history, microscopy and fungal culture in the case of purulent facial lesions. It is, however, worth noting that fungal cultures may be negative as in case 2. Once a diagnosis was established in these cases, institution of treatment with oral antifungal agents and oral steroids resulted in minimal scarring in the former, and complete resolution in the later case, although prolonged treatment was required. The isolation of *Trichophyton rubrum* is also worth noting as, although a rare isolate in the case of kerion, reports have associated it with scarring[4-6]. We think that it is important to highlight this curable condition which, given its rarity, is sometimes overlooked as a diagnosis and that can be exacerbated by surgical intervention. Table 1 contrasts the infective causes of folliculitis of the beard area and includes a guide to aid with its diagnosis and treatment.

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References

1. Craft N, Lee PK, Zipoli MT, Weinberg AN, Swartz MN, Johnson RA. Superficial cutaneous infections and pyodermas. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Editors Fitzpatrick's Dermatology in General Medicine. 7th ed. Mc Graw Hill; 2008. p1698.
2. Szepietowski JC. Tinea barbae. E Medicine http://emedicine.medscape.com/article/1091252-overview#a0199.
3. De Vroey C. Epidemiology of ringworm (dermatophytosis). Seminars in Dermatology. 1985;4:185-200.
4. Xavier M, Torturella DM, Rehfeldt F, Alvariño C, Gaspar N, Rochael M, Cunha F. Sycosiform tinea barbae caused by Trichophyton rubrum. Dermatology online journal. 2008;14:10.
5. Beswick SJ, Das S, Lawrence CM, Tan BB. Kerion formation due to Trichophyton rubrum. British Journal of Dermatology. 1999;141:953-4.
6. Ive FA. Kerion formation caused by Trichophyton rubrum. British Journal of Dermatology. 2000;142:1065-6.

Efficiency of Computerised Discharge Letters

Sir,

Continuity of care between acute hospitals and general practitioners is of the utmost importance in ensuring patients receive appropriate and timely care after discharge from hospital. Increasingly, general hospitals use a computerised system to generate discharge summaries for inpatients at the point of discharge. Computer generated letters are clearly legible, often quick to complete, detailed, and some offer protection against transcription errors whereby incorrect drug dosages are highlighted to the person writing the discharge summary. In order to evaluate the efficiency of receipt of the computerised discharge system in Tallaght Hospital (TEAMS), an audit was performed of 100 consecutive discharges from the department of age –related health care and stroke-service. In the case of Tallaght Hospital, discharge summaries are sent both by post, and electronically via Healthlink to participating GP practices.

The audit consisted of determining how many of the discharge letters were received by the correct GP, and in clarifying the factors associated with failure to receive a discharge summary. A total of 85 hospital discharge letters (85%) had been received by the appropriate practice by post and/or electronically, but there was no record of receipt for 15 (15%). Of the fifteen letters not received, three had no discharge summary completed. Of these, two were same day discharges. One patient episode was ascribed erroneously to the department, and the discharge summary had not been completed by the responsible clinical team. Two discharge summaries went to the wrong GP due to the incorrect GP details being entered into the Patient information management system (PiMS). One was an inter-hospital transfer where the discharge summary was sent to the referring hospital. The remaining nine cases of non-receipt of discharge letter occurred to GP practices who were not participants in Healthlink. This data suggests that there is a sizeable minority of discharge summaries, almost one in ten, which are not recorded as received by their general practitioners. In addition, a smaller number had not been written at the time of discharge, and for one in 50, the incorrect GP was recorded in the case-notes.

This study also highlights the importance of electronic transmission of discharge summaries, as no Healthlink practice reported missing letters. This audit was facilitated by the computerised discharge system in the hospital, and suggests that a review of the processes for sending out discharge summaries should be undertaken by liaison committees of GPs and their local hospitals. A confirmation with the patient on their current GP details by administration staff on admission should be performed at each care episode. It is also important to review the process from generating the discharge letter through to sending in the post within the hospital, and possibly a centralized mail-out of discharge letters would eliminate variability in this process. Our results confirm that secure electronic communication plays a major role in maximizing the efficiency of communication of transitions of care of patients between hospitals and their general practitioners, and its universal use should be encouraged.

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Creation of an Electronic Referral Pathway for Pelvic and Acetabular Fractures in Times of Austerity

Sir,

The Adelaide and Meath Hospital in Tallaght is the national referral centre for all pelvic and acetabular trauma in Ireland. Referrals were made by contacting the trauma registrar on call and forwarding a letter with a copy of the patient's films (routinely by taxi) for review. Once the films were reviewed, a decision was made as to whether surgical intervention was necessary and if so,

the patient was accepted for transfer. This referral system had a number of failings, in that there was a time delay and no formal record of the consultation. Another issue was that x-ray films could go missing in transit. These factors contributed to delays in patient transfer and ultimately time to surgery. Therefore it was decided to create a new referral system that would address these issues.

Initially a database was established on the trauma departmental office computers. However, this was not successful as it was not universally adopted with data being entered retrospectively without capture of all the relevant information and x-rays still being sent manually with frequent delays. This then lead to discussions with the IT department about a possible solution. The intention was to create a new electronic referral pathway that would address all concerns with minimal cost to the hospital. The hospital already had an internal internet and emailing system which allowed group emails to be sent to people on specified lists or within departments. It was also possible to restrict access on this system to designated people. This software formed the basis of the solution to the problem and additional software at the cost of only €400 was all that had to be purchased by the hospital. A web page on the internal hospital internet was created, to which all pelvic referrals would be sent and permanently recorded. All the doctors listed as members of the trauma department were allowed access to this web page. The electronic referral system is now operational for 2 years and operates as follows, to make a referral, the trauma registrar on call is contacted and informed of the case. The person making the referral then sends an email to pelvic&acetabulartrauma@amnch.ie documenting patient details with appropriate images so that a decision can be made about surgical intervention. The system then emails the hospital email account of listed doctors, informing them of a referral. The referral email is automatically permanently stored with the time and date of referral noted.

Since operational, the vast majority of the referrals are now received through this system. One of the main bonuses of this system, in conjunction with the instant access to the data, is the permanent record that it provides of all data received, which can be later used for research purposes. There are further areas of improvement for this system, however we believe we have made a good start.

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Turner Syndrome: Awareness of Health Issues

Sir,

Turner syndrome (TS) is an important cause of short stature in girls and occurs in approximately 1 in every 2000 live female births. Affected girls may also experience a wide range of problems. We aim to examine the perception of health issues that are related to TS.

An increased prevalence of obesity, hypertension, autoimmune thyroiditis, coeliac diseases, inflammatory bowel disease and social vulnerability has been found in adolescent patients with TS[1,2]. Adults with TS may need counselling and preparation concerning assisted fertility[2] and may exhibit a wide range of problems such as obesity, hypertension, aortic dilation, osteoporosis, autoimmune thyroiditis or sensorineural deafness, for example[1,2]. In adults with TS, life expectancy may be affected due to an increased risk of aortic dissection and ischemic heart disease[3]. Those, who did not have access to focused health care, may have low Quality of life[3]. Follow up by a multidisciplinary team to improve life expectancy and reduce morbidity was recommended[3]. We therefore set out to examine the perception of health issues that are related to TS. Ethical approval was obtained from our local hospital ethics committee. Girls with TS were recruited to the study if they genetically confirmed TS and aged over 12 years. Of 35 girls who were invited, 32 agreed to participate. The participants have been asked to complete self-assessment questionnaire regarding the health problems which adult with TS can experience. Girls with TS and their parents or guardians were contacted either in the outpatient clinic or by telephone. Those who expressed initial agreement received questionnaire form. A minimum duration of 1 week was given to return the form. To our knowledge, this is the first study to examine the perception of health issues in Irish girls with TS.

Data were available from 32 girls with TS (Table 1). Mean (SD) age is 16.7(2.61) years (range 12.4-20.2 years). Approximately, half of the girls reported that health issues related to TS include obesity [18 (56.3%)] or heart problems [17 (53.1%)]. Of 32 girls, 14 (43.8 %), 11 (34.4%) and 10 (31.3%) perceived that adults with TS experience hearing issues, eye problems and fractures, respectively (Table 1). Approximately 1 in 6 girls (15.63%) reported that adults with TS exhibit numbers of health issues including heart, hearing, obesity, fracture and ocular. Of 32 girls, 2 (6.3%) feel that TS patients experience no health issues. We underline the importance of discussing the health issues that are related to TS with girls with TS and their parents.

Table 1The transition management-health problems perception

Problems	Frequency (%)	Problems	Frequency (%)
Heart	4(12.5%)	Heart and hearing	1(3.125%)
Heart and fracture	1(3.125%)	Heart and obesity	1(3.125%)
Heart, obesity and hearing	2(6.250%)	Heart, vision and obesity	1(3.125%)
Heart, hearing, obesity and fracture	1(3.125%)	Heart, hearing, vision and obesity	1(3.125%)
Heart, hearing, obesity, fracture, and vision	5(15.63%)	Hearing	1(3.125%)
Vision	1(3.125%)	Fracture	1(3.125%)
Obesity	3(9.375%)	Obesity, fracture and vision	1(3.125%)
Obesity, fracture and hearing	1(3.125%)	Obesity, hearing and vision	2(6.25%)
Do not know	2(6.25%)	No answer	1(3.125%)
No Problems	2(6.25%)		

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References

1. Collett-Solberg PF1, Gallicchio CT, Coelho SC, Siqueira RA, Alves ST, Guimarães MM. Endocrine diseases, perspectives and care in Turner syndrome, Arq Bras Endocrinol Metabol 2011;55:550-8.
2. Donaldson MD, Gault EJ, Tan KW, Dunger DB. Optimising management in Turner syndrome: from infancy to adult transfer, Arch Dis Child2006;91:513-20.
3. Elsheikh M, Dunger DB, Conway GS, Wass JA. Turner's syndrome in adulthood, Endocr Rev 2002;23:120-40.

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Epidermal Growth Factor Receptor (EGFR) Mutation Testing, From Bench to Practice: A Single Institute Experience

H Shikhrakab, YY Elamin, C O'Brien, K Gately, S Finn, K O'Byrne, N Osman. Ir Med J. 2014; 107: 201-4.

Question 1
The number of patients tested for EGFR was

a) 199
b) 209
c) 219
d) 229
e) 239

Question 2
The mean of patients at testing was

a) 61 years
b) 63 years
c) 65 years
d) 67 years
e) 69 years

Question 3
The number of patients with a EGFR mutation was

a) 29
b) 31
c) 33
d) 35
e) 37

Question 4
The proportion of patients with a EGFR mutation who were female was

a) 59.3%
b) 61.3%
c) 63.3%
d) 65.3%
e) 67.3%

Question 5
The proportion of patients with EGFR mutations who had never smoked was

a) 58%
b) 60%
c) 62%
d) 64%
e) 66%

Is the NHS Best Practice Tariff for Type 1 Diabetes Applicable in the Irish Context?

N O' Brien, SM McGlacken-Byrne, CP Hawkes, N Murphy. Ir Med J. 2014; 107: 204-7.

Question 1
The number of diabetic children included in the study were

a) 306
b) 308
c) 310
d) 312
e) 314

Question 2
The number of children diagnosed with diabetes in 2012 was

a) 47
b) 49
c) 51
d) 53
e) 55

Question 3
The number of children on insulin pumps is

a) 104
b) 106
c) 108
d) 110
e) 112

Question 4
The overall proportion of children with HbA1c < 7.5% was

a) 18.33%
b) 20.33%
c) 22.33%
d) 24.33%
e) 26.33%

Question 5
The overall proportion of children with HbA1c >9% was

a) 6.16%
b) 7.16%
c) 8.16%
d) 9.16%
e) 10.16%

Pulmonary Non-Tuberculous Mycobacteria in a General Respiratory Population

SG Chong, BD Kent, S Fitzgerald, TJ McDonnell. Ir Med J. 2014; 107: 207-9.

Question 1
The number of patients in the study was

a) 33
b) 35
c) 37
d) 39
e) 41

Question 2
The number of patients with mycobacterium avium was

a) 20
b) 22
c) 24
d) 26
e) 28

Question 3
The proportion of the patients who had bronchiectasis was

a) 28%
b) 30%
c) 32%
d) 34%
e) 36%

Question 4
The number of the patients who were commenced on treatment were

a) 6
b) 8
c) 10
d) 12
e) 14

Question 5
The mean age of the patients was

a) 58.8 years
b) 60.8 years
c) 62.8 years
d) 64.8 years
e) 66.8 years

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