War stimulates scientific research. Vennevar Bush was President Roosevelt's top advisor on matters of technology in the Second World War, and one of the pioneers of US radar research. In 1945, he speculated that one day, it would be possible to sit down at a desk or machine that would house or access all human knowledge. He called this machine a memex, a portmanteau of "memory" and "extender" or "memory" and "index", and described it as desk and camera combination that could record anything a user wrote, and then link it to other pieces of information indexed in its storage space. This essay prefigured hypertext, the personal computer, the Internet, the World Wide Web, speech recognition and online encyclopedias.1

The general public has had access to the web since the late 1990s,2 and this has almost inevitably led to the notion of open access publishing. Open access implies free (at point of access) retrieval of scholarly and peer-reviewed research online. This form of open access is technically known as gold open access publishing and is only possible due to the very cheap distribution and dissemination of such materials online. The main advantage is that such material becomes instantly available.

However “open don’t mean free” since overseeing the peer-review process, information technology (hardware and software) outlays and online publishing costs must be contended with.

Thus, established publishers who have moved to the open access model typically charge authors fees in the region of £1000 or more for the publication of a paper once a paper has been through the mill of the conventional peer-review process and has been accepted.3 Clearly, open access proposes a redistribution of costs – “there ain’t no such thing as a free lunch”.4

The model has worked in the main.5 However, the principal disadvantage is that with the prevailing publish or perish mentality, it is easy for a new journal to start up and shortly become inundated with authors who need their work to be published in order to further their career.

Fees are therefore easily levied by publishers and paid up by authors, often from research funds.

Indeed, this author’s email (and I am sure, the readers’ too) frequently receives invitations for the submission of papers to newly fledged, open access journals. It is only when one scrutinizes the fine print that the nontrivial publishing fees become apparent.

Established publishers are therefore concerned that the lure of lucre may compromise the peer-review process and allow the publication of substandard papers by unscrupulous publishers. Shut one eye – as long as the author pays the processing fee. Such attitudes will inevitably diminish standards, and authors publishing in unprincipled journals may not find their work well regarded.

Readers are exhorted to vet the vehicle for their publication with care. Lists of such “predatory” journals and publishers may be readily found online.

References

Victor Grech
Editor
Malta Medical Journal
Objective: To evaluate the early outcomes after coronary surgery in the elderly.

Methods: A retrospective analysis (April 1995-January 2012) of mortality, morbidity and hospital stay, derived from a single surgeon’s practice. Outcomes of patients over 70 (group A, n=785) were compared with those of controls under 70 (group B, n=2772).

Results: Intervention rate was significantly higher (1502/10^6 vs 467/10^6, p<0.0001). There were significantly fewer single and quintuple grafts, and significantly more double grafts in group A. The use of an internal thoracic artery (ITA) was lower in group A (748/785, 95.3% vs 2695/2772, 97.2%, p=0.006). Mortality for the entire coronary surgical practice was 1.2%. The overall mortality was 2.7% in group A and 0.8% in group B (p<0.0001). Freedom from any postoperative complication occurred in 57.7% in group A and in 75.6% in group B (p<0.0001). Cardiac complications (except for perioperative MI and atrial flutter) were significantly higher in group A, as were major neurological, renal and respiratory complications, as well as minor wound complications.

Conclusions: Although mortality and morbidity remain significantly higher, taken in the context of the overall clinical problem, cardiac surgery has much to offer in this select group of patients.

Keywords
Coronary surgery, elderly, outcome

Introduction
Life expectancy and the demand for a meaningful and satisfying quality of life are increasing steadily every year. At the millennium Maltese males could expect to reach the age of 75 and females that of 79 years.¹ Twelve years later these figures increased to 78 and 82 years respectively.² This, in large part, reflects a higher standard of living with its attendant improved health care facilities. The treatment of cardiovascular disease, one of the major contributors to premature death, plays a role in achieving this goal.³ Physicians’ and patients’ attitudes are evolving with the realisation that surgery can achieve a worthwhile improvement in longevity and quality of life with acceptable morbidity.⁴ Suffice it to say that 30 years ago patients over 65 were likely to be refused admission to an intensive care facility because of their age, and yet 28% of local patients were over 70 at the time of their coronary bypass surgery in 2011.
Patients and methods

A retrospective analysis of a single surgeon’s coronary patient population was undertaken, from the start of the local cardiac surgical service in Malta in April 1995 until January 2012 (n=3557). For the purposes of this study elderly patients were defined as those over 70 years old (group A, n=785) and their data and outcomes were compared with those of patients under the age of 70 (group B, n=2772).

Patients were referred for surgery on the basis of the clinical picture and coronary angiography. The decision to operate was determined by the suitability for surgical correction, the symptomatic class as well as the possible prognostic benefit attributed to the procedure. Although projected increased longevity from surgery played a major role in group B, it has been increasingly applied to group A, particularly in the absence of serious co-morbid conditions. The possible risk/benefit assessment of surgery was openly discussed with the patient before a decision to proceed was taken. Risk stratification was calculated in all patients, using the Parsonnet score for the entire study period and the EuroSCORE for the years 2000-2011.

Peri-operative death was defined as death within 30 days of surgery or at any time during the postoperative in-hospital stay. Complications were classified according to system and further assigned to a major or minor category (Table 1).

Table 1: Complications by system

<table>
<thead>
<tr>
<th>System</th>
<th>complication</th>
<th>group A</th>
<th>group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>major</td>
<td>61.7</td>
<td>96.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>IABP</td>
<td>33.9</td>
<td>60.2</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>peri-operative MI</td>
<td>4.0</td>
<td>10.4</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>permanent pacemaker</td>
<td>6.7</td>
<td>4.0</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>ventricular arrhythmias</td>
<td>18.2</td>
<td>22.0</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>minor</td>
<td>394.5</td>
<td>658.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>ischemic &gt;24hr</td>
<td>218.7</td>
<td>402.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>renal dialysis</td>
<td>165.21</td>
<td>260.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>renal failure</td>
<td>11.4</td>
<td>36.1</td>
<td>0.82</td>
</tr>
<tr>
<td>Neurological</td>
<td>major</td>
<td>18.2</td>
<td>24.0</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>CVA/RIND (&gt;24hr)</td>
<td>8.0</td>
<td>19.0</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>minor</td>
<td>5.6</td>
<td>10.4</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>transient ischaemic attack</td>
<td>1.0</td>
<td>3.7</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>confusion</td>
<td>2.8</td>
<td>2.0</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>peripheral neuropathy</td>
<td>2.0</td>
<td>2.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Renal</td>
<td>major</td>
<td>4.1</td>
<td>4.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>dialysis</td>
<td>20.5</td>
<td>31.1</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>minor</td>
<td>3.0</td>
<td>5.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>major</td>
<td>9.1</td>
<td>23.0</td>
<td>0.41</td>
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<tr>
<td></td>
<td>abdominal catastrophe</td>
<td>3.4</td>
<td>5.2</td>
<td>0.29</td>
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<tr>
<td></td>
<td>haemorrhage</td>
<td>1.1</td>
<td>23.0</td>
<td>0.41</td>
</tr>
<tr>
<td>Respiratory</td>
<td>major</td>
<td>23.9</td>
<td>44.1</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>ventilation &gt;24hr</td>
<td>18.2</td>
<td>40.52</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>minor</td>
<td>9.1</td>
<td>26.0</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>chest infection</td>
<td>9.1</td>
<td>14.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Infective</td>
<td>major</td>
<td>12.6</td>
<td>31.2</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>sepsis/endoendritis</td>
<td>6.8</td>
<td>16.0</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>major wound infection</td>
<td>6.8</td>
<td>15.0</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>minor</td>
<td>25.3</td>
<td>52.1</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Complications were recorded by attending medical staff on a daily ward round and entered into the database when the patient was discharged from hospital.

Clinical protocol

Cardiac

Drugs were not routinely used as prophylaxis for atrial fibrillation. All preoperative drugs were continued until surgery except Aspirin and Clopidogrel, which were stopped one week before when possible. The decision to use inotropic support was taken in the operating theatre on the basis of the preoperative ventriculogram and renal function, coupled with the prevailing haemodynamic status. The post-operative weaning of these drugs was also determined by the patient’s clinical status. Swan-Ganz catheters were used selectively to monitor continuous cardiac output and venous saturation, as well as other derived parameters. Intra-aortic balloon counterpulsation was employed when inotropic support coupled with appropriate preload and afterload manipulation were insufficient to achieve a stable haemodynamic situation. The diagnosis of peri-operative myocardial infarction was made on the basis of new Q waves on the 12 lead ECG coupled with the clinical picture. A permanent pacemaker was implanted for 2nd or 3rd degree heart block following a suitable period of observation.

Neurological

Cerebrovascular accident (CVA) with permanent sequelae as well as reversible ischaemic neurological deficit (RIND) lasting more than 24 hours were classified as major neurological complications. Transient ischaemic attack (TIA), with complete recovery within 24 hours, was classified as a minor complication but was investigated and treated appropriately. Post-operative confusional state and peripheral neuropathy were also included as minor neurological complications. Preoperative carotid Doppler study, followed by angiography where appropriate, was performed in the presence of a carotid bruit, history of CVA or TIA or the presence of peripheral vascular disease and concomitant carotid endarterectomy performed when indicated.

Renal

When renal impairment was present preoperatively every effort was made to achieve an optimal haemodynamic state in order to maintain adequate glomerular filtration rate. Temporary hyperkalaemia was treated with insulin/dextrose infusion and/or oral calcium resonium. Haemodialysis was instituted when these measures failed to maintain fluid, electrolyte and pH balance.
Gastrointestinal

Ranitidine or omeprazole were used prophylactically when there was a clear history of peptic ulcer disease or gastritis documented by endoscopy. Aspirin was administered routinely, starting on the first post-operative day.

Antibiotics

Prophylactic antibiotics consisted of Cefuroxime 750mg iv. at induction and 2 subsequent doses at 8 hour intervals. Further antibiotics were administered according to the clinical picture and bacteriological results.

Statistical analysis

Statistical analysis was performed using Excel software (Microsoft, Redmond, USA, version 11.6.5 2004). Pearson’s chi squared test and Fisher’s exact test were used to assess differences between categoric variables. Chi squared test with Yates correction was used to calculate significance of trends. Students t test was used to assess differences between populations. Differences were considered significant for p values less than 0.05.

Results

Age distribution

The age distribution for both groups is illustrated (Figure 1).

The mean age of the total surgical population was 61.9 years (61.0 in 1995, rising to 63.3 in 2011). The mean age±SD for group A was 73.5±3.21 and for group B was 58.6±7.21. The annual percentage of patients over 70 ranged from 15.6% to 31.3% (mean 23.1%). The mean for the years 1995-2001 was 18.7% and the mean for 2002-2011 was 26.2% (Figure 2).

Intervention rate

The mean intervention rate up to 2001 (after which the service was increased to 3 consultants) was of 1502 per million per year in group A (population 30,735 at end December 1999) and 467 per million per year in group B (population 349,466, \( p < 0.0001 \)).

Repeat operations were performed in 0.51% in group A and in 0.47% in group B (\( p = 0.055 \)).

Risk stratification

The mean Parsonnet risk stratification score was 12.8 for group A and 4.4 for group B. This is in keeping with the increased incremental score attached to age exceeding 70, 75 and 80 years. The trends in Parsonnet score with time in Group A and B are presented in Figures 3 and 4. The mean EuroSCORE risk stratification score was 4.8 for group A and 1.9 for group B. The trends for EuroSCORE, for the years 2000-2011, are presented in Figures 5 and 6.

Grafting strategy

Triple coronary artery bypass grafting was the commonest procedure (group A average 3.1 grafts per case, group B average 3.2). Figure 7 shows the graft distribution per case. There were significantly fewer single and quintuple grafts, and significantly more double grafts in group A. The use of an internal thoracic artery (ITA) was lower in group A (748/785, 95.3%) than in group B (2695/2772, 97.2%, \( p = 0.006 \)).
Figure 3: Parsonnet trends group A

Figure 4: Parsonnet trends group B

Figure 5: EuroSCORE trends group A

Figure 6: EuroSCORE trends group B
Freedom from any post-operative complication occurred in 57.7% in group A and in 75.6% in group B ($p<0.0001$). All complications resulted in patient morbidity but cerebrovascular accident had the worst impact in that it contributed to perioperative death in 8 of the 18 cases in group A and in 4 of the 24 cases in group B ($p=0.049$). Other complications resolved with time and some patients required further treatment on an out-patient basis. No patient required long term dialysis.

Ninety six percent of patients who developed new atrial fibrillation were cardioverted before discharge; the remaining few were anticoagulated for three months, within which time they were successfully cardioverted. The incidence of this post-operative complication was comparable to that in other units employing perioperative pharmacologic prophylaxis.$^6-9$ Patients requiring a permanent pacemaker observed the usual follow-up protocol.

Gastrointestinal catastrophes secondary to ischaemic bowel and perforated diverticulitis were rare but uniformly fatal. Two cases of perforated duodenal ulcer underwent successful surgery. Gastroduodenal haemorrhage was commoner and was always treated conservatively.

The requirement for ventilation beyond 24 hours because of poor respiratory function was rare but significantly greater in group A.

**Hospital stay**

Figure 9 shows the post-operative hospital stay on the intensive care unit (ITU), high dependency unit (HDU) and the cardiac surgical ward (CSW). Average length of stay on intensive care was similar (1.19±1.84 days for group A and 1.13±1.48 days for group B, $p=0.38$).
The average HDU stay was longer in group A (1.43±2.70 vs 0.95±3.68 days, \( p=0.006 \)) as was the average CSW stay (4.00±3.33 vs 3.25±2.23 days, \( p<0.0001 \)).

**The very elderly**

Figure 10 shows the trends in patients over 75 and over 80 in the female and male populations, expressed as a percentage of the total surgical populations for three consecutive 5 year periods (females in groups A and B, males in groups A and B). There was a significant increase in both female and male patients over 75 from the period 95-00 to 01-05 (\( p=0.0005 \) for females, \( p=0.00003 \) for males), and in male patients over 80 for the same period (\( p=0.006 \)). Although the trend remained upwards in recent years, with 19% of females and 11.9% of males over 75, the rise did not reach statistical significance.

**Figure 10: The very elderly cohorts**

**Discussion**

The incidence of cardiovascular disease increases with advancing age and presents a continuing health care challenge in an aging population, such as ours. Finite health service provisions necessitate an allocation of resources to those patients who are more likely to benefit from treatment both on symptomatic and prophylactic grounds. Hospital stay reflected peri-operative morbidity, the extent of the rehabilitation programme and an evolving health care mission for earlier discharge.

Group A patients required an additional half day of high-dependency care and an additional 0.75 days on the cardiac surgical ward. This study demonstrates an intervention rate in the elderly 3.2 times that in younger patient with a demonstrable increase over the 17 years. Coronary artery bypass grafting was as extensive and complete in the elderly. The significantly lesser utilisation of the internal thoracic artery was not based on age alone but on technical considerations at surgery, including more distal coronary disease as well as an unsuitable ITA because of intrinsic disease or small size when grafting the distal left anterior descending (LAD) coronary artery. Since bypass grafting has not been shown to influence the ten-year survival in the over 70’s \(^4\) we have generally tended to offer surgery to those patients with significant symptoms not amenable to other treatment modalities. However, in a subgroup with significant left main stem or proximal LAD disease, surgery was considered the first line of treatment. We were also more likely to advocate medical therapy or angioplasty in preference to re-operation for recurrent coronary artery disease in this group because of increased mortality and reduced long-term survival. \(^10\) The overall mortality was significantly higher in this group with multiple cardiovascular as well as co-morbid factors influencing this outcome. Our growing experience has resulted in an increased awareness of the expected complications and a more aggressive approach in managing them. \(^11\)

Both the Parsonnet and EuroSCORE risk stratification systems weight female gender with one unit, and this partially explains the higher scores in the vast majority of years. However, when one factors in further weighting due to advancing age, this gender difference assumed less prominence.

Postoperative cardiac complications were higher in this group, necessitating more intensive treatment, a longer hospital stay with attendant costs, but rarely affecting the long-term outcome. Our policy of early intervention with pharmacological or electrical cardioversion for atrial fibrillation and flutter lessened the impact of this common complication on resource utilisation.

In contrast, permanent neurological damage remains a major problem, with a 2.6-fold increased incidence in the elderly. As in other studies\(^12\) it was more likely to result in early postoperative death, and in the survivors rehabilitation was likely to be more prolonged and ultimately less effective. Our increased awareness of this clinical problem and its treatment with carotid endarterectomy at the time of cardiac surgery should improve patients’ outlook over the subsequent years but is unlikely to lower the immediate postoperative neurological complication rate. \(^13\)

**Conclusion**

The demand for cardiac surgical intervention in the elderly is high and likely to increase if we are to
follow the trend in more developed nations. The switch from a health funded to a privately funded service may also impact on service provision. Although mortality and morbidity remain significantly higher, taken in the context of the overall clinical problem, cardiac surgery has much to offer in this select and growing population.

References
Abstract
There is growing concern about the association of school indoor air quality (SIAQ) with asthma, rhinitis and rhinoconjunctivitis. The most commonly studied allergens are cat (Fel d 1), dog (Can f 1) and dust mite (Der f 1, Der p 1). Very few studies have analysed the significance of cockroach (Bla g 1 and 2) and mould allergens in schools and not much is known about SIAQ in island nations such as Malta. Schools with high allergen levels have an increased incidence of atopic disease resulting in a negative impact on the childrens’ health and performance. An acceptable SIAQ can be achieved by adopting published recommendations regarding the control and prevention of indoor allergens. The absence of a European SIAQ monitoring programme highlights the urgent need for more research in this field so as to issue the necessary evidence based recommendations specific to the individual countries.

Key words
Allergens, Air, Asthma, Indoor, School.

Introduction
The importance of school indoor air quality (SIAQ) has been increasingly recognised since children spend most of their time outside home within the school environment. Although several studies of school indoor air quality and health complications in schools exist, there is no comprehensive analysis of existing literature and data with special reference to European schools.

Background
In Europe more than 71 million kindergarten, primary and secondary students attend school on a daily basis. Poor SIAQ will therefore have a negative impact on the children’s health, growth and performance both at school and within society in general.

SIAQ has negative effects on asthma, rhinitis, rhinoconjunctivitis and allergies. Various indoor pollutants such as moulds, bacteria and airborne dust have been found within the school indoor environment.

Aim of review
The primary aim of this review is to describe the current evidence indoor air allergens in primary schools. Another aim is to study the effect these indoor air allergens have on the respiratory health of the children. We will also look at what data exists about SIAQ and allergens in island nations such as Malta due to their unique geographical and environmental characteristics and to determine the need and significance of new research within this field.

Method
This review was conducted by looking at online bibliographic databases, web reports and expert opinions and finally a manual search of reference lists. The concept words used in our search were indoor, allergens, school, asthma, allergic rhinitis and atopic eczema. A search was initially performed using the individual concept words and completed using all concept words with the word ‘AND’ between them. The bibliographic databases used where PubMed, Embase, Medline and Web of Science. Both the World
Health Organisation and American Thoracic Society websites where searched for relevant studies. The practical screening criteria used in our search included looking at studies on SIAQ due to allergens published between 1987 and 2012, studies performed in primary schools and manuscripts written in English and Italian were reviewed. Studies dealing specifically with food allergen contamination were eliminated from the review. Methodological screening criteria were utilised so as to include studies that had reliable and valid data sources, appropriate analytical methods and robust and significant statistical analysis. Any studies which did not conform with these practical and methodological criteria were excluded.

Allergen exposure in schools and its impact on asthma and atopic disease

Asthma is one of the most common conditions diagnosed in children and recent studies have shown that allergens produced by dust mite, cockroach, cats, dogs and fungi all contribute to the development or progression of the disease. The prevalence of wheezing and rhinitis in Maltese 5 to 8 year old school children in 2001 surpassed the global mean with an upward trend seen when compared to the ISAAC Phase 1 data in 1994. A negative correlation exists between acute asthma admissions in Malta and mean monthly ambient temperatures which might suggest that temperature is a proxy for the time spent indoors.

School environments with high levels of cat, dog, mould and dust allergens have an increased incidence of asthma diagnosis among the pupils. This trend has been confirmed by an increase in eosinophil peroxidase (EPO) and myeloperoxidase (MPO) in sputum of exposed children. Adult school personnel exposed to high amounts of dust allergens had an increased incidence of nasal obstruction confirmed by acoustic rhinometry. Classes with more than 18% of the pupils owning cats at home who found to have a significant decrease in peak expiratory flow rates and increased asthma symptoms and use of asthma medications in those children who did not report direct contacts with pets.

Asthma prevalence rates correlated positively with the mean levels of Bla g 1/2 in the schools (r=0.001). Furthermore cockroach allergen in schools was positively correlated with an increase in asthma symptoms. Viable mould in the school environment is associated with increased asthma symptoms with Swedish schools showing that viable mould in classrooms is positively correlated with asthma when compared to schools with better indoor air quality. Aspergillus sp was found to result in a decrease in nasal patency while ECP and lysozyme levels in NAL where increased. The HESE Study showed that Aspergillus/Penicillium DNA was significantly positively associated with wheeze, while Aspergillus versicolor DNA correlated positively with wheeze, rhinitis, and cough.

Allergens in the school indoor environment.

The most commonly studied allergens within the school indoor environment are Cat (Fel d 1), dog (Can f 1) and the dust mite (Der f 1, Der p 1). Studies have also looked at the presence of cockroach (Bla g 1 and 2) and mould allergens in schools.

Dust mite allergens

The concentration of dust mite Der f 1, Der p 1 allergens in daycare facilities and schools is usually similar or minimally reduced when compared to other indoor environments especially homes. In 60 primary schools in the United States only 2.5% of the classrooms had dust mite levels exceeding recommended levels. Classrooms in both the US and Europe having carpeting and furnishings especially mattresses, pillows and stuffed animals are characterised by significantly high dust mite levels while non-carpeted rooms have low levels of Der f1 and Der p 1. Low levels of dust mite allergens have also been found in Norwegian classrooms with detectable levels in less than 1% of rooms. Dust mite allergen levels in four primary schools in Western Australia were found to be much lower than the recommended sensitizing thresholds. There was no difference in levels between the standard schools and ‘low allergen’ schools.

Cat and dog allergens

Cat and dog allergen levels have been found to be higher in school classrooms when compared to homes with no pets. The two most common isolated allergens are cat (Fel d 1) and dog (Can f 1). Allergen levels in classroom dust samples have been found to be as high as 1300ng/g and 1650ng/g for cat and dog allergens respectively. Floor levels and pupil cat ownership rates were positively correlated (r2=0.93, p=0.0003) while children from homes with cats carried allergen on their clothes (mean Fel d 1, 6.10microg per garment). Children who are in daily contact with cats and dogs in the home environment have been shown to carry cat and dog allergens to school via their shoes and bags and human hair.

Furnishings and textiles are associated with higher levels of cat and dog allergens. The presence of open shelves and curtains resulted in higher levels of pet allergens although these were lower in classrooms which were cleaned more often. In rooms with carpet and hard-surfaced flooring, levels of Can f
Cockroach allergens

Cockroach allergen correlated positively with the presence of carpets and soft furnishings, and allergen levels were detected (>0.003 microg/g) in 71% of the dust samples and 22% of airborne samples from the schools. Inner city schools serving low income populations have been shown to have higher levels of allergens with particular reference to food related areas which had significantly higher levels of cockroach allergen when compared to classrooms (p=0.048).

Fungal allergens

Fungal exposure has been assessed by indirect methods utilising spores as a marker of allergen presence and little data exists regarding the presence of fungal allergens in schools with most studies carried out in the US. Mould spores for Aspergillus and Alternaria had a high prevalence in school classrooms. A study carried out in Texan schools showed that more than half of the tested classrooms had fungal spore counts of > 10,000 col/g (median 14,400 col/g).

In summary, although the majority of schools have house dust mite levels which are comparable to the home environment, the presence of indoor soft furnishings and carpets favours the presence of Der p 1, Der f 1 allergens in schools. Cat (Fel d 1) and dog (Can f 1) allergens have been isolated in schools and those children who are in daily contact with cats and dogs within the home environment carry these allergens to school via clothes, shoes, bags and hair.

As with house dust mite there is a positive correlation between cat and dog allergens and the presence of carpets and soft furnishings within the school environment. Interestingly cockroach allergen was detected in 71% of dust samples and 22% of airborne samples from the schools. Aspergillus and Alternaria moulds had a high prevalence in school classrooms with higher levels seen in carpeted floors. School children spend a large part of their time within a school environment thus putting them at risk for exposure to these allergens. This is of importance since during the first few years of life children develop IgE mediated sensitivity to specific allergens thus increasing the prevalence of future atopic disease.

Prevention strategies

The evidence shows that sensitization to indoor allergens in schools is associated with increased eNO levels and therefore strategies favouring better SIAQ should be developed. Both the American Thoracic Society (ATS) Workshop on indoor air pollution and the WHO air quality guidelines have recommendations regarding the control of allergens within the indoor environment.

When analysing of the data available we have concluded that prevention strategies in schools for indoor allergens should be divided into a preventive phase and an interventional phase. The preventive phase should target those allergens that are commonly found within the school environment. A standardised regular cost effective maintenance schedule in schools should be implemented thus decreasing the levels of allergens in classrooms. This will prevent accumulation of dust, entry of pets and pests especially cockroach and finally avoid the establishment of mould by regular maintenance of both the external structures and plumbing systems. Staff should be specially trained to target these pollutants specifically and regular assessment of the indoor environment should be carried out. Both children and their parents should be educated in how to avoid exposure to pet allergens with emphasis on clothing, shoes and hair transfer of allergens.

The interventional phase should include the use of high efficiency particulate air (HEPA) with negative ions, filtration and electrostatic precipitation. A regular pest eradication programme has to be implemented and should reflect the geographical and environmental characteristics of the area. Any established mould should be immediately treated on a regular basis using environmentally friendly products.

Limitations of review

One of the major limitations of our review is that most studies involve relatively small numbers of children thus limiting the significance of results. Studies are mostly non standardised using different protocols and criteria.

Conclusions

Although the prevalence of respiratory disease has increased in Europe, not enough information is available about the quality of school air and indeed its impact on the pupils’ health. Future research needs.

The absence of a European SIAQ monitoring programme for indoor air allergens highlights the urgent need for more research in this field so as to issue the necessary evidence based recommendations specific to the particular country. To date all studies in Europe have not been standardised and mostly analysed small numbers of children in a limited number of northern countries. Although the subject has been discussed in previous publications, to our knowledge this is the first review of SIAQ which highlights the need of new data from European schools so as to enable policy makers issue the necessary recommendations. Due to the heterogeneous characteristics making up European countries it is very difficult to issue recommendations based on the
evidence currently available. No standardised studies have been carried out looking at school allergens in island nations such as Sicily Malta and Cyprus. These countries have unique environmental and air quality characteristics which differ from mainland Europe and US schools. Local studies have shown that the prevalence of asthma in school children is increasing and therefore it is important to obtain data with regards to what school indoor allergens exit locally. This will influence what preventive recommendations are needed both at school level and politically. Two European Union funded studies (SINPHONIE\textsuperscript{45} and RESPIRA)\textsuperscript{46} are currently assessing SIAQ in Maltese schools using standardised methodology and these should provide us with some urgently needed local data.

References

30. Munir AK, Einarsson R, Schou C, Dreborg SK. Allergens in school dust. I. The amount of the major cat (Fel d I) and dog (Can f I) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. J Allergy Clin Immunol. 1993 May;91(5):1067-74.


Does a simple educational exercise influence practice in acute tonsillitis in children?

Shirley Mulvaney, Simon Attard Montalto

Abstract
Aim: To assess the concordance of treatment of children attending with tonsillitis in Paediatric Accident and Emergency with established guidelines, and subsequent review of the management of this condition after a simple educational exercise.

Methods: An audit on children with tonsillitis was carried out amongst doctors working in the Paediatric Accident and Emergency Department during a three month period in 2009. Eleven doctors completed an anonymous questionnaire requesting details on presentation, symptoms, investigations and treatment of children presenting with acute tonsillitis. The results obtained from this questionnaire were compared to NICE guidelines and modified Centor (McIsaac) criteria, and fed back to the participating doctors together with copies of these guidelines via a simple, structured educational exercise. Three months later, a second identical questionnaire was again completed by the same cohort of doctors.

Results: The first questionnaire showed that there was a tendency towards unnecessary prescription of antibiotics and investigations in children with acute tonsillitis, when compared to recommendations in the guidelines. Following educational feedback, the second questionnaire showed a reduction in antibiotic prescriptions by 9% (p=0.5) and investigations by 37% (p=0.1). Compliance with guidelines had improved significantly with regard to non-prescribing of antibiotics with a fever of <38°C (Phi -0.76, p=0.0005), and with tonsillar pus but no fever (Phi -0.68, p=0.002). Increased compliance was observed when prescribing antibiotics in the presence of pus plus a fever, lymphadenopathy >1cm and presence of underlying disease although these changes were not statistically significant.

Conclusion: Although doctors were initially only partly compliant with established guidelines for children with acute tonsillitis, compliance improved significantly after a simple educational exercise.

Key words: Management acute tonsillitis, compliance, guidelines

Introduction
Acute tonsillitis is an acute inflammatory infection of the tonsils caused by several infective agents. Viral causes including adenovirus, rhinovirus, influenza, coronavirus and respiratory syncytial virus, often result in mild symptoms. Coxsackie virus may result in blisters on the tonsils and roof of the mouth that erupt after a few days leaving painful scabs. Children with infectious mononucleosis (EBV) present with an exudative, almost necrotic, tonsillitis and impressive cervical lymphadenopathy. An enlarged spleen is classically described although infrequently found. Children with bacterial tonsillitis, for example due to Group A beta haemolytic streptococcus (GABHS) are generally toxic with a high fever, swollen, purulent sore throat and halitosis. Other bacterial causes include staphylococcus aureus, streptococcus pneumoniae, mycoplasma pneumoniae, chlamydia pneumoniae, pertussis, fusobacterium, diphtheria, syphilis and gonorrhoea.
Tonsillitis most often occurs in children older than 2 years of age. Tonsillitis caused by Streptococcus species typically occurs in children aged 5-15 years, while viral tonsillitis is more common in younger children.²

In practice, as listed in Table 1, symptoms in children with acute tonsillitis vary widely and it is impossible to differentiate between viral and bacterial on inspection alone.

**Table 1: Signs and symptoms of acute tonsillitis with cause**

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Viral origin</th>
<th>Bacterial origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>cough</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>headache</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pain neck, ears</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>dysphagia</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>lethargy</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>vomiting</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>red, swollen tonsils</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>pus on tonsils</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Furred tongue</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>halitosis</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>cervical lymphadenopathy</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Fever, cough, lethargy, headache, swollen red tonsils and lymphadenopathy are common to both viral and bacterial tonsillitis. However, pus on the tonsils with furring of the tongue and halitosis are more commonly seen in bacterial tonsillitis. A complete blood count (CBC) will usually show a higher white blood cell count (WBC) in bacterial versus viral tonsillitis, as well as a higher shift in granulocytes versus lymphocytes.³ In practice, since patients with viral tonsillitis do not require antibiotics, it is important to differentiate viral from bacterial tonsillitis, and especially to diagnose tonsillitis due to Strep. Pyogenes (GABHS).

Unsurprisingly, the management of this condition has tended to fluctuate widely between institutions as well as individual physicians.⁴⁻⁵ As a result, recommendations have been drawn up by several authoritative bodies in an attempt to diagnose strep. tonsillitis and standardise treatment that is evidence based. The guidelines focus on specific criteria (summarised in Table 2) that allow for the computation of a ‘Strep. Score’, that is then used to guide therapy. The Centor Criteria⁶ (with McIsaac modification for children and adjusted for patient age⁷) advise antibiotic prescribing for tonsillitis in the presence of: 1) fever, 2) tonsillar exudates, 3) no cough and 4) tender anterior cervical lymphadenopathy. Studies show that patients with just one or none of these criteria are unlikely to have Group A beta haemolytic streptococci (GABHS), those with two criteria may merit testing whilst antibiotics are indicated in those exhibiting 3 or 4 criteria.²

The National Institute for Health and Clinical Excellence (NICE) lists the following parameters that should lower the threshold for antibiotic prescribing: 1) marked systemic upset, 2) patients with symptoms and signs suggestive of serious illness such as mastoiditis and peritonsillar cellulitis, and 3) children at risk of complications due to pre-existing comorbidity such as immunosuppression or underlying disease.⁸⁻⁹ When indicated, NICE advises that penicillin is the drug of choice, preferably given for ten days (and not less). Macrolides including erythromycin and azithromycin for five days can be used in those with penicillin allergy.⁸

Despite these evidence-based guidelines, variations in the management of acute tonsillitis persist. This study set out to assess the compliance of a cohort of paediatricians with current NICE and modified Centor (McIsaac) guidelines, and explored whether a brief educational programme whereby the same cohort was presented with a refresher of the guidelines, was followed by an improvement in guideline compliance.
Table 2: Basis for the current guidelines in the management of acute tonsillitis

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Throat swabs should not be performed routinely.  
Swabs may be helpful in high risk groups as or with treatment failure. | Reassurance and a supportive approach is sufficient management for most patients. |
| Antistreptolysin O (ASO) titre indicates recent infection and may be useful in patients who do not improve or in those who develop complications. | Gargles may be helpful but there is no evidence base to support their use. |
| EBV should be considered in adolescents or young adults with a severe sore throat. A Paul Bunnell or equivalent test may be indicated. | Antipyretic analgesics such as paracetamol and NSAID’s are of value. |
|                                         | For most patients, antibiotics have little effect on the severity or duration of the condition. |

Running title: education in management acute tonsillitis

Methods

All medical personnel working in the Paediatric Accident and Emergency Department for a three month rotation period at Mater Dei Hospital, Malta, were invited to participate in the study carried out between July and September 2009. Participants required at least one year working experience in the Emergency Department, and were asked to anonymously complete a two-part questionnaire on tonsillitis defined as ‘Inflammation of the tonsils, manifest by redness and swelling, with or without pus and/or an exudate’. Section A requested demographic details including age, gender, year of graduation, level of training and years of working experience in Paediatric A&E. Section B included questions regarding the number and age of patients with tonsillitis seen per week, their symptoms, investigations carried out and treatment recommended. Questions were included to establish what criteria were being used to prescribe antibiotics and, if so, what antibiotics were given and what was the duration of treatment. For every question, several options were provided and more than one answer box could be ticked, as appropriate. The results obtained from the initial questionnaires were then compared to the NICE guidelines and Centor criteria (with McIsaac modification). A printed copy of these results together with the current guidelines was returned to the doctors involved in the study. In addition, a list of the guidelines was made available in the paediatric emergency room as a reference point for the doctors during their shifts. At the end of their three month rotation, a second, identical questionnaire was sent to the same cohort of doctors and the results obtained were compared to those of the first questionnaire. Chi squared (with Fisher correction for small numbers) was used to determine any difference in the two sets of results obtained, taking $p \leq 0.05$ to confirm a significant difference.

Results

Eleven (5 male, 6 female) doctors, aged 23–40 years, were employed in the Paediatric A&E Department during the study period and all completed both sets of questionnaires. They included General Practitioner (3) and Paediatric (8) trainees (ranging from BST to Resident Specialist grade), and all had spent more than twelve months covering acute cases in this Department during daytime and night-time ‘on call’ hours.

Initial Survey

The initial review confirmed that an average of 5 patients, mostly aged 3 – 4 years (31%), presented in the Paediatric Emergency Department with tonsillitis per day. Most presented with fever (77%), decreased appetite (61%), dysphagia (50%), pus on the tonsils (45%), lymphadenopathy (43%) and throat pain (9%). Other less common symptoms included headaches, abdominal pain, ear pain and vomiting. Most (>70%) were self-referred with <30% referred from other medical practitioners. Seven (63%) of the doctors did not carry out investigations to diagnose tonsillitis, whilst 4 (36%) ordered a throat swab. None opted for an ASOT whilst 2 (18%) tested for EBV antibodies. Paracetamol was prescribed for pain relief by all doctors, whilst 7 (64%) prescribed non-steroidal therapy. Two (18%) offered reassurance without any treatment and 1 (9%) advised gargles.

All doctors prescribed antibiotics if the child appeared ‘toxic’. Eight (73%) of the doctors did so with a fever >38°C, a fever <38°C that persisted for more than 3 days, or with tonsils meeting in the midline. Seven (64%) of the doctors prescribed antibiotics with pus on the tonsils and no fever, whilst 5 (45%) with both pus and fever present. Two (18%) doctors used cervical lymphadenopathy as a criterion for antibiotic prescribing, depending on whether these
were more than 1 cm in diameter. Only 1 doctor (9%) prescribed antibiotics if the child complained of dysphagia with decreased appetite, in patients with underlying chronic conditions such as diabetes, when other antibiotics had been prescribed with no effect and with parental concern. The results obtained from the first questionnaire showed that the criteria used by doctors to prescribe antibiotics differed from established guidelines, leading to a tendency towards unnecessary prescription of antibiotics by a factor of 2.7-fold. Similarly, there was a tendency toward unnecessary investigations such as throat swabs and EBV titres, in children with acute tonsillitis.

**Second Survey**

Following feedback on the initial survey and an update of current guidelines, there was a reduction from 6 to 2 doctors (37%, \( p=0.1 \)) carrying out unnecessary investigations, and a small reduction from 8 to 7 doctors (9%, \( p=0.5 \)) prescribing antibiotics. Despite there being a very minimal decrease in the number of doctors who prescribed antibiotics, the criteria that were being used now reflected those advised by NICE and modified Centor Guidelines. Hence, the second questionnaire showed that compliance with guidelines had improved significantly with regard to non-prescribing of antibiotics with a fever of <38°C (\( \Phi=-0.76, p=0.0005 \)), and with tonsillar pus but no fever (\( \Phi=-0.68, p=0.002 \)). Increased compliance was observed when prescribing antibiotics in the presence of pus plus a fever (from 64 to 73%), lymphadenopathy >1cm (from 45 to 55%), and presence of underlying disease although these changes were not statistically significant.

Small changes were observed in the type of antibiotic prescribed, with amoxicillin plus clavulanic acid and cephalosporin being the first and second preferences, respectively. In this regard, compliance with guidelines had increased from 55 to 73% between the two surveys. There was a slight increase, by 1 doctor, in a shorter duration of antibiotic treatment averaging 5-7 days compared with 7-10 days and, therefore, less compliance with a prolonged course as suggested in the guidelines. Less doctors asked patients to return for a review.

**Discussion**

Many controversies in the management of acute tonsillitis focus on the indications for prescribing antibiotics, as well as the type and duration of antibiotics. The effect of antibiotics on symptom reduction is debatable with headaches, sore throat and fever possibly being reduced by up to 50%, but this generally occurs by the third day when natural resolution takes place.\(^{10}\) A Cochrane review carried out in 2006 showed that about 90% of both treated and untreated patients were symptom-free by one week. These authors concluded that absolute benefits are modest and antibiotics only confer relative benefits with regard to sore throat, but these would not justify the cost of treating many children with antibiotics.\(^{11}\)

It has also been reported that antibiotics shorten the duration of symptoms by a mean of just one day half way through the illness (the time of maximal effect), and by about 16 hours overall.\(^{10}\) In support of antibiotic use in this condition, the review reported a trend in the protection against acute glomerulonephritis and acute rheumatic fever by antibiotic prescribing in children with acute tonsillitis. Antibiotics have also been shown to reduce the incidence of acute otitis media by about 25%, and acute sinusitis by about 50% compared with placebo, as well as a reduction in the incidence of quinsy.\(^{10}\)

In an elegant study, three groups of children with tonsillitis were given either 10 days of antibiotics, no antibiotics or an ‘optional’ prescription only to be used if symptoms had not settled by the third day. This study showed no difference in outcome between the three groups and, in the ‘optional’ group, only 69% used their prescription.\(^{12}\)

Guidelines, including Centor\(^6\), McIsaac\(^7\) and NICE guidelines\(^8\), have been developed to facilitate clinical decision making and, in particular, the use or otherwise of antibiotics in the context of acute tonsillitis. They do not advocate antibiotics for all patients with acute tonsillitis, but reinforce that these should be prescribed in accordance with the presence of specific clinical criteria and advocate the type and duration of antibiotics. These guidelines have been validated in large population-based studies\(^{13,14}\) and allow for the computation of a clinical ‘Strep. Score’ with a risk assessment for GABHS infection. Hence, in adults, a score of 0-1 does not require antibiotics or a throat culture; 2 is associated with a 15% risk of GABHS and 3 carries a 32% risk. A throat culture should be considered with scores of 2-3 and, if positive, antibiotics started. Scores of 4-5 imply a risk of ≥56% and dictate empiric antibiotics.\(^{13}\) Similarly, in children, scores of 0, 1, 2, 3 and 4 have been associated with the probability of GABHS infection of 1, 4, 9, 21 and 43%, respectively.\(^{14}\) When compared with these guidelines, doctors working in Paediatric Emergency in this study were found to be only partly compliant with the guidelines. Encouragingly, this study showed that improvements in compliance, albeit modest, were observed in the second survey after a simple educational brief. This was seen consistently in terms of a reduction in unnecessary investigations (from 64 to 91%), and improvements in antibiotic prescribing in line with the Centor/McIsaac criteria of fever (from 73
to 82%), exudates (64 to 73%), and lymphadenopathy (from 45 to 55%). The reverse, however, was seen for the duration of antibiotic courses prescribed with more doctors prescribing shorter rather than ten day courses, specifically against NICE guidelines.

The results and conclusions from this study must, however, be interpreted in the light of the small study cohort. Similarly, the time frame of three months over which the study was completed was also short. Unfortunately, neither of these two limitations could be circumvented; the absolute small number of participants still represented 100% of possible recruits and the second questionnaire had to be distributed after a maximum three month period in line with doctor rotations within the department. Furthermore, this study was based in Paediatric A&E and not in the community where more cases of tonsillitis are likely to present, and data was collected using a non standardised questionnaire.

The ‘gold standard’ in the diagnosis of bacterial tonsillitis remains culture testing on appropriate media, but this inherently involves a delay in reporting. In practice, in addition to the use of guidelines, the diagnosis of GABHS can be hastened by the use of rapid antigen testing (RAT) at the bedside. Several commercial kits are available and most achieve specificity in the order of >95% and sensitivity ≥90%, thereby making them acceptably accurate for bedside diagnosis. Indeed, several guidelines including McIsaac criteria used in this study, combine the Strep. Score with advice to perform rapid antigen testing (e.g. with scores of 2 or 3), and to proceed with antibiotics if this is positive, or formal culture testing if RAT is negative. Unfortunately, rapid antigen testing was not available in the Paediatric Emergency Department and its impact could therefore not be assessed in this study.

Conclusion

This study has shown that modest improvements in compliance with guidelines can be brought about in the Emergency Department with a limited educational effort, although caution is required in the interpretation of all results in view of the small sample size. It is likely, however, that significant improvements would require repeated reinforcement of the guidelines through an ongoing educational programme. This would need to be repeated for all doctors as they commence their rotation in the Paediatric Emergency Department if effective and long term compliance is to be achieved.

Acknowledgements

We are grateful to all those doctors in Paediatric A&E who completed the questionnaires.

References

Factors determining gender ratio in the Maltese population

Stephanie Savona-Ventura, Charles Savona-Ventura

Abstract

Introduction: The Male/Female ratio at birth has been described to favour the male conceptus, a situation that persists throughout most of childhood and into the reproductive phase of life. The reasons behind this preferential male-favouring remain elusive.

Methodology: The various relevant obstetric and population national registers kept by the Department of Health information and the National Statistics Office of the Maltese Islands were reviewed to elucidate the age-related M/F ratios differences in the population starting with the third trimester of the antenatal period. In addition, third trimester M/F ratios in women with specific metabolic-related disorders were assessed and compared to the on-affected individuals. The role of foetal congenital malformations was also investigated.

Results: It would appear that the M/F ratio starts favouring the male conceptus as early as the third trimester of the antenatal period. It remains favoured right through the reproductive age reaching par after the age of 45 years when it shifts to favour the female. This relationship was significantly altered during the 1930s as a result of the emigration patterns prevalent during that period. The results further show that the maternal nutritional and biochemical milieu may influence the M/F ratio at the beginning of the third trimester with women suffering from adiposity, diabetes and thyroid disease having higher M/R ratios. In spite of this preference to the male conceptus, malts have a higher mortality throughout life with mortality rates being higher for males from the third trimester up to the age of 75 years. On the other hand, female foetuses with malformations appear to have a higher mortality during intrauterine life than corresponding male foetuses.

Conclusion: The M/F ratio appears to favour the male conceptus during antenatal life and is definitely evident by the beginning of the third trimester of pregnancy, the selection mechanism possibly being a greater predisposition of female foetal loss in the presence of malformations. These biological observations may present advantages within the breath of human reproductive ecology, ensuring a healthy reproductive female individual who has the option of choosing her mate from a competing male community.

Keywords

Male/Female Ratio, Demography, Malta, Migration, Reproductive ecology

Introduction

The mechanism of meiosis whereby spermatozoa are produced should result in an equal distribution of X and Y chromosome carrying spermatozoa. Thus, the Male-Female potential determined by each ejaculation should be a ratio of 0.500. However, biological mechanisms appear to favour the male conceptus, so that proportionately more male than female infants are born.20 This altered Male-Female [M/F] ratio is approximately maintained throughout childhood and adulthood, a factor that has long-term effects on a community’s demography.19 The present study attempts to assess the mechanisms favouring the male
conceptus in a small island population in the Central Mediterranean. This population has been shown to have maintained a steady live birth M/F ratio of 0.517 throughout the larger part of the twentieth century (1916-1995), though this had decreased from the 0.523 level during the late 19th century (1890-1899).13

Methodology

The present study attempts to compare the M/F ratios at various points from the intrapartum period to late adulthood during two particular periods – the 1930s and the 2000s. Data related to population gender distribution by age was obtained from Census Reports for 1931 and 2005.5,18 Gender-based mortality data by age for the periods 1930-1939 and 2000-2009 were obtained from published sources of the National Statistics Office and the National Obstetrics Information System [NOIS] database.8,9,19 The NOIS is a database that collects national data about all births registered in the Maltese Islands and is maintained by the Department of Health Information and Research. This database provided M/F ratios for stillbirths, live births and total births for the period 2000-2010. The latter can be assumed to represent the M/F ratio at the beginning of the third trimester. Stillbirths in this database are defined as the birth of a dead infant of a gestational age of 22 weeks [154 days] or more, or an infant born with a birth weight of 500 g or more. During the earlier period in the 1930s, stillbirths were defined as births of dead children after 28 weeks of gestation differentiating stillbirths from late miscarriages. Information relating to causality of deaths and congenital abnormalities for the period 2000-2009 was obtained from published sources reflecting the National Mortality Register and the Malta Congenital Anomalies Registry maintained by the Department of Health Information and Research.6,11

The two periods under review reflect two contrasting periods in Maltese social history. The 1930s were characterised by a generally low socio-economic level of the population that resulted in a high emigration rate caused by low employment opportunities. The population was generally undernourished. The birth rate in 1935 was 34.0 per 1000 population, while the crude death rate was 23.5 per 1000 population. The stillbirth rate was 50.2 per 1000 total births; while the infant mortality rate was 285.7 per 1000 live births.8 The latter half of the twentieth century saw a major change in the socio-economic situation of the population resulting in better overall health and nutrition. In 2000, the birth rate was 11.1 per 1000 population, while the crude death rate was 7.8 per 1000 population. The stillbirth rate was 4.0 per 1000 total births; while the infant mortality rate was 6.1 per 1000 live births.19

The Male-Female ratio [M/F ratio] was calculated as the ratio of total males and the total population being assessed. Population-based M/F ratios were calculated for various age groups starting at the beginning of the third trimester of pregnancy thus including live births and stillbirths; at birth including live births, and at age groups 0-9 years, 10-24 years, 25-34 years, 35-44 years, 45-54 years, 55-74 years and 75+ years. Mortality-based M/F ratios at the various age groups were similarly assessed. Further information related to population losses through emigration was similarly assessed. Because of the relatively small size of the population, vital-event registration and statistics have been very accurate since the initiation of their compilation by formal legislation. Where appropriate, statistical significance of M/F ratios between populations with different characteristics was tested using the chi square test.

Results

During the 2000-2009 period, the M/F ratio at the beginning of the third trimester of pregnancy stood at 0.518. At birth the figure decreased minimally to 0.517 reflecting a proportionately higher mortality in males noted during the third trimester of intrauterine life. This figure further decreased slightly to 0.511 during the first decade of life and was approximately maintained until the age of 44 years. In the age group 45-54 years, the gender ratio was on par. It eventually shifted favouring females after 55 years of age. The gender ratio pattern during the 1930-1939 period followed a different trend. The gender ratio during the third trimester stood at 0.530 favouring males. The M/F ratio subsequently dropped to 0.523 in live births reflecting a higher stillbirth mortality in the male. The subsequent early years of life saw a further drop in M/F ratio reaching 0.505 at 24 years of age. The subsequent age groups exhibited a predominance of females in the population with a reversed M/F ratio reflecting a preponderance of females in the subsequent age groups (Table 1 / Figure 1).

The 2000-2009 NOIS data suggests that the nutritional and biochemical milieu of the mother may influence the M/F ratio at the beginning of the third trimester (Table 2). Pre-pregnant adipose women, defined as a pre-pregnancy BMI >25 kg/m², delivered live and stillborn infants with a gender ratio of 0.523 favouring males in contrast to the 0.507 figure noted in non-adipose women (p=0.014). Similarly women suffering from some form of diabetes during their pregnancy gave birth to live and stillborn infants with an elevated M/F ratio of 0.549, though this was not statistically significant (p=0.14) when compared to the
remaining non-diabetic population. Similarly, women with thyroid disorders appeared to have a similarly elevated M/F ratio of 0.558 ($p=0.36$).

Table 1 / Figure 1: Population-based M/F ratio by different Age groups – Census years for all age groups except for 3rd trimester and ‘at birth’ ratios estimated as mean of decades 1930-1939 and 2000-2009.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>1931</th>
<th>2005</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd trimester</td>
<td>0.530</td>
<td>0.518</td>
<td></td>
</tr>
<tr>
<td>At birth</td>
<td>0.523</td>
<td>0.517</td>
<td></td>
</tr>
<tr>
<td>0-9 years</td>
<td>0.506</td>
<td>0.511</td>
<td></td>
</tr>
<tr>
<td>10-24 years</td>
<td>0.505</td>
<td>0.513</td>
<td></td>
</tr>
<tr>
<td>25-34 years</td>
<td>0.496</td>
<td>0.513</td>
<td></td>
</tr>
<tr>
<td>35-44 years</td>
<td>0.460</td>
<td>0.512</td>
<td></td>
</tr>
<tr>
<td>45-54 years</td>
<td>0.499</td>
<td>0.500</td>
<td></td>
</tr>
<tr>
<td>55-64 years</td>
<td>0.491</td>
<td>0.492</td>
<td></td>
</tr>
<tr>
<td>65+ years</td>
<td>0.485</td>
<td>0.424</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Third trimester M/F ratios by maternal endocrine disorders: Maltese Islands 2000-2009

<table>
<thead>
<tr>
<th>Age Group</th>
<th>With disease</th>
<th>Without disease</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiposity</td>
<td>0.523</td>
<td>0.507</td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.549</td>
<td>0.514</td>
<td>0.14</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>0.558</td>
<td>0.515</td>
<td>0.36</td>
</tr>
</tbody>
</table>

The mortality M/F ratio data suggest that during the 2000-2009 period, male infants were more susceptible to death throughout life starting from the third trimester of the antenatal period. This male bias for mortality is particularly elevated in the 10-44 year age groups. This risk persists right up to the 75+ years age group when a shift occurs in risk and proportionately more females die. The generally higher mortality risk for males was also extant during the 1930-1939 period, though in the latter, a reversal in mortality rates with proportionately more females dying in the 24-44 years age group is observed (Table 3/Figure 2).

Table 3 / Figure 2: Mortality M/F ratio by different Age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>1930-1939</th>
<th>2000-2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd trimester</td>
<td>0.661</td>
<td>0.587</td>
</tr>
<tr>
<td>0-9 years</td>
<td>0.533</td>
<td>0.542</td>
</tr>
<tr>
<td>10-24 years</td>
<td>0.545</td>
<td>0.744</td>
</tr>
<tr>
<td>25-34 years</td>
<td>0.411</td>
<td>0.736</td>
</tr>
<tr>
<td>35-44 years</td>
<td>0.457</td>
<td>0.673</td>
</tr>
<tr>
<td>45-54 years</td>
<td>0.568</td>
<td>0.669</td>
</tr>
<tr>
<td>55-74 years</td>
<td>0.528</td>
<td>0.597</td>
</tr>
<tr>
<td>75+ years</td>
<td>0.468</td>
<td>0.446</td>
</tr>
</tbody>
</table>

Analysing the M/F ratio of foetal deaths (with >500g birth weight) for the period 2000-2009 confirms that male foetuses were more likely to die during intrauterine life than female foetuses (M/F ratio 0.601). However when analysed by cause of death, female foetuses appeared to have a greater likelihood of dying during intrauterine life from a congenital malformation than male foetuses (M/F ratio 0.483). This female bias is present in spite of the fact that more male infants were born with an identified malformation during the same period (M/F ratio 0.577). The reverse risk applies for deaths due to other causes with male foetuses having a greater risk of dying during intrauterine life (M/F ratio 0.627). Childhood deaths due to congenital malformations appear to show a bias towards male deaths (M/F ratio 0.574) attributable to the higher proportion of malformations present in male live birth (M/F ratio 0.579). In contrast, proportionately more males than females succumb during the childhood years (Table 4).

Population loss is dependant not only on mortality but also from the losses resulting from emigration. This loss has also a gender bias towards males. The period November 1918 to March 1931 had seen an emigration drive affecting particularly males rather
than females. This M/F bias in emigration persisted even when one considers the M/F proportion of returning migrants. The M/F ratio of remaining migrants who are thus lost to the overall population was 0.764 (Table 5).

Table 4: Mortality and birth M/F ratios by cause of death: Maltese Islands 2000-2009

<table>
<thead>
<tr>
<th>Age Group</th>
<th>With malformation</th>
<th>Without malformation</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total births</td>
<td>0.577 [n=1297]</td>
<td>0.516 [n=43012]</td>
<td>0.518 [n=44309]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Foetal deaths (&gt;500g)</td>
<td>0.483 [n=29]</td>
<td>0.627 [n=134]</td>
<td>0.601 [n=163]</td>
<td>0.291</td>
</tr>
<tr>
<td>Total live births</td>
<td>0.579 [n=1268]</td>
<td>0.516 [n=42845]</td>
<td>0.517 [n=44113]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Childhood mortality [0-14 years]</td>
<td>0.574 [n=115]</td>
<td>0.546 [n=207]</td>
<td>0.556 [n=322]</td>
<td>0.715</td>
</tr>
</tbody>
</table>

Table 5: Emigration statistics: Maltese Islands – November 1918 to March 1931

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males</th>
<th>Females</th>
<th>Children Gender not identified</th>
<th>M/F ratio Excluding children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emigrants</td>
<td>32671</td>
<td>3927</td>
<td>3606</td>
<td>0.893</td>
</tr>
<tr>
<td>Returning migrants</td>
<td>24533</td>
<td>1407</td>
<td>1670</td>
<td>0.946</td>
</tr>
<tr>
<td>Remaining migrants</td>
<td>8138</td>
<td>2520</td>
<td>1936</td>
<td>0.764</td>
</tr>
</tbody>
</table>

In 1930, the number of non-returning emigrants amounted to 916 persons including 560 males, 242 females and 114 children [M/F ratio 0.698]. The average number of emigrants of all genders and ages for the period 1931-1938 amounted to 1573 persons per annum. There was little or no emigration during 1939 because of WWII. The statistical data regarding emigrants during the 1930s is unfortunately incomplete. However, because of immigration legislative regulations, the larger majority of the migrants were persons in the reproductive age group, thus affecting adversely the demographic structure of the Maltese population. The increased bias towards male migrants aged 20-39 years can be observed by analysing the available statistical data for the period 1947-1957 (Table 6).

Mechanisms are therefore extant that help significantly skew the M/F ratio at the time of conception and during the first trimester of intrauterine life. The Y-containing spermatozoa are considered to be advantaged over the X-containing spermatozoa since it contains about 3-4% less DNA material. The differential motility thus allows the Y-containing spermatozoa to reach the ovum earlier and thus stands a greater likelihood to achieve fertilization.

Table 6 / Figure 3: Gender ratios of emigrants by age groups – Maltese 1947-1957

<table>
<thead>
<tr>
<th>Age group</th>
<th>Male</th>
<th>Female</th>
<th>M/F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>905</td>
<td>896</td>
<td>0.502</td>
</tr>
<tr>
<td>5-9</td>
<td>3308</td>
<td>3155</td>
<td>0.512</td>
</tr>
<tr>
<td>10-14</td>
<td>3779</td>
<td>3745</td>
<td>0.502</td>
</tr>
<tr>
<td>15-19</td>
<td>2483</td>
<td>2098</td>
<td>0.542</td>
</tr>
<tr>
<td>20-24</td>
<td>6997</td>
<td>2982</td>
<td>0.701</td>
</tr>
<tr>
<td>25-29</td>
<td>6861</td>
<td>2898</td>
<td>0.703</td>
</tr>
<tr>
<td>30-34</td>
<td>4888</td>
<td>2518</td>
<td>0.660</td>
</tr>
<tr>
<td>35-39</td>
<td>3552</td>
<td>1750</td>
<td>0.670</td>
</tr>
<tr>
<td>40-44</td>
<td>1989</td>
<td>1166</td>
<td>0.630</td>
</tr>
<tr>
<td>45-49</td>
<td>1893</td>
<td>998</td>
<td>0.655</td>
</tr>
<tr>
<td>50-54</td>
<td>1218</td>
<td>694</td>
<td>0.637</td>
</tr>
<tr>
<td>55-59</td>
<td>685</td>
<td>480</td>
<td>0.588</td>
</tr>
<tr>
<td>60-64</td>
<td>391</td>
<td>282</td>
<td>0.581</td>
</tr>
<tr>
<td>65+</td>
<td>292</td>
<td>276</td>
<td>0.514</td>
</tr>
</tbody>
</table>

The skew may also be contributed to by other factors other than swimming speed. It has been demonstrated that bovine sperm actually swim at the same speed in stationary fluids, but differ in their linearity and straightness of path. The male conceptus in humans may also make the transition to blastocyst better than the female. The female zygote also appears to have a greater likelihood of being spontaneously miscarried during embryogenesis, implantation and early foetal development. Assessment of pregnancy material obtained during a spontaneous miscarriage at 10 weeks of pregnancy have shown a predisposition for female first trimester loss exhibiting a M/F ratio of 0.364. This predisposition towards increased loss of the female zygote has been partly associated to chromosomal and other congenital abnormalities. In this situation, the
M/F ratio has been shown to be 0.467, while in miscarriages caused by idiopathic or other causes, the M/F ratio has been reported as 0.270. Second trimester loss can occur but the numbers are not generally significant. This study has suggested that there is a predisposition towards a continued increased loss of the female foetus with a congenital malformation during the third trimester, further favouring an elevated M/F ratio at birth. The apparent protection of the male congenitally malformed foetus during intrauterine life appears to be lost after birth with these children being more susceptible to death than their female counterparts. A number of environmental and biological factors have been postulated as being contributory to the altered M/F ratios noted in different circumstances. The observation that M/F ratio decrease with increasing latitude on the European continent has led to the suggestion that meteorological factors might play a role. While a seasonal trend could be observed in births from the Maltese Islands, these trends were not statistically significant. The present study has suggested a link between a raised M/F ratio to the nutritional and biochemical status of the mother with elevated ratios being noted in adipose, diabetic and hypothyroid women. A possible inter-relationship between gender determination and maternal diet has been previously postulated. There also appears to be a fall in M/F ratios at the beginning of the third trimester and subsequently at birth over the decades from the 0.530 level in 1931 to the 0.518 level in 2005. Such a decrease in M/F ratios has been previously described. Various possible potential causes have been proposed. Socio-economic improvements would be expected to increase rather than decrease the M/F ratio. The observation linking congenital malformations with an earlier loss of the female conceptus with anomalies may explain the decreasing M/F ratio with time. Congenital anomalies are commoner in the elderly women, and there has been proportionately a decrease in elderly women giving birth over the last decades. In 2005, the proportion of women aged more than 35 years delivering in the Maltese Islands was 10.7%. In 1959, the proportion was 18.0%. The mechanisms favouring the development and survival of the male embryo at the time of conception and throughout the first trimester ensures that proportionately more male embryos reach the end of the second trimester of pregnancy resulting in a current M/F ratio of 0.518. The subsequent intra-uterine existence during the third trimester presents particular hazards to the developing male foetus which exhibits a greater tendency to die in utero, during childhood and early adulthood. In spite of the increased male mortality, the male gender in Maltese demography retains its majority well until the age 44 year age group, becomes proportionally on par with female in the 44-54 year age group, and subsequently falls into the minority in later age groups. The pattern was similar during the 1930s, although in contrast there appeared to be a reversal in mortality gender ratios for the age group 25-44 years. This may be accounted for by gender-bias emigration resulting in the preferential loss of males from the population. In spite of the apparent relative protection of the male congenitally malformed foetus during intrauterine life, there still appears a definite higher stillbirth rate in male foetuses. Various theoretical possibilities may contribute to this higher stillbirth M/F ratio noted in several population studies including the present study. The main causes for stillbirths identified in the first Report of the U.K. Perinatal Mortality Survey of 1958 included anoxia (48.2%), congenital malformations (17.5%), cerebral birth trauma (9.5%), and haemolytic disease of the newborn (4.4%). In the Maltese population during the period 1979-1987, the commonest cause of perinatal death reported was antepartum anoxia that accounted for about 37.0% of cases. Prematurity and congenital malformations accounted for 27.4% and 23.9% respectively, while intrapartum anoxia or birth trauma accounted for 10.6%. The commonest contributor of antepartum anoxia was hypertensive disease of pregnancy causing placental insufficiency and subsequent antenatal death of the foetus. This was associated with 25.5% of all stillbirths and 8.2% of early neonatal deaths in 1979-1987. There have been numerous reports of high M/F sex ratios in pre-eclampsia and eclampsia in singleton pregnancies with a reported M/F ratio of 0.529 suggesting that the primigravid woman carrying a male foetus is more likely to develop pre-eclampsia hence placing the male foetus at increased risk of placental insufficiency and an increased risk of dying during antenatal life. An alternative reason for a greater likelihood of the male foetus to be stillborn is the greater risk the generally higher weight male infant has towards prolonged labour and intrapartum birth anoxia and/or trauma, though this is unlikely to play an important role in Maltese obstetrics today with a reported Caesarean section rate of 29.9% in 2001-2010. Several biological processes ensure that at birth the population is represented by a higher proportion of males over females. It appears that this preponderance of males remains right through middle age in spite of the fact that mortality rates are higher in the male population. The higher M/F ratio must present biological advantages within the wide breath of human reproductive ecology. While no information is
available as to the birth M/F ratios of our hunter-gatherer and Neolithic ancestors, it is reasonable to assume a similar pattern of male preponderance. This preponderance would have presented a competitive situation whereby the female reproductive element of the species has the choice of choosing the ideal male partner – the stronger more intelligent male – to the benefit of species development. A better understanding of the dynamics affecting the M/F ratio in human reproductive processes would help understand the possible effects of environmental, nutritional, hormonal and sociological changes on human reproduction and their consequences on human population ecology.

Acknowledgements

Acknowledgements are due to Dr. Miriam Gatt for making unpublished detailed data available in the National Obstetrics Information System kept by the Department of Health Information and Research, Malta.

References

Abstract

Introduction: The male to female ratio of live births is expressed as the ratio of male live births divided by total live births (M/F). Although this would be more accurately abbreviated as M/T (male births divided by total births), it is widely (albeit technically incorrectly) abbreviated as M/F, and this will be used throughout. Globally, over the past four decades, this is expected to be 0.515, with a slight (1.5%) male excess. M/F exhibits an unexplained contrasting latitude gradient. More males are born towards the south of Europe, and the south of Asia, while more males are born toward the north in North American continent. M/F is also declining overall, in both of these continents. This study investigates secular trends and latitude gradients in M/F in Australia and New Zealand from a World Health Organization (WHO) dataset that includes the past sixty years.

Methods: Permission was obtained to source WHO datasets going back to 1950, following which Microsoft Excel was used to calculate M/F ratios. Australian and New Zealand data were available for the years 1950-2006 and 1950-2009 respectively. Chi tests for trend were used for annual male and female births. These were performed using the Bio-Med-Stat Excel add-in for contingency tables.

Results: There were 17035325 births for Australia and New Zealand during this period. M/F ratios ranged between 0.507-0.519. No latitude variations in M/F were found between Australia (9° to 44°) and New Zealand (29° to 53°). The overall M/F was 0.5134 - lower than the anticipated 0.515, with an estimated male birth deficit of 28009. Cycles of 30 years duration are apparent in the dataset but not at statistically significant levels.

Discussion: The lack of latitude gradient in this region is not unexpected as there is a wide latitude overlap between Australia and New Zealand. It has been hypothesised that M/F exhibits a 30 year cycle due to an unknown mechanism that negatively correlates M/F with the adult sex ratio at the time of conception.

Conclusion: The factor/s that are causing a decline in M/F ratios in Europe, North America and Asia are absent or not so strongly influential in Australasia.

Keywords
Australasia, Sex Ratio, Birth Rate/*trends, Infant, Newborn

Introduction

The male to female ratio of live births is expressed as the ratio of male live births divided by total live births (M/F). Globally, this is expected to be around 0.515, with a slight (1.5%) male excess. M/F exhibits a contrasting latitude gradient. More males are born towards the south of Europe and south of Asia, while more males are born toward the north in North American continent. This remains unexplained. M/F is also declining overall in both continents. This trend in M/F ratios may be important as the pregnant human female is more prone to spontaneously abort a male fetus than a female fetus if adverse environmental conditions are experienced.

These include warfare, earthquakes, environmental disasters, and a plethora of other factors. For these reasons M/F has been proposed as a surrogate sentinel health indicator.
This study investigates secular trends and latitude gradients in M/F in Australia and New Zealand, separately and jointly, from a World Health Organization (WHO) dataset that includes the past sixty years.

Methods
Chi tests for trend were used for annual male and female births. These were performed using the Bio-Med-Stat Excel add-in for contingency tables. This add-in is based on the original work by Cochran and Armitage (Dr. Peter Slezák, Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, personal communication). 8,9

The quadratic equations of Fleiss were used for exact calculations of 95% confidence intervals for ratios. 10 p<0.05 was taken as statistically significant.

Results
There were 17035325 births for Australia (1950-2006) and New Zealand (1950-2009). Overall, there were 8745183 male births and 8290142 female births (M/F 0.5134, 95% CL 0.5131-0.5136).

Table 1: 5 year total live births and sex ratios at births, in 5 year intervals

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>507666</td>
<td>559474</td>
<td>602835</td>
<td>662359</td>
<td>584262</td>
<td>604746</td>
<td>632530</td>
<td>661109</td>
<td>646556</td>
<td>642904</td>
<td>268672</td>
<td>6971687</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>482364</td>
<td>530174</td>
<td>569396</td>
<td>629335</td>
<td>552339</td>
<td>573130</td>
<td>600561</td>
<td>626131</td>
<td>613796</td>
<td>609521</td>
<td>254525</td>
<td>6608556</td>
<td></td>
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<tr>
<td>T</td>
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<td>13580243</td>
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<tr>
<td>UCI</td>
<td>0.5138</td>
<td>0.5144</td>
<td>0.5152</td>
<td>0.5143</td>
<td>0.5136</td>
<td>0.5150</td>
<td>0.5143</td>
<td>0.5138</td>
<td>0.5145</td>
<td>0.5137</td>
<td>0.5149</td>
<td>0.5136</td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>0.5128</td>
<td>0.5134</td>
<td>0.5143</td>
<td>0.5134</td>
<td>0.5128</td>
<td>0.5140</td>
<td>0.5134</td>
<td>0.5130</td>
<td>0.5136</td>
<td>0.5130</td>
<td>0.5133</td>
<td>0.5135</td>
<td>0.5134</td>
</tr>
<tr>
<td>LCI</td>
<td>0.5118</td>
<td>0.5125</td>
<td>0.5134</td>
<td>0.5125</td>
<td>0.5119</td>
<td>0.5131</td>
<td>0.5125</td>
<td>0.5121</td>
<td>0.5127</td>
<td>0.5121</td>
<td>0.5125</td>
<td>0.5122</td>
<td>0.5131</td>
</tr>
</tbody>
</table>

New Zealand

| M         | 132380  | 150555  | 164561  | 157064  | 158816  | 137938  | 130133  | 141220  | 152185  | 145247  | 143631  | 159766  | 1773496 |
| F         | 124925  | 142702  | 156024  | 149319  | 151129  | 131293  | 123251  | 134293  | 143537  | 137057  | 136997  | 151059  | 1681586 |
| T         | 257305  | 293257  | 320585  | 306383  | 309945  | 269231  | 253384  | 275513  | 295722  | 282304  | 280628  | 310825  | 3455082 |
| UCI       | 0.5164  | 0.5152  | 0.5150  | 0.5144  | 0.5142  | 0.5142  | 0.5155  | 0.5144  | 0.5164  | 0.5164  | 0.5137  | 0.5158  | 0.5138  |
| M/F       | 0.5145  | 0.5134  | 0.5133  | 0.5126  | 0.5124  | 0.5123  | 0.5136  | 0.5126  | 0.5145  | 0.5145  | 0.5118  | 0.5140  | 0.5133  |
| LCI       | 0.5126  | 0.5116  | 0.5116  | 0.5109  | 0.5106  | 0.5105  | 0.5116  | 0.5107  | 0.5128  | 0.5127  | 0.5100  | 0.5122  | 0.5128  |

Five-year trends are shown in table 1 and figures 1 and 2. No significant secular trends overall were found in either country (Australia chi for trend=0.1, p=0.7, New Zealand chi for trend=3, p=0.9) and in the amalgamated male and female totals (chi for trend=0.04, p=0.8).

Visual inspection of the data showed declining and increasing trends in different time periods. Cycles of 30 years duration are apparent in the dataset but not at statistically significant levels but separate analysis of these eras also failed to show any significant trends (table 2).

No latitude variations were found between Australia (9° to 44°) and New Zealand (29° to 53°), and there were no significant differences. The overall M/F was 0.5134 (95% CI: 0.5131-0.5136), which is lower than that expected at 0.515. This resulted in an estimated male birth deficit of 28009 for the period studied.
Discussion

The lack of latitude gradient in this region is not unexpected as there is a wide latitude overlap between Australia (9° to 44°) and New Zealand (29° to 53°). M/F appears to have been below the expected value for the period under study, with no significant secular trends and an overall male birth deficit.

It has been proposed that M/F exhibits a thirty year cycle due to an unknown homeostatic mechanism that negatively correlates M/F with the adult sex ratio at the time of conception, and cycles of this approximate duration are apparent in the dataset, albeit not at statistically significant levels.11

The lack of secular trends and the nonsignificance of the observed cycles may be due to the relatively smaller numbers involved in this study when compared with studies that embraced larger datasets, such as Europe or the North American continent.2,3

Asia is a close neighbor to Australasia. Interestingly, a study utilizing the same dataset and dealing with Asia over the same era (and encompassing 245938211 live births) showed an overall increasing trend in M/F (p < 0.0001). A latitude gradient was also present, with more boys being born in southern, warmer latitudes (p < 0.0001). There was also an overall deficit of 1351757 male births based on an anticipated M/F of 0.515.12 The same latitude gradient was noted in Europe, with an excess of males in southern latitudes.2 The present study is clearly in contrast with Asia and Europe.

Conclusion

The factor/s that are causing declining M/F ratios in Europe and North America and increasing M/F ratios in Asia appear to be absent or not so strongly influential in Australasia.

Acknowledgments

Mie Inoue and Gauden Galea (Europe) from the World Health Organisation.

Competing interests:

None

Funding:

This study was carried out on time sponsored by the University of Malta.

References

Simple measures can improve care in our hospitals - an audit of venous thromboembolism practice

Thomas Lofaro, Stephanie Azzopardi, Sarah Busuttil, John Cordina

Abstract
Venous thromboembolism (VTE) is a serious but preventable complication of hospitalisation. Doctors still sometimes fail to adhere to them, thus putting patients at risk and incurring considerable expense for the national health service. We chose to audit the practice of doctors in our geriatric facility, and assessed the effect of a memoie to increase compliance. We also explore how our hospitals can learn from the experience of other centres, where the risk of litigation has brought this condition to the forefront. Compliance improved from 30.7% to 63.3%, which was statistically significant. We would suggest that a centralised and organised approach could produce even greater levels of compliance.

Keywords
Deep vein thrombosis, pulmonary embolism, venous thromboembolism, prophylaxis, geriatric medicine

Hospitalisation is known to be a particularly important risk factor for venous thromboembolism (VTE), and good clinical practice requires that all inpatients are risk-assessed repeatedly for predisposition to this disease. Medical patients are less likely to be adequately risk-assessed than other patients, despite accounting for the majority of reported cases of VTE. We wanted to investigate the level of compliance with guidelines in our geriatric facility, and whether we could improve it with simple measures to increase awareness.

Method
We used the guidelines by the Scottish Intercollegiate Network (SIGN) as our benchmark, and data was collected by retrospective review of patient-notes. We included the first 40 patients discharged from hospital or deceased, starting from an arbitrary date. This value was chosen because it corresponded to 20% of the inpatient capacity at the time. Patients were only excluded if they were on anticoagulation or if their notes were irretrievable. Risks of thrombosis were considered high if patients had more than two risk factors for VTE, or if they were recovering from hip, knee or abdomino-pelvic surgery. We noted the indications for prophylaxis, documentation of risk-assessment, preventative measures used and any contraindications. For each case, we noted whether management followed guidelines as suggested by SIGN. Since most patients are transferred from acute care, some were already on prophylaxis at the time of admission to our facility. We reported outcome as the proportion of patients adequately risk-assessed and treated.

We designed a simple memoie on an A4-sheet to remind different members of the multidisciplinary team of the importance of risk-assessment (see figure 1). It included a list of the commoner risk factors, and was circulated to all wards and attached to patients’ treatment charts. We then repeated our audit a few months later and compared the outcomes.
Figure 1: Reproduction of the proforma used for the purpose of the audit.

1. Risk Factors for Venous thromboembolism:
   1. Active malignancy within 6 months
   2. Obesity
   3. Previous venous thromboembolism
   4. Nephrotic syndrome
   5. Decompensated congestive cardiac failure
   6. Varicose veins
   7. Sepsis
   8. Medications e.g. HRT, high-dose Progestogens, Tamoxifen, Thalidomide
   9. Other: Thrombophils, Polycythemia, Paraproteinaemias, Myeloproliferative disease, Behçet’s disease, Paroxysmal nocturnal haemoglobinuria, Heparin-induced thrombocytopenia, Inflammatory bowel disease, Central venous catheterization

*Preferred in most patients, unless contraindicated.
#Should not be used routinely in medical patients. Preferred if pharmacological methods are contraindicated. May be used in combination with medical therapy in high risk patients, and particularly in orthopaedic patients.
One should consider contraindications before implementing mechanical methods.

*The dose of enoxaparin may need to be decreased in patients with a creatinine clearance <30ml/min and in those with low body weight.

**ORTHOPAEDIC SURGERY:**
Patients undergoing THR/TKR should receive pharmacological prophylaxis in combination with physical methods.
Treatment should be continued for 14 days after TKR.
Treatment should be continued for 28-35 days after THR/hip fracture surgery and in all those with additional risk factors.

**SUTURICAL AND GENERAL SURGERY:**
Prophylaxis should be considered for all patients undergoing major surgery, and for those having minor procedures if they have additional risk factors for VTE.
Mechanical methods, UFH or LMWH are all effective. Combination of mechanical and pharmacological methods should be used after abdominal surgery. Prophylaxis is indicated until mobility is regained, and for a further 24 weeks in high risk individuals.

Abbreviations: VTE: venous thromboembolism, UFH: unfractionated heparin, LMWH: low molecular weight heparin, TKR: total knee replacement, THR: total hip replacement
This document is based on current guidance by SIGN, ACCP and NICE. It is intended for use in the care of the elderly undergoing physical rehabilitation. Newer medical methods of prophylaxis (e.g. pentasaccharides, dagabatran) are not included due to problems of availability, but may be considered in individual cases.
This information was compiled for the Department of Geriatrics by Dr. Thomas Loste, under the guidance of Dr. John Cordina. 1st March 2010.
Ethics
The need for individual informed consent was waived because this was a retrospective analysis of the routine care of patients, and there was no breach of privacy or anonymity.

Results
The characteristics of the two populations are outlined in table 1. In the first arm, compliance was found to be only 30.7% (95% confidence interval 12.4% - 60.0%). This had improved to 63.3% in the second arm (95% confidence interval 45.5% - 78.2%). This difference was found to be statistically significant (one-tailed p value 0.02). Medical patients formed the largest single group in both arms, although there were more surgical and orthopaedic patients in the second part of our audit (table 1). The most common risk factors in our patients were immobility, active medical disease and obesity, and the most common active medical conditions listed were sepsis and pulmonary oedema.

Discussion
VTE prophylaxis is known to efficacious, safe and cost-effective. Our audit suggests that a lot more needs to be done to improve compliance with guidelines. However, we also find the outcome encouraging, as it suggests that simple measures can greatly improve the level of care we provide. The main limitations of our audit are its small size and its retrospective approach. It was not powered to answer detailed questions about how we use VTE prophylaxis. During the same time period, an admission proforma was implemented at the main acute facility including a reminder to risk-assess patients for VTE, and may have contributed to our results. The larger number of orthopaedic patients in the second part of our audit may also have contributed to the increase in compliance seen.

We can’t overemphasise the importance of documentation – both of indications and contraindications for VTE, and of any patient preferences that influence clinical decisions. Simple measures, like hydration and early mobilisation, should be implemented generally for all patients.

Conclusion
We should be guided by the experience of other centres, which have achieved excellent results using a variety of simple measures, regular re-audit and individual feedback. We would particularly recommend making better use of our IT system which can be a powerful way to prompt staff to think of VTE. We can also implement the same strategy in other areas of concern in patient management.

Table 1: A comparison between the two legs of the audit, outlining patient characteristics and results.

<table>
<thead>
<tr>
<th></th>
<th>1st leg of audit</th>
<th>2nd leg of audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Number of patients excluded</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Males (%)</td>
<td>17 (44.7%)</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Age ≤60 (%)</td>
<td>0 (0%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Age 61-70 (%)</td>
<td>2 (5.3%)</td>
<td>2 (5.0%)</td>
</tr>
<tr>
<td>Age 71-80 (%)</td>
<td>16 (42.1%)</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Age 81-90 (%)</td>
<td>18 (47.4%)</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Age &gt;90 (%)</td>
<td>2 (5.3%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Reasons for primary admission*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>24 (63.2%)</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Surgical</td>
<td>2 (5.3%)</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>4 (10.5%)</td>
<td>15 (37.5%)</td>
</tr>
<tr>
<td>Other (neurosurgery, rehabilitation, social issues)</td>
<td>8 (21.1%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>DVT prophylaxis at time of referral</td>
<td>7 (18.4%)</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Prophylaxis indicated at any time during admission*</td>
<td>13 (34.2%)</td>
<td>30 (75%)</td>
</tr>
<tr>
<td>Prophylaxis appropriately administered</td>
<td>4/13 (30.7%)</td>
<td>19/30 (63.3%)</td>
</tr>
</tbody>
</table>

*Primary admission: for those patients transferred from other centres, refers to the reason for requiring acute care.
*Risk factors cited: active medical conditions (e.g. heart failure, sepsis, acute coronary syndromes, NMS), active malignancy, decreased mobility (including stroke), obesity, previous VTE.
References
Introduction

Empty Nose Syndrome (ENS) is a term first introduced by Kern and Moore which is used to describe a rare spectrum of various symptoms suffered by patients who had had previous radical turbinate surgery with a CT scan appearance of the paranasal sinuses after gross tissue loss. The most common symptom is so-called ‘paradoxical’ nasal obstruction, reported by the patient despite objectively permeable cavities on clinical examination with no obstacle found on imaging or rhinomanometry and acoustic rhinometry. In most cases, the inferior turbinate (IT) has been resected radically even though middle turbinate (MT) resection has also been implicated. Incidence is unknown, as there have been no specific studies published. The estimated rate of ENS following inferior turbinate resection is 20%, which induces simple dry nose. Houser distinguished several subtypes of ENS according to the resected turbinate: inferior, medial, both, or fourthly, a subtype in which turbinate structures paradoxically appear normal. ENS subcategories are based on the type of tissue that is resected; hence “ENS-both” indicates both the IT and MT were at least partially resected. The management is problematic. We report an elderly gentleman of high social standing with long-standing nasal discharge and chronically blocked nose post radical turbinate surgery many years prior to his presentation, and the management options of ENS.

Keywords
Empty nose syndrome, ENS subtypes, presentation, treatment options.

Case report

A 59-year-old Chinese gentleman of high social standing presented at the ENT clinic with a chronic nasal problem of 30 years duration. His symptoms were mainly nasal blockage, post nasal drip with occasional mucoid yellowish phlegm, and intermittent voice changes. His sense of smell was intact. He had radical turbinate surgery and septoplasty back in 1984 which gave him some symptomatic relief for about 1 year. Endonasal endoscopic examinations revealed very patent nasal cavities as were all the ostia apart from the left middle ostium which was relatively narrow. There were thick mucoid secretions and synechiae between the left superior turbinate and the septum with evidence of remnants of the left middle and inferior turbinates. Initially he was treated conservatively by steroid nasal sprays, mucolytics and oral antibiotics with follow-up on a three monthly basis. Subsequently his symptoms had been fairly relieved, however these worsened intermittently with infections and the nasal blockage and secretions never really settled.

For persistent of the nasal symptoms despite optimal medical treatment. CT scan of the paranasal sinuses was performed and showed evidence of previous sinus and reductive turbinate surgery with wide right maxillary ostium. (Figure 1) The CT scan finding is consistent with empty nose syndrome. Conservative management was continued despite mild to moderate improvement of nasal symptoms.
the suction power of the lungs, forcing the patient to breathe in much harder to receive normal amounts of oxygen. This phenomenon manifests itself as chronic shortness of breath, and is known as “paradoxical obstruction”. The paradox being the fact that although the nose is wide and open, the end result is nasal obstruction. ENS is difficult to diagnose due to lack of consensual clinical definition, the variety of symptoms and the associated psychological and social distress. Diagnosis is clinical, founded on subjectively reported symptomatology and clinical examination based on nasal cavity endoscopy performed during consultation. The characteristic presenting symptom is a sensation of nasal obstruction, sometimes associated with sensations of suffocation, breathlessness or difficult breathing. Other symptoms are also reported like pain, rhinopharyngeal dryness, loss of concentration (nasal aprosexia), fatigue, anxiety, irritability and depression. Symptom intensity varies, and may restrict everyday activity. Endonasal endoscopic examination finds permeable nasal cavities enlarged by previous surgery, with turbinal structures missing or greatly reduced. The mucosa is generally pale and dries with crusts. ENS is subcategories based on their anatomic characteristics indicating the type of tissue that resected; hence “ENS-IT” indicates that the inferior turbinate (IT) fully or sub totally resected and “ENS-MT” indicates similar insult to the middle turbinate (MT), whereas “ENS-both” indicates both the IT and MT at least partially resected. ENS-IT is the most frequent. The basic complaint is paradoxical nasal obstruction and very dry mucosa. One hypothesis for such frequent obstruction following inferior turbinatectomy would concern its role in modulating nasal airflow. ENS-MT is rarer. As well as the typical nasal obstruction, it involves pain on respiration; possibly due to lack of mucosa protecting the pterygopalatine ganglion.

Table 1 summarizes the findings in 8 patients who have different type of reductive turbinate surgery and ENS subtypes. The onset of ENS symptoms after turbinate surgery is variable. In ENS-both subtype symptoms usually occur within weeks. Indications for any turbinate surgery should be carefully considered, and functional exploration should be generalized to prevent ENS. Surgery used to aim at maximal resection to maximize gain in nasal cavity volume; with improvements in knowledge of the complications of total and subtotal turbinatectomy, including ENS, present attitudes favour conservative surgery. The techniques currently recommended are laser surgery and electrical catherization; partial turbinectomy; submucosal turbinoplasty; submucosal resection by micro-debrider; and radiofrequency surgery.
Table 1: Characteristic of the patients with ENS subtypes after different reductive turbinate surgery

<table>
<thead>
<tr>
<th>Case</th>
<th>Prior Surgery</th>
<th>ENS Subtypes</th>
<th>Onset of symptoms</th>
<th>Additional Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MT resection</td>
<td>ENS-MT</td>
<td>Within days</td>
<td>Dryness, pain</td>
</tr>
<tr>
<td>2</td>
<td>IT resection</td>
<td>ENS-IT</td>
<td>Within months</td>
<td>Dryness, difficulty breathing</td>
</tr>
<tr>
<td>3</td>
<td>Turbinate resection</td>
<td>ENS-type</td>
<td>Within months</td>
<td>Dryness, thick postnasal drip</td>
</tr>
<tr>
<td>4</td>
<td>MT resection</td>
<td>ENS-MT</td>
<td>Within days</td>
<td>Pain, feeling of suffocation</td>
</tr>
<tr>
<td>5</td>
<td>Turbinate resection</td>
<td>ENS-type</td>
<td>Within 1-2 years</td>
<td>difficulty breathing, fatigue</td>
</tr>
<tr>
<td>6</td>
<td>IT and MT resection</td>
<td>ENS-both</td>
<td>within days</td>
<td>Dryness, crust, pressure</td>
</tr>
<tr>
<td>7</td>
<td>MT resection</td>
<td>ENS-MT</td>
<td>Within days</td>
<td>Cough, dryness, difficulty breathing</td>
</tr>
<tr>
<td>8</td>
<td>Turbinate resection</td>
<td>ENS-type</td>
<td>Within days</td>
<td>Dryness, too open</td>
</tr>
</tbody>
</table>

Medical treatment is the first-line treatment focusing on moisturization and an honest discussion of patient’s concerns. It includes nasal lavage by physiological saline, nasal hydration ointment, directed antibiotic therapy and local corticosteroids. Adding menthol to the classical local treatments may provide benefit in terms of the nasal obstruction sensation. Follow-up should include psychological support for patients showing signs of depression. The objectives of endonasal repair surgery are: to reduce nasal cavity volume to increase resistance to airflow, to reduce airflow to increase air humidity, and deviate airflow from the surgical site toward a healthy or non-operated area. The principle consists in positioning an implant on the septum, floor or lateral wall. Creating a neo-turbinate has been achieved by submucosal implantation of a turbinal or septal cartilage graft to restore inferior turbinate volume. The aim is to restore a mucosal area sufficient to ensure the physiological functions of warming, filtering and humidification of inhaled air. Biomaterials materials (hydroxyapatite, goretex, teflon, plastipore) have also given satisfactory results. Hyaluronic acid gel, an injectable can improve symptoms without increasing complications. Houser described a technique of submucosal acellular dermis graft filling. The dermis showed integration within 3 to 6 months, and the resultant volume proved durably effective. These techniques are only possible if there is some residual turbinate. Otherwise, the problem confronting surgery is more complex.

The ENS-both subtype patients may benefit from a large septal implant bridging the regions of the IT and MT and the grafts becomes incorporated within the patient’s tissue within 3 months following implantation. Deploying the full range of simple nasal cavity hygiene and humidification techniques, will usually be sufficient in the majority of cases, with surgery reserved for the most severe cases. Whatever the technique, surgery aims at partial filling of the nasal airway. Prevention is the most important strategy as the ENS therapy is unsatisfactory for both patient and doctor.

Minimal invasive surgery on the turbinate which preserves the mucosa remains one of the most important principles for rhinosurgical therapy.

References


Introduction
A case report of Portal Vein Thrombosis (PVT) as a complication of protein S deficiency. PVT has been increasingly diagnosed over the years, particularly through the use of ultrasound-Doppler equipment. The lifetime risk of getting PVT in the general population has recently reported to be 1%. While this condition has traditionally been associated with cirrhosis or liver malignancy, it may also occur without any liver disease.

The case report is followed by a discussion of the aetiology and clinical presentations of PVT, as well as a review of the investigations and management proposed in the literature.

Keywords
Hypertension, portal; Portasystemic Shunt, Surgical; Esophageal and Gastric Varices; Splenomegaly.

Case Report
A 36 year old lady was referred with non-specific abdominal pain, elevated liver enzymes and a prolonged INR. Abdominal examination revealed hepatosplenomegaly, which was confirmed on ultrasound. She was investigated through several blood tests; namely a full blood count, inflammatory markers, INR, haematinics, serum copper as well as caeruloplamin and alpha-antitrypsin levels. An autoimmune screen, viral screen, leishmaniasis screen and serum protein electrophoresis were also negative, as was a trephine biopsy. No abnormalities were detected.

As the cause of the hepatomegaly was obscure, a liver biopsy was arranged; this showed sinusoidal dilatation suggestive of portal vein thrombosis or Budd-Chiari syndrome. CT scan confirmed portal and splenic vein thrombosis but the superior mesenteric vein was patent. The patient was started on anticoagulants, with a target INR of 2-2.5. A thrombophilic screen was done; this confirmed protein S deficiency.

An oesophagogastroduodenoscopy (OGD) was performed, which showed Grade B oesophageal varices, gastric varices and portal hypertensive changes. In view of this, the patient was started on propranolol. She remained clinically stable for four years and was followed up by repeat OGDs.

Four years after presentation, a follow-up OGD showed progression of the oesophageal varices to Grade C, red wale signs, and small gastric ulcers. The varices were banded and the patient was started on a proton pump inhibitor (PPI).

The patient experienced her first upper GI bleed five years after her initial presentation. An emergency OGD showed Grade C varices with red wale signs, requiring banding 5 times. Warfarin was omitted despite an INR which was almost within the target range, and maximal PPI doses were administered: omeprazole 40mg bd IV. She was started on piperacillin-tazobactam 4.5mg tds IV and an octreotide pump, set at a rate of 2.5mcg/hr for a total of five days.

The patient scored 6 on the Rockall score, and was in fact managed at the Intensive Care Unit. She required several transfusions of packed red cells and...
fresh frozen plasma in view of anaemia and persistently elevated INR.

During the same admission, she had further episodes of fresh bleeding; a second emergency OGD showed oesophageal ulcers, prominent gastric varices and signs of recent bleeding. She was kept on maximal PPI doses and started on sucralfate 1g qds po, as well as terlipressin 1mg tds IV. The patient was referred for emergency surgery, and a mesentero-right-common-iliac shunt was performed. She did considerably well in the post-operative period, and her ascites was controlled with diuretics. A haematological consultation advised testing for Janus kinase (JAK)-2 gene mutation; this was positive, suggesting the presence of a myeloproliferative disorder.

She was discharged on subcutaneous enoxoparin, with regular follow-up from the gastrointestinal and haematological point of view.

**Discussion**

**Aetiology**

Portal vein thrombosis as a complication of cirrhosis and hepatocellular carcinoma has long been recognized. Over the years, it has been shown that PVT can also occur as a cause of several thrombophilic states and local abdominal conditions. Some studies have shown the involvement of multiple factors in the development of PVT.

As shown in Table 1, prothrombotic states can be inherited or acquired. Inherited thrombophilias include genetic disorders such as factor V Leiden mutation, factor II gene mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency and methylene-tetrahydrofolate-reductase (MTHR) gene mutation. Other inherited thrombophilias include primary myeloproliferative disorders such as polycythaemia rubra vera; PVT may actually be the first manifestation of this disease. Other acquired prothrombotic states include paroxysmal nocturnal haemoglobinuria, hyperhomocysteinemia, antiphospholipid syndrome, increased factor VIII levels and thrombin activatable fibrinolysis inhibitor (TAFI) gene mutation.

Acquired thrombophilias include primary myeloproliferative disorders such as polycythaemia rubra vera; PVT may actually be the first manifestation of this disease. Other acquired prothrombotic states include paroxysmal nocturnal haemoglobinuria, hyperhomocysteinemia, antiphospholipid syndrome, increased factor VIII levels and thrombin activatable fibrinolysis inhibitor (TAFI) gene mutation. A variety of intra-abdominal inflammatory conditions may lead to PVT. These include pancreatitis and local injury to the portal vein, for example after abdominal trauma or surgery. Uncommonly, portal vein thrombosis may occur as a complication of liver transplantation.

Pregnancy, use of oral contraceptives, chronic inflammatory diseases and malignancies represent an increased risk in patients with prothrombotic states. Other aetiological agents include infection with cytomegalovirus and *Bacteroides fragilis* while approximately 10-30% of cases are idiopathic.

<table>
<thead>
<tr>
<th>Table 1: Aetiology of PVT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inherited Prothrombotic state</strong></td>
</tr>
<tr>
<td>- Protein C deficiency</td>
</tr>
<tr>
<td>- Protein S deficiency</td>
</tr>
<tr>
<td>- Antithrombin III deficiency</td>
</tr>
<tr>
<td>- Factor V Leiden mutation</td>
</tr>
<tr>
<td>- Factor II gene mutation</td>
</tr>
<tr>
<td>- Methylene-tetrahydrofolate-reductase (MTHR) gene mutation</td>
</tr>
<tr>
<td><strong>Acquired Prothrombotic state</strong></td>
</tr>
<tr>
<td>- Primary myeloproliferative disorder (e.g. polycythaemia rubra vera)</td>
</tr>
<tr>
<td>- Paroxysmal nocturnal haemoglobinuria</td>
</tr>
<tr>
<td>- Hyperhomocysteinemia</td>
</tr>
<tr>
<td>- Antiphospholipid syndrome</td>
</tr>
<tr>
<td>- Increased factor VIII levels</td>
</tr>
<tr>
<td>- Thrombin activatable fibrinolysis inhibitor (TAFI) gene mutation</td>
</tr>
<tr>
<td><strong>Intra-abdominal inflammation</strong></td>
</tr>
<tr>
<td>- Pancreatitis, appendicitis, diverticulitis</td>
</tr>
<tr>
<td>- Portal vein injury e.g. abdominal trauma, surgical procedures</td>
</tr>
<tr>
<td><strong>Portal hypertension</strong></td>
</tr>
<tr>
<td>- Liver cirrhosis</td>
</tr>
<tr>
<td>- Budd-Chiari syndrome</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
</tr>
<tr>
<td>- Hepatocellular carcinoma</td>
</tr>
<tr>
<td>- Pancreatic carcinoma</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td>- Cytomegalovirus</td>
</tr>
<tr>
<td>- <em>Bacteroides fragilis</em></td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
</tr>
<tr>
<td><strong>Drugs (e.g. oral contraceptives)</strong></td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
</tr>
</tbody>
</table>
Presentation

The clinical presentation of PVT may be acute or chronic. This classification is not so clear-cut, as there is no definitive time frame which distinguishes the two. Studies have generally considered the presentation to be acute if symptoms develop less than 60 days prior to hospital assessment.\(^9\) PVT is also regarded as acute if imaging has ruled out the presence of significant collaterals and there is no evidence of portal hypertension.

Acute PVT is characterised by abdominal pain and nausea, though it may also be asymptomatic. Symptom severity depends on the rapidity and extent of the thrombosis. Involvement of the superior mesenteric vein may lead to bowel infarction; patients may then present with haematochezia, fever, rebound tenderness, and ascites. Such a complication is associated with a poor prognosis.\(^20\) Acute PVT may then undergo spontaneous resolution, or progress to chronic thrombosis.

Chronic PVT presents with the complications of portal hypertension, including variceal bleeding (which is usually well-tolerated), splenomegaly or hypersplenism.\(^16\) Patients may complain of abdominal discomfort as a cause of the splenomegaly. Chronic PVT may also be asymptomatic and discovered incidentally on imaging.

The presence of cirrhosis, cancer and mesenteric vein thrombosis are negative prognostic factors. In fact, studies have shown that mortality is influenced more by associated disease rather than variceal bleeding per se.\(^4\)

Investigations

The investigation of choice is abdominal ultrasound. Sonographic findings include the presence of solid echoes within the portal vein and demonstration of a portal cavernoma.\(^21\) Additional information can then be obtained through other non-invasive imaging modalities, including doppler ultrasound, CT scan, magnetic resonance angiography and endoscopic ultrasound.\(^22-23\)

In our patient, while abdominal ultrasound revealed splenomegaly, it was the CT scan which clinched the diagnosis of PVT. CT scan can also be used to differentiate between recent and old thrombosis; the presence of portosystemic collaterals and cavernoma formation are both suggestive of old thrombosis.\(^24\)

The next step is a thorough investigation of the cause of the thrombosis. Local abdominal factors can be identified through imaging; investigation for a systemic cause, including myeloproliferative disorders and prothrombotic tendencies, is carried out through blood tests.\(^24\) Identification of the aetiological agent is vital, as the underlying condition may require specific treatment, and will influence the use and duration of anticoagulation.\(^25\)

In our patient, investigations for the presence of cirrhosis and for local abdominal causes of thrombosis were negative. A thrombophilic screen then confirmed protein S deficiency, and a positive test for JAK-2 gene mutation suggested the presence of a myeloproliferative disorder.

Treatment

The aim of the treatment is two-fold: to prevent or reverse thrombus advancement in the portal venous system, and to treat any complications that may arise.\(^25\)

Recommendations on the use of anticoagulation differ in acute and chronic PVT. While several studies have supported the role of anticoagulation in patients with acute PVT,\(^26\) little information exists on the duration and extent of anticoagulation. It has been suggested that patients with a self-limiting course of PVT, such as acute pancreatitis, should be given a course of 3-6 months.\(^25\) On the other hand, anticoagulation can be continued in patients with prothrombotic tendencies, a family history of venous thrombosis or confirmed extensive thrombosis.

Thrombolytic therapy has also been shown to lead to the resolution of acute PVT.\(^27\) Studies have reported the use of thrombolytics such as recombinant tissue plasminogen activator, both systemically and through a catheter-directed infusion.\(^16\) These techniques have been very promising with regard to resolution of thrombus, resulting in improved symptomatology and avoidance of bowel resection.\(^28\) However, they have had a very high rate of major complications, including bleeding. It was thus recommended that thrombolysis is reserved for patients with severe disease, while a more conservative approach should be taken for others.

The use of anticoagulation in chronic PVT is more controversial, due to the presence of varices as a complication of portal hypertension. Nevertheless, it has been shown that the benefit-risk ratio in such a scenario favours the use of anticoagulant therapy.\(^29\) In the case presented above, the patient was in fact kept on life-long anticoagulation.

Management of the complications of PVT is mostly concerned with prophylaxis and treatment of gastro-oesophageal variceal bleeds. This has mostly been studied in patients with portal hypertension and cirrhosis, rather than isolated PVT. The use of beta-blockers as prophylaxis in patients with varices, has successfully reduced the rate of the first variceal bleed, and recent studies have shown that variceal band ligation (VBL) is just as effective.\(^30\) Both medical therapy and VBL are also equally effective in secondary prevention of variceal bleeds.\(^31\)

There remains a lack of information on whether one can extrapolate such data to patients with PVT. It
has been suggested that beta blockers will theoretically decrease splanchnic blood flow which may lead to progression of thrombosis. However there is no evidence for this, as yet. In the case presented above, the patient was kept on beta-blockers, and VBL was performed as primary prophylaxis. Her first episode of variceal bleeding occurred five years as presentation, and this was once again treated with banding.

The role of decompressive shunt surgery in PVT is also not clear. Indications include failed endoscopic therapy, and symptomatic hypersplenism. Techniques include a selective distal splenorenal shunt (Warren Zeppa) or a mesenteric left portal bypass (Rex shunt). Liver transplantation is indicated rarely in cirrhotics. A retrospective analysis . Ann Surg 1986 ; 203 : 286–91.


Abstract
Aspects of the structure, molecular biology and control of the tight junctions that regulate paracellular transport by the small intestine are reviewed so as to understand the limitations of intestinal permeability as a bedside tool to investigate diarrhoea. Examples of the altered structure and behaviour of tight junctions during abnormal permeability are used to gain insight into the pathogenesis of diarrhoeal diseases and potential new therapies.

Keywords
Tight junctions, permeability, paracellular, diarrhoea, zonulin

Introduction
The healthy epithelium of the duodenum and upper jejunum responds to a meal by urgent net secretion of water and solute molecules, many of which are salvaged by avid reabsorption along with digested nutrients by the ileum. The fed gut is tasked with maintaining an integral barrier against high inward concentration gradients of bacterial toxins and food antigens which are only sampled very selectively in order to educate the immune system. A healthy gut barrier function results from a strict cellular polarity with abundant cell-to-cell attachments between the lateral walls of adjacent enterocytes as well as an apical (luminal) membrane consisting of a lipid bilayer which is very hydrophilic on its luminal and cytoplasmic surfaces while possessing a very hydrophobic interior. During evolution transmembrane proteins with hydrophilic interiors have been inserted like collar studs across the apical membrane to allow the entry and transcellular passage of solutes and charged or polar molecules.

Ions and charged nutrients such as amino acids and fatty acids as well as glucose that are not soluble in the lipid bilayer are transported by these protein carriers as long as the necessary concentration gradients are generated by ATP-driven pumps in the basolateral membrane. The accompanying molecules are not always of opposite charge so that cumulative osmotic and electrical gradients, and measurable voltage differences, develop across the membrane and have to be “neutralised” by the complimentary paracellular flow of water and ions. This process although more primitive and dependent on concentration and electrical gradients is also highly regulated and selective. The mechanisms of dysregulation of this paracellular flow of solutes and water are the focus of exciting research aimed at finding new therapies for challenging high volume diarrhoeal illnesses.

Permeability: the intestinal gate-keeper
Freeze-fracture electron microscopy (EM) reveals that the uppermost part of the paracellular space, just below the bases of the microvilli, is interlaced by a continuous belt of reticular ridges or strands as if for fluid percolation. The strands consist of points of apposition or “kisses” of adjacent lateral membranes and can be shown to impede the passage of electron dense material by EM (see Figure 1). The ridges whose number is inversely related to the permeability of the tight junction belt consist of rows of many “tight junctions” formed by the interlocking of transmembrane proteins at the points of apposition of adjacent lateral cell membranes.

Tight junctions form intercellular rate-limiting pores that are narrower than the subjacent paracellular space which measures 75 Angstrom (one Angstrom (Å) = 0.9 nanometer). They restrict paracellular flow since their maximum diameter is 9 Å at the villous tip although this increases to a maximum diameter of 60 Å in the crypts which are always more “leaky”. Tight junctions may have evolved and adapted from rivet-like structures called desmosomes. The interdigitating transmembrane proteins of desmosomes (cadherins) attach via plaque proteins to elastic cytoskeletal elements called tonofilaments which anchor cell walls to the cytoplasm to prevent cellular collapse.
Desmosomes may have assumed a tubular morphology while evolving into “gap junctions.” These 30 Å channels are surrounded by hydrophilic connexon proteins that allow intercellular piping of molecules. They enable excitation spread in neural and cardiac tissue. Unlike gap junction, tight junctions can be opened and closed by contractile elements within the cytoskeleton that respond to intracellular signals generated by events such as alteration in cell hydration or transcellular transport. Inflammation may release cytokines which alter signal transduction and disrupt the crosstalk between the paracellular and transcellular routes thus causing diarrhoea.

Open sesame!

The molecular structure of two key tight junction proteins (occludins, claudins) was unravelled by Shoichiro Tsukitas and Mikio Furuse at Kyoto University. Occludins span the apical region of the enterocyte lateral membrane four times (figure 2). Most of their charge is located in the cytoplasmic domain, which contains both the amino and carboxyl ends, leaving the two extracellular loops uncharged and therefore very hydrophobic. Homotypic binding (binding of identical proteins) of the two occludin loops is thought to help seal the pore. Exactly how occludin achieves a pore-size limit for solutes (approximately 600 Daltons) is not yet understood.

In contrast, claudins, the other family of tight junction proteins, the extracellular loops are highly charged and confer cation-specificity to various ions. Twenty-four isoforms of claudins have so far been discovered in the gut and elsewhere. Claudin-2 is abundant in the gut and is selective for sodium ions. Some claudins are pore-forming and increase intestinal permeability while others appear to close the junction. By having different proportions of the various claudins in different parts of the gut, charge-selectivity and size-selectivity patterns vary regionally in the small intestine. Elsewhere mutations in claudin-16 cause abnormal renal tubular transport of two major cations resulting in Familial Hypomagnesaemic Hypercalcaemic Nephrocalcinosis (FHHNC). Signalng (to open and close the pore) may result from homotypic binding of occludin to extracellular ligands (e.g. toxins, antigens, nutrients) or arise from binding of intracellular messengers (inside-out signaling) such as those released by pro-inflammatory cytokines. The carboxyl terminus of claudins also binds to scaffolding proteins which group and tether signaling components to the membrane, insulating them from other signal proteins and thus increasing signal transduction.

It’s all about muscle!

A ring of bipolar actin filaments containing myosin II surrounds the apical junction complex. The carboxyl terminal of occludin attaches to a cytoplasmic plaque protein called ZO1 (zonula occludens protein 1) which links the tight junction to the actin-myosin complex making it possible for actin-myosin sliding to transmit forces to the tight junction (figure 2). ZO1 together with the other cytoplasmic plaque proteins namely ZO2 and 130KD protein belong to the family of kinases known as MAGUKs (membrane-associated guanyline-kinase homologues). This suggests that they recruit proteins which anchor the actin filaments to the plasma membrane. Isoforms of ZO1 probably determine the mechanical plasticity of the tight junction. Intracellular messengers such as the calcium–calmodulin complex increase ATP-ase activity in the myosin-actin complex and cause classic actin-myosin contraction. The centrifugal force is then transmitted through the plaque proteins so as to open the pore. Other intracellular messengers such as cyclic AMP probably bring about shortening by altering the polymerisation of the actin chain.
selective solvent drag of mannitol by rapid paracellular but the discrepancy is more likely to be explained by initially thought to be due to transcellular transport of intestinal permeability.

0.03 are indicative of a pathological increase in small lactulose i.e. a lactulose:mannitol recovery ratio. Recoveries are 21.5% for mannitol and only 0.47% for intestinal surface-area and transit-time. Typical compensating for inter-individual variations in helps to standardize estimates of permeability by two probes. The use of two simultaneous oral probes urine collected for 6 hours after oral dosing of these concentrations of lactulose and mannitol recovered in permeability is estimated from the ratios of the ratio of 0.78.

radius of 9 Å, typically with a lactulose : mannitol flux across villous tight junctions which have a maximum concentration on the “luminal” side using the classic Ussing chamber. Two probes commonly used to study paracellular transport in vitro are lactulose and mannitol. Mannitol is a polyhydric alcohol with a molecular size of 3.9 Å while lactulose is a disaccharide with a molecular size of 5.1 Å. Both are absorbed paracellularly to a similar extent in vitro across villous tight junctions which have a maximum radius of 9 Å, typically with a lactulose : mannitol flux ratio of 0.78. At the bed-side small intestinal permeability is estimated from the ratios of the concentrations of lactulose and mannitol recovered in urine collected for 6 hours after oral dosing of these two probes. The use of two simultaneous oral probes helps to standardize estimates of permeability by compensating for inter-individual variations in intestinal surface-area and transit-time. Typical recoveries are 21.5% for mannitol and only 0.47% for lactulose i.e. a lactulose:mannitol recovery ratio (L:M) of 0.022. In clinical practice L:M ratios above 0.03 are indicative of a pathological increase in small intestinal permeability.

The higher mannitol recovery in-vivo was initially thought to be due to transcellular transport but the discrepancy is more likely to be explained by selective solvent drag of mannitol by rapid paracellular

entry of water pulled by the hyperosmolality in the tips of the villi that results from their rich blood supply and countercurrent exchange. Ischemia or loss of villi as in coeliac disease therefore results in reduced urinary recovery of administered mannitol.

Permeability, a marker of disease to come?

Permeability testing has the potential to detect early aberrations in intestinal physiology. For example prematurity in neonates is associated with high L:M ratios which fall rapidly as the epithelium responds to the trophic effects of feeding. L:M ratios are independent of growth in mucosal surface area, which would increase the absorption of both probes. Conversely progressive malnutrition is associated with proportional increases in permeability, even in the absence of villous atrophy. Other studies have shown that malnutrition augments bacterial translocation, increases antigen presentation to lamina propria T cells and raises circulating CRP and IL-6. Nathavitharana et al reported significantly higher L:M ratios in children suffering from severe villous atrophy but permeability testing could not discriminate between patients with milder villous atrophy and healthy controls. The same authors found that high L:M ratios almost completely normalized within twelve weeks of gluten-withdrawal while subsequent gluten challenge was associated with a rapid increase in intestinal permeability. Bedside permeability testing is therefore not sensitive enough to screen for coeliac disease in the general population but may help to determine the optimal timing of duodenal biopsy during gluten challenge. Elevated L:M ratios which are reported with widely varying prevalence in first-degree relatives of coeliac patients increase the likelihood of celiac disease.

Elevated circulating proinflammatory cytokines have been reported, and implicated in pathogenesis, in many but not all studies in patients with diarrhoea-predominant irritable bowel syndrome (D-IBS). Dunlop et al found elevated intestinal permeability in both ordinary and post-infectious D-IBS (but not in constipated IBS patients) compared to healthy controls. The same authors found activation of mast cells, enterochromaffin cells and T-cells in rectal biopsies of other D-IBS patients. Jejunal mast cells are thought to be the main target of corticotrophin releasing factor during stress and their products, histamine and prostaglandins, are implicated in the increased jejunal permeability of D-IBS. The proximity of mast cells to the enteric nerves has also been implicated in the abdominal pain of IBS. Mast cells have not been found to be increased in postinfectious D-IBS patients who also show a lesser increase in intestinal permeability, presumably by a mast cell-independent mechanism. Bertiaux-Vandaële et al found striking

Figure 2: Interdigitation of TJ proteins (occludin and claudin) and their attachment to the sliding actin-myosin complex via plaque proteins (e.g ZO1, ZO2/3). Reproduced from Yu D, Turner JR. Stimulus-induced reorganization of tight junction structure: The role of membrane traffic. Biochimica et Biophysica Acta (BBA) 2008; 1778(3)709 -716 with permission from Elsevier
Cholera-related research recently discovered that the normal intestine also produces luminal agents which control permeability. Besides the classic 84kD toxin which catastrophically opens enterocyte apical chloride channels, Vibrio cholerae produces a second “Zonula Occludens” Toxin (ZOT) which binds to surface receptors present on enterocytes (but not on colonocytes) to cause protein kinase C-dependent polymerisation of actin filaments that open the tight junctions (Figure 2). The paucity of ZOT receptors in the crypts, which are leaky anyway as compared to the villi, led to the search for an endogenous ZOT-like substance that the enterocyte may release to regulate villous permeability. A 47 kD analogue of ZOT called Zonulin is in fact produced by the intestine as part of host defence after exposure to bacteria even if these are commensals or killed by gentamycin allowing the small intestine (but not the colon) to flush itself of bacterial overgrowth.

Heightened zonulin secretion characterises the early phase of coeliac disease and may predispose to type 1 diabetes mellitus and other autoimmune diseases by increasing entry of luminal antigens. Quantitative immunoblots from intestinal tissue in coeliac disease patients showed significantly higher zonulin than in controls. An octapeptide zonulin-receptor inhibitor joins propyl dipeptidases and transglaminase inhibitors in the list of candidate future oral agents that aim to restore wheat tolerance in coeliac patients.

**Conclusion**

The paracellular route of transport of fluids and solutes in between the enterocytes of the human small intestine, regulated by tight junctions, holds the key to unravelling the mechanisms underlying the clinical problem of high-volume diarrhoea that spans many inflammatory, allergic and autoimmune diseases. An understanding of the altered physiology in these scenarios will likely result in the testing of many exciting new therapeutic strategies.

**References**


Overview of the blood transfusion policy in preterms on the Neonatal Intensive Care Unit

Valerie Said Conti, Eugenio Azzopardi, Raymond Parascandalo, Paul Soler, Simon Attard Montalto

Abstract

Preterm infants on the Neonatal Intensive Care Unit receive a greater number of red cell transfusions than any other hospitalised group. Over the past twenty years research has focused on setting standards to determine when it is necessary to transfuse packed cells in this cohort, whilst exploring the use of red cell growth factors and other substrates judiciously in order to reduce and/or avoid red cell transfusions and limit donor exposure. One hundred and eighty-one blood transfusions were administered to 106 preterms less than 35 weeks gestation on the NICU during 2009 in Malta. The median (range) volume of blood used from each bag supplied by the Blood Transfusion Department was 25.8mls (10-50mls), the rest of which was discarded. Risk factors for transfusion included Extremely Low Birth Weight (less than 1kg) and a gestation of less than 30 weeks. The blood transfusion guidelines presently in use on the local NICU were reviewed and compared with more restrictive guidelines on other units and suggestions made to reduce transfusions in line with these guidelines.

A reduction in transfusion aliquots provided for neonates to just 50mls from the customary 250mls in a dedicated single-donor programme will safeguard limited health resources and minimise donor exposure.

Keywords

Infants, standards, blood transfusions, birth weight, health resources

Introduction

Preterm infants on the neonatal intensive care unit (NICU) receive a greater number of red cell transfusions (RCTs) than any other hospitalised group. During the first weeks after birth when blood sampling is frequent, approximately 50% of extremely low birth weight (ELBW) infants receive their first transfusion. By the time of discharge, approximately 85% of ELBW infants would have been transfused. A RCT aims to provide an immediate increase in oxygen delivery to tissues. Oxygen delivery can be increased by a RCT or by administering red cell growth factors (RCGF). Although the risk of transmission of known infectious agents (eg hepatitis B and C virus, human immunodeficiency virus) is relatively low, the risk of infectious agents newly identified in transfused blood (eg Plasmodium sp, Parvovirus B19) remains to be determined.

Research to evaluate the efficacy of restrictive transfusion guidelines have lead to strategies to decrease RCTs in preterms. Controversy surrounds the haemoglobin value and clinical circumstances under which RCTs should be administered. If a preterm with a low haematocrit needs an immediate increase in oxygen to tissues then a RCT is required otherwise treatment with RCGF and appropriate substrates such as folic acid and oral iron should be considered. Limiting donor exposure is prudent for infants who are likely to receive multiple transfusions. Single-donor programmes limit donor exposure, cost less and lead to better preservation of limited blood resources without incurring additional risk. This programme involves dedicating an adult bag of red cells to a particular preterm by dividing the volume into aliquots for use by this preterm.

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* corresponding author
Our study was designed to quantify the number of RCTs administered to preterms less than 35 weeks gestation, and to identify the cohort by birth weight and by gestation that was most likely to require repeated transfusions and would, therefore, benefit from a single-donor transfusion programme. The ideal volume of blood in each aliquot to make best use of resources was determined. Finally, the number of transfusions administered according to the local guidelines was compared with the number required if more restrictive guidelines were applied.

Methods

A prospective study on the NICU was carried out between 1st January and 31st December 2009. Gestational age, birth weight, date of admission/discharge, any complications of prematurity including periventricular leucomalacia, intraventricular haemorrhage, chronic lung disease, necrotising enterocolitis, retinopathy of prematurity and any surgical intervention were recorded. The number of days on ventilatory support, nasal continuous positive airway pressure (nCPAP), nasal prong oxygen and with umbilical arterial/venous access or peripheral arterial access, were documented for each infant.

For each transfusion administered we noted the date, gestation and weight at transfusion; whether the baby was symptomatic with poor feeding, tachycardia, bradycardia, apnoeas/desaturations; the need for inotropes; the mode of ventilation and any improvement post-transfusion, as well as the amount in millilitres of blood transfused/discard, and haemoglobin pre- and post- transfusion.

Results

RCT by birth weight and gestation (Table 1).

Table 1: RCT by birth weight

<table>
<thead>
<tr>
<th>Birth weight category</th>
<th>Number of preterms admitted</th>
<th>% of all preterms admitted</th>
<th>Number of preterms transfused</th>
<th>% of category preterms transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000g ELBW</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>92</td>
</tr>
<tr>
<td>1001-1500g VLBW</td>
<td>22</td>
<td>21</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>1501-2500g LBW</td>
<td>59</td>
<td>56</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>&gt;2501g</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>100</td>
<td>40</td>
<td>37.7</td>
</tr>
</tbody>
</table>

106 preterms less than 35 weeks gestation were admitted during the study period. 12 (92%) ELBW babies were transfused; 12 (55%) VLBW babies required a transfusion; 15 (25%) LBW preterms were transfused and 1 (8%) preterm less than 2.5kg was transfused. The most heavily transfused were the ELBW babies, followed by those of VLBW. 8% of preterms were between 24-26 weeks gestation and, of these, 75% required a RCT. 12% were between 27-29 weeks and all required a RCT. In comparison, 28% were between 30-32 weeks gestation and 50% required a RCT, whereas 52% were between 33-35 weeks and only 7% of these required a RCT (Table 2). These data show that babies less than 30 weeks gestation are the most heavily transfused.

Table 2: RCT by gestational age

<table>
<thead>
<tr>
<th>Birth weight category</th>
<th>Number of preterms admitted</th>
<th>% of all preterms admitted</th>
<th>Number of preterms transfused</th>
<th>% of category preterms transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000g</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>92</td>
</tr>
<tr>
<td>1001-1500g</td>
<td>22</td>
<td>21</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>1501-2500g</td>
<td>59</td>
<td>56</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>&gt;2501g</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>100</td>
<td>40</td>
<td>37.7</td>
</tr>
</tbody>
</table>

RCTs in individual preterms by birth weight (Figure 1)

All infants less than 1000g required 4 or more RCTs (with the exception of two babies, one of whom was recruited in the last days of the study and data from 2010 was omitted, and another who died within a few hours from birth). 80% of babies less than 1500g had 2 or more transfusions. Most preterms greater than 1501g required only one blood transfusion. The cohort most highly transfused and most likely to benefit from
a single-donor transfusion programme included preterms weighing less than 1500g.

**RCTs in individual preterms by gestational age (Figure 2)**

![Figure 2: Number of RCT by gestation](image)

All infants between 24-26 weeks had 4 or more RCTs, whilst 77% of those between 27-29 weeks received more than 4 RCTs. 56% of 30-32 week gestation babies received more than 2 RCTs, and all preterms greater than 33 weeks gestation had one RCT. Thus preterms less than 32 weeks gestation are most highly transfused and would benefit from having a single-donor programme.

**Determination of best aliquot size (Figure 3)**

![Figure 3: Volume of red cells required for each transfusion](image)

The total number of RCTs administered during the study period was 181. Each volume transfused was 20mLs/kg body weight. The mean (mode, range) volume of packed cells transfused was 25.8mLs (20mLs, 10-50mLs). During the study period, at least 150-200mLs of blood per bag was discarded. In this study ‘high-risk’ preterms less than 32 weeks gestation received 162 bags of red cells. However, if a single-donor transfusion programme was in operation, only 56 bags (assuming 5 aliquots of 50mL per 250mL bag) would have been required. This would translate in a net reduction of 106 bags (65% less).

**Comparison of transfusion guidelines**

Each neonatal unit has its own transfusion guidelines. Using local criteria (Table 3) 156 (86%) transfusions were required in oxygen-dependent preterms (70 in ventilated preterms, 61 in preterms on nCPAP, 25 in preterms on nasal prong oxygen), whilst 25 (14%) were required in preterms in room air (23 babies were asymptomatic, 1 was feeding poorly, 1 had apnoea/oxygen desaturations).

**Table 3: Recommendations for the administration of RCT in preterm infants in Malta**

<table>
<thead>
<tr>
<th>Criteria for administering packed RCT</th>
<th>Hb Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates who are in oxygen, whether ventilated, on nasal CPAP or using nasal prongs</td>
<td>&lt; 12g/dL</td>
</tr>
<tr>
<td>Neonates who are not in oxygen and who have a reticulocyte count of &lt; 100 000/uL</td>
<td>&lt; 10g/dL</td>
</tr>
</tbody>
</table>

Comparison with British transfusion guidelines for neonates receiving intensive care showed that the same number of transfusions would have been required. We equated chronic oxygen dependency in the British guidelines to nCPAP/nasal prong oxygen in the local guideline. Using British criteria (Table 4), 34 less transfusions would have been required (86 transfusions given locally to babies on nCPAP/nasal prongs vs. 52 if British criteria were used).

**Table 4: Recommendations for RCT in preterm infants proposed by the British Standards in Haematology Transfusion Task Force 2009**

<table>
<thead>
<tr>
<th>Criteria for administering packed RCT</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia in the first 24h</td>
<td>Hb &lt; 12 g/dL</td>
</tr>
<tr>
<td>Cumulative blood loss in 1 week, receiving intensive care</td>
<td>10% blood volume</td>
</tr>
<tr>
<td>Neonate receiving intensive care</td>
<td>Hb &lt; 12 g/dL</td>
</tr>
<tr>
<td>Acute blood loss</td>
<td>10% blood volume</td>
</tr>
<tr>
<td>Chronic oxygen dependency</td>
<td>Hb &lt; 11 g/dL</td>
</tr>
<tr>
<td>Late anaemia, stable patient</td>
<td>Hb &lt; 7 g/dL</td>
</tr>
</tbody>
</table>

Late anaemia in the stable patient by British standards was equated to asymptomatic babies in room air: 9 less transfusions would have been given (23 vs. 14) in this subgroup. Using a single-donor system and restrictive guidelines in clinically stable preterms would translate...
in an overall further total reduction of 4 bags. An attempt was made to correlate the presence of indwelling arterial/central venous lines with increased risk for RCT due to increased phlebotomy losses but the number was too small and there were too many confounding factors to draw any conclusions.

Discussion

181 RCTs were administered to preterms during the study period. The most heavily transfused were preterms between 24–29 weeks gestation closely followed by those between 30–32 weeks gestation and those less than 1000g closely followed by those weighing 1001–1500g. Thus, a gestation of less than 32 weeks and weight of less than 1.5kg are the major risk factors for transfusion.

This study shows that aliquots of 50mls of blood would be adequate. With this practice the number of donor units required can be reduced by 65% leading to more cost-effective use of this limited resource.

With a single-donor programme high-risk preterms are identified, and the Blood Transfusion Department will dedicate a set of aliquots, reducing the risks of donor exposure.

Adopting restrictive guidelines on our NICU, as is the trend in Europe, Canada and the US would translate into a smaller number of transfusions without any additional risks to babies. Indeed, comparison with these guidelines shows that for intensive care babies the present protocol of transfusing when the haemoglobin is below 12g/dL is recommended by both. However, it would appear to be safe practice to adopt more restrictive transfusion guidelines in the more stable, chronic cohort. Two randomized clinical trials have addressed the controversy of whether restrictive or liberal RCT criteria should be applied in infants but the number was too small and there were too many confounding factors to draw any conclusions.

A number of non-transfusion approaches have been suggested, including cord blood collection as a form of ‘autologous’ donation and delayed cord clamping (30s delay transfers 10-15mL/kg body weight of blood). Studies found lower rates of intraventricular hemorrhage and late-onset sepsis in the infants who underwent delayed cord clamping. In other studies, a delay in cord clamping of 30s resulted in improved iron status, fewer transfusions, and an association with improved neurodevelopmental outcomes.

Controversy still surrounds the use of erythropoietin (EPO) and erythropoiesis-stimulating agents. A Cochrane meta-analysis concluded that late administration of rhEPO (after the first postnatal week) reduced the number and volume of RCTs, but the clinical importance of this was considered marginal. In a second Cochrane meta-analysis comparing late with early (first postnatal week) administration of EPO, the authors reached similar conclusions and observed an increase in the risk of retinopathy of prematurity. They could not recommend early or late administration of EPO and suggested that future studies focus on methods for reducing donor exposure and phlebotomy losses.

Materno-fetal transfer of minerals, vitamins and iron mainly occurs in the last trimester of pregnancy therefore preterms become deficient rather easily. This fact, together with their higher requirements for growth and need to combat serious illness, makes adequate supplementation of vitamin B12, folate and iron important in preventing anaemia.

Conclusion

The introduction of a single donor programme for high-risk preterms would significantly reduce the number of donor units required by up to 65%. Furthermore, this study has shown that the provision of red cell aliquots of 50mls of blood would suffice and significantly reduce wastage in this limited resource.

References


12. Aher S, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2012 Issue 10

13. Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2006, Issue 3

Corinthia Group Prize in Paediatrics, 2013

The Corinthia Group Prize in Paediatrics for 2013 was awarded to Dr Jessica Pace, who obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Whilst offering our congratulations to Dr Pace, we would also like to congratulate all those who performed admirably during the undergraduate course in Paediatrics, some of whom were only marginally ‘pipped to the post’ by Dr Pace. In the accompanying photograph, Dr Pace is seen receiving a cheque for €233 from Professor Simon Attard Montalto, Head of Paediatrics, in the Medical School Museum. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.

Professor Simon Attard Montalto
Abstract
Notwithstanding the high rates of pertussis infant vaccination coverage in developed countries, \textit{Bordetella pertussis} infections are manifesting a changing epidemiological pattern of disease. Of notable concern is the rise of pertussis in adolescents and adults. This changing picture is largely attributable to waning immunity after natural infection or vaccination. The belief that pertussis is chiefly a childhood disease is a common misconception. A significant rise of pertussis cases in Malta in older age groups was recorded in 2011. The addition of an adolescent and/or an adult booster dose against pertussis should be strongly considered.

Key words: pertussis, infant, vaccination, immunity, adults.

Introduction
Pertussis (whooping cough) is a highly contagious, acute infection caused by the gram-negative bacterium \textit{Bordetella pertussis}. The classical clinical features of pertussis progress in stages and start with an irritating cough (catarrhal stage) which within 1-2 weeks becomes increasingly paroxysmal. The paroxysmal stage, which lasts for 2 weeks, is characterised by paroxysms of violent coughing that continue uninterrupted and may be followed by the characteristic inspiratory whoop and or post-tussive vomiting. After a period of violent paroxysms, the severity of the cough tapers off with an extensive convalescent period that may range between 2-6 weeks and in some cases may last up to 3 months.\textsuperscript{1,2}

Infants have the highest reported rates of illness.\textsuperscript{3} However, pertussis may affect persons of all ages\textsuperscript{4} and is increasingly being reported in adolescents and adults in many European countries (e.g. Austria, France, Germany) and in the USA irrespective of vaccination status.\textsuperscript{5-7} Global incidence of pertussis (mostly in developing countries) has been estimated at 48.5 million cases, with 295,000 deaths, per year.\textsuperscript{8}

Transmission of \textit{B. pertussis} occurs from person to person via aerosol or by direct contact with infected respiratory secretions. Secondary attack rates in non-immune households reach up to 90%.\textsuperscript{2,8} Even in countries where an effective childhood immunisation programme against pertussis is established, increasing rates of infection among adolescents and adults, as a result of waning of vaccine induced immunity, has been reported.\textsuperscript{6,8,9} In these cases, and in contrast to the pre-vaccine era, the manifestations are atypical, may be less severe and may lack the pathognomonic inspiratory whoop and/or post-tussive vomiting.\textsuperscript{10} (pertussis should be considered in the differential diagnosis of cough illness lasting more than 1-2wks).\textsuperscript{11} Furthermore, pertussis infections in adults and adolescents can often be asymptomatic.\textsuperscript{12-13}
Pertussis complications in adolescents and adults include pneumonia, rib fractures, and encephalopathy. One study reported that 31% of adults suffering from acute exacerbations of chronic obstructive pulmonary disease (COPD) were also infected with *B. pertussis*. The socioeconomic burden can be significant: a French study found that half of 77 health-care workers with suspected pertussis missed 5 days of work accounting for 42% loss in productivity.

In spite of the high rates of vaccination coverage in developed countries, the changing epidemiological pattern of pertussis, in particular its rise in adolescents and adults is a cause of concern. The belief that pertussis is chiefly a childhood disease is a common misconception. On the contrary, it is infected adolescents and adults who pose a transmission risk to non-immune infants. In this study we investigated changes in the trends of pertussis in Malta by comparing reported cases of pertussis in 2011 with the previous decade.

**Methods**

As a statutory notifiable disease the collection of pertussis data in the Maltese islands were dependent on notifications from hospital and community based medical practitioners. Pertussis data in the Maltese population, from 2001 to 2011, were extracted from the national database of the Directorate for Health Promotion and Disease Prevention (IDCU). The European Centre for Disease Prevention and Control (ECDC) definition criteria for pertussis was used to subdivide cases into confirmed cases (clinical compatible cases with laboratory confirmation), probable cases (clinical compatible cases with an epidemiological link) and possible cases (cases with a clinical compatible nature only). Notified cases that did not confirm with the ECDC definition were excluded from the national data base and not included in the study.

Chi-square test was used to analyse any differences between the notifications in 2011 and the previous decade while confidence intervals were calculated. All the yearly notified cases of pertussis in the previous decade of 2001-2010 were reviewed in the national database and reproduced for comparison (table I).

**Results**

In 2011 an increase in the number of pertussis cases in Malta was reported (Figure 1). Four clusters consisting of three clusters of 2 cases each and one cluster of 5 cases making up a total of 11 cases (9 laboratory confirmed, 2 epidemiologically linked) were reported. In addition 20 single notifications of pertussis were reported. Of the total number ($n=31$) of cases notified five cases were excluded from and 26 were included in the disease register according to the ECDC’s definition.

Serologically confirmed cases were those that registered significantly high pertussis toxin IgA and IgG as measured by ELISA. *Bordetella pertussis* culture or PCR were not performed because cases presented outside the necessary window period of two weeks post disease onset. (Tests were performed in Bioscientia Laboratories, Germany).

There was a definite rise in the number of confirmed reported cases in 2011 (14 confirmed cases: four clusters with 9 confirmed cases; while 5 were confirmed sporadic cases) and 12 probable and possible cases (14+12: $n=26$) as compared to the reported cases over the previous ten years (Table 1), that is 2001-2010 ($n=30$, with an average notification of 3/year [95% confidence interval: 1.95-4.04]). This means a greater than eightfold significant rise (Chisquare test with Yates correction 16.1, $p<0.0001$, 0.5% significance) in 2011 over the average yearly figure of the previous decade. For the calculation the figure of the mid-year population of Malta for the year 2011 was considered as the average population in that year (population 416,110), whereas the mid-year population in 2005 (population 404,962) was considered as the average Maltese population of the previous decade (2001-2010).

The average duration of symptoms at time of notification was 4.35 weeks while the range was 2-8 weeks. Out of all the notified cases (and excluding the epidemiologically linked cases in the clusters) ten cases (mean age 20.1yrs; range 2-40yrs) claimed to have received a pertussis vaccine (full vaccination status could not be verified since the question on previous immunisation was too generic), three were not vaccinated (age range 44–85 yrs) while six cases (mean age 45 yrs; range 20-70yrs) did not know their vaccination status.

All the cases presented between March and September with 69% (18/26) occurring in the three-month period between March-May 2011. Case gender distribution was almost equal (14 M:12 F).

In 2011 pertussis was more common in adolescents (age range: 10-14 years) and adults (age range 20-85). The reported cases in the previous decade (2001-2010) were mainly in children and to a lesser extent, in adolescents (Figure 1).
Table 1: Yearly notified pertussis cases during the period 2001-2010; *including 3 sporadic cases and two clusters of two persons each in 2005.

<table>
<thead>
<tr>
<th>Year</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005*</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

The pertussis incidence rate (all cases) in Malta during 2011 was 6.32/100,000 population whereas the average incidence rate in EU/EEA countries was 4.7/100,000 (range 0.2 (Cyprus) – 35.7/100,000 (Estonia)). These contrasting figures are limited by differences in vaccination policies, case definitions, reporting procedures and surveillance systems.

Discussion

Notable differences in the age groups of the reported cases can be observed (Figure 1). In 2011 pertussis was commoner in adolescents and adults as compared to the reported cases in the previous decade where pertussis occurred predominantly in children.

The reported incidence of pertussis is probably lower than the actual rates as under-reporting and under-recognition or mis-diagnosis in adolescents and adults are common. This is likely to be due to the altered clinical features of the disease in these age groups - as prolonged cough may be the only clinical feature present. Under-recognition may occur, some may present late while others may not present at all.

The limited local data, the possibility of an increased ascertainment of disease, a change in the diagnostic practice or a change in population characteristics and changes in disease susceptibility all confound the recent rise in pertussis cases in Malta. In addition, although four-yearly epidemic trends of pertussis have been reported elsewhere, these have not been observed in Malta; the national database does not reflect the true epidemiological picture over the years as it relies solely on notification from medical practitioners.

The Maltese National Immunisation Service (NIS) electronic database records National Health Service immunisation data as well as data of reported vaccinations from the private sector. The latter is marked by under-reporting and is thought to result in apparent lower national rates of vaccination as shown by the 3rd dose uptake of pertussis vaccine in figure 2.

In September 2010, the whole cell pertussis vaccine formulation recommended by the National Immunisation Schedule was changed to an acellular pertussis containing vaccine, with the first dose being administered at 6 weeks, the 2nd at 3 months and the 3rd at 4 months of age. Combination vaccines containing acellular pertussis had been previously available on the private market for a number of years. A fourth acellular pertussis vaccine dose was also introduced on the National Immunisation Schedule in 2010 as part of a combination vaccine (Diphtheria, Tetanus, Inactivated Polio, Haemophilus Influenzae type b and acellular Pertussis vaccine) for 18 month old toddlers. This explains the higher 4th dose vaccination notification rates from 2010 onwards, with the rates reported in previous years being from the private sector.
Despite high vaccination rates, *B. pertussis* infections have persisted as a consequence of waning vaccine-induced (lasting for 4-12 years) and naturally acquired immunity (lasting for 4-20 years). In the absence of further boosting, adolescents and adults (especially mothers) are likely to remain a reservoir of infection and play an important role in transmitting *B. pertussis* infection to incompletely immunised or unimmunised infants.

Current literature supports the addition of a single adolescent and/or an adult booster dose of pertussis vaccine. In some countries this is already being implemented following thorough country-specific evaluations of the epidemiology of pertussis. Other countries have considered administering booster doses to specific target groups such as new mothers, health care workers and adults (e.g. new parents) who are likely to have close contact with a non-immune or incompletely immune infant (<12 months) (cocoon vaccination strategy).

**Conclusions**

The increasing reports of pertussis in Malta in 2011 are of concern. A universal pertussis booster dose for adolescents and perhaps adults as well, is likely to reduce morbidity in adolescents and adults and protect susceptible infants through a reduction in transmission. Other specific groups, such as post-partum mothers can alternatively or concomitantly be targeted prior being discharged from hospital. However, feasibility and cost-effective analyses are essential.

A switch from the low dose diphtheria, tetanus and inactivated polio vaccine (dT-IPV which is administered at 16 yrs of age on the national immunisation schedule) to a similar combination vaccine that includes acellular pertussis (dTap-IPV) for adolescents and adults could be one simple measure. Other authors have recommended a regular dTaP booster vaccine every 10 years for adults; however this poses a substantial resource challenge.

There is also the need for introducing more sensitive laboratory methods, like molecular techniques, to improve the diagnosis of pertussis, however late notifications are likely to hinder this. In addition, doctors need to become more aware of the possibility of pertussis amongst adults and adolescents especially in individuals with a persistent cough.

Early accurate diagnosis is necessary to control transmission of the disease and enable prompt antibiotic treatment. The atypical presentations indicate that clinical diagnosis is not likely to be enough as it was in the pre-vaccination era and regular laboratory testing is essential.

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References


