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All that glitters …

Victor Grech

Introduction

The full human genome sequence (via the Human Genome Project) was mapped and published 15 years ago, a 10 year project that cost circa $30bn.[1] Since then technological advances and cheap computing power have markedly accelerated genomic sequencing at a reduced cost, to under $500. For example, the company Oxford Nanopore has taken sequencing to point-of-care status by developing a hand-held reader that can sequence genetic material in minutes.[2] The applications will not be just for healthcare but also, for example, to establish the provenance of foodstuffs, the presence of dangerous microbes and crime scene DNA analysis.[2]

This is possible as the Nanopore reader squeezes individual DNA strands though a nanopore (an individual hole) and then proceeds to read the DNA sequence electrically. It has been speculated that within the next 10 years, everyone will be genetically sequenced at birth with the corollary that preventative steps can be taken early vis-à-vis genetic predispositions to diseases.[2]

The combination of this type of data analysis, along with other variables, may further improve the prevention, diagnosis and treatment of diseases. For example, researchers at Brigham and Women's Hospital in Boston, Massachusetts used such data combinations to highlight an increased risk of developing type 2 diabetes among shift workers.[3] A concise and elegant summary by Janssens and van Duijn states:

> Genomics research will substantially increase our understanding of disease pathogenesis, particularly through the identification of novel disease pathways and new biomarkers … one of the major promises is that these advances will lead to personalized medicine, in which preventive and therapeutic interventions for complex diseases are tailored to individuals based on their genetic profiles … Yet, the etiology of complex diseases is essentially different from that of monogenic diseases, and hence translating the new emerging genomic knowledge into public health and medical care is one of the major challenges for the next decades.[4]

What if?

Science fiction has explored the "what if" scenario of universal genetic profiling, and the dystopian film GATTACA does precisely this, with the added twist of the additional availability of embryo genetic selection so as to ensure that offspring possess the best hereditary traits of their parents.[5]

The film commences with a famous quote: "As night-fall does not come at once, neither does oppression...It is in such twilight that we all must be aware of change in the air - however slight - lest we become victims of the darkness" by Justice William O. Douglas (1898 –1980), the longest-serving justice in the history of the Supreme Court.[6]

In this fictional, not very distant future, universal genetic profiling at birth had led to the creation of a genetic database that is used to classify individuals. Individuals may be antenatally enhanced as explained by a geneticist to a prospective couple:

> You've already specified blue eyes, dark hair and fair skin. I have taken the liberty of eradicating any potentially prejudicial conditions - premature baldness, myopia, alcoholism and

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> addictive susceptibility, propensity for violence and obesity … You want to give your child the best possible start. Believe me, we have enough imperfection built-in already. Your child doesn't need any additional burdens. And keep in mind, this child is still you, simply the best of you. You could conceive naturally a thousand times and never get such a result…Is there any reason you'd want a left-handed child? … Some believe it is associated with creativity, although there's no evidence. Also for sports like baseball it can be an advantage…he's going to be at least a head taller than you.

The parents want even more, the imposition of what is to them, a normative heterosexual inclination: "we were hoping he would get married and have children. We'd like grandchildren." The geneticist reassures them "I understand. That's already been taken care of." He also however adds:

> Now you appreciate I can only work with the raw material I have at my disposal but for a little extra...I could also attempt to insert sequences associated with enhanced mathematical or musical ability…I have to caution you it's not fool-proof. With multi-gene traits there can be no guarantees.

In this future, genetic discrimination is illegal, but genotype profiling is still used to identify the genetically enhanced for professional employment, while normal conceptions are relegated to menial jobs, and this is precisely what the storyline revolves around, along with the possibility that the individual may actually exceed his/her expected potential. This is evidenced in GATTACA's poster with the statement that "there is no gene for the human spirit" (figure 1)

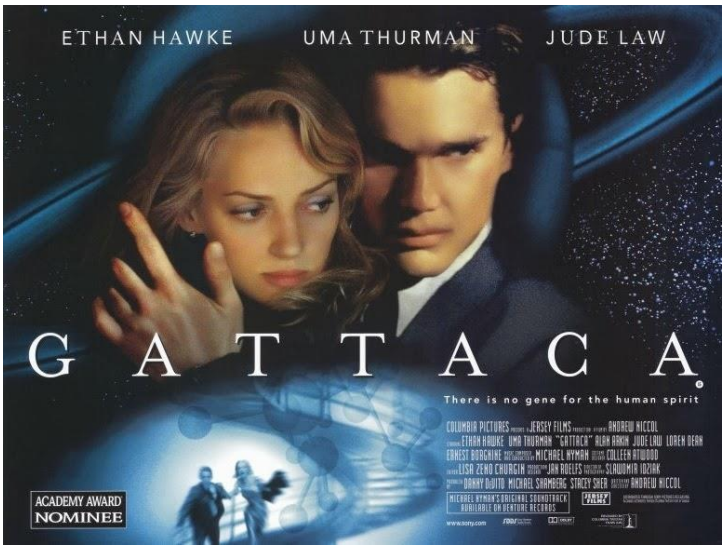
Inevitably

One can easily take this further and imagine the repercussions, say, of individual insurance prospects, both life and health, were disease predisposition made available to insurance companies. Discrimination would be almost inevitable, with highly negative personal economic consequences, not only in insurance, but also in occupation and so on. Truly, "before implementation in health care, all applications of genetic profiling need appropriate evaluation to assess whether the predictive value is sufficient e.g. to improve population health or to improve the efficiency or quality of health care".[4]

Furthermore, the active implementation of genetic antenatal embryo changes no longer lies solely within the demesne of science fiction. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology forms the basis of a technique that can specifically change genes within organisms.[7-8] The dystopia that is GATTACA thus lies within our grasp.

Therefore in this field too, all that glitters is not gold, and once this particular genie emerges from its bottle, it will be well-nigh impossible to avoid these consequences.

Figure 1



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Cover Picture:
"Valletta Nocturne'
Oil on canvas with palette knife
By Victor Grech

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Original Article

A review of amputation and revascularisation rates in a small European state

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Abstract

Background: Until 2007 vascular services in Malta were provided by general surgeons with a vascular interest. In late 2007 a vascular specialist was recruited to contribute to the service. This catered for a gradual transfer of services to a pure vascular specialist service in 2014.

The aim was to assess the impact of the introduction of vascular specialist services on lower limb major and minor amputation rates and open revascularisation procedures in Malta.

Methods: This is a retrospective analysis of prospectively collected data. Data from the Hospital annual surgical operation reports and the Vascular Database was analysed between 2002 and 2014. Data was analysed by time period (Period 1: 2002-2007 – no vascular specialist service; Period 2: 2008-2013 - partial vascular specialist service; Period 3 – January to December 2014 complete vascular specialist service).

Results: There was a significant drop in the average rate of major amputations/year between Period 1 and Period 2 (120 vs 96; *p=0.008*) and between Period 1 and Period 3 (120 vs 64; *p<0.001*). A significant increase in minor amputations/year between period 1 and period 2 (102 vs 242; p<0.001) and between period 1 and period 3 (102 vs 449; *p<0.001*) was noted. There was significant increase in open revascularisation rates between period 1 and period 2 (21.5 vs 73.2; *p<0.001*) and between period 1 and period 3 (21.5 vs 144; *p<0.001*).

Conclusion: The employment of vascular specialists can lead to a significant increase in lower limb open revascularisation rates and a concomitant significant reduction in lower limb major amputation rates.

Key words

limb salvage, amputations, blood vessel prosthesis implantation, diabetic angiopathies, peripheral vascular diseases

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Introduction

The availability of specialised vascular services has increased dramatically over the last decades throughout Europe and around the world. There are however many areas where patients with vascular problems are still treated by general surgeons with or without a vascular interest. This may be due to limited financial or human resources and occasionally because of geographical isolation and logistics. It is generally agreed that patients with vascular problems treated by vascular specialists have better outcomes. It has been shown that in parts of the United States, the supply of more vascular specialists resulted in an increase in the rate of major bypass procedures and a reduction in lower limb amputations.[1] Indeed significant regional variations exist in major amputation rates even within the same country as shown in a study from the United Kingdom[2] which could be in part explained by the different access to vascular

services. In other countries differences in outcomes have been related to socioeconomic groups [3-4] or ethnicity[5] which may in turn be related to the level of access to specialised vascular care.

The impact of revascularisation on major amputation rates has been debated and evidence has been conflicting with some publications reporting a correlation between revascularisation rates and amputation rates[6] while others have failed to demonstrate any clear correlation.[7-8]

Malta is an island state in the Mediterranean, an EU member state since 2004 with a population of 417,432.[9] There is one major referral hospital, St Luke's Hospital which migrated to Mater Dei Hospital, Msida in October 2007. Malta has a national health service which is free at point of care with all services from primary to tertiary care being free and funded by central government. The hospital provides both acute and elective vascular care for the whole country.

The prevalence of diabetes in Malta was reported as 10% of the population in 2005[10] which is one of the highest in Europe. The World Health Organisation estimated that the total number of diabetics in Malta in 2000 was 39,000 and predicts that by 2030 this figure will reach 57,000.[11] The 2005 census had estimated the national population to be 404,962 while in the previous census held in 1995 this was 378,132. No census was held in 2000 but the estimated population in the year 2000 based on the 1995 and 2005 census figures was around 391,500. Using this latter figure as the denominator the prevalence of diabetes in the Maltese population in 2000 was 9.96%. The UK average prevalence in 2011 was reported as 4.45% while in Germany this is reported to be 7.7%.

Until September 2007 patients with vascular disease were cared for by general surgeons with a vascular interest who provided on call cover on a 1 in 3 basis. Their vascular work was in addition to their general surgery commitment. In August 2007 a vascular surgeon who had trained and become a Consultant in a UK vascular unit, was appointed to the service and as from September 2007 started to contribute to the vascular service. The vascular surgeon's clinical commitment was solely in vascular disease. The national vascular on call cover as from September 2007 was provided by the vascular surgeon on alternate weeks and by one of the three general surgeons with a vascular interest on the other week. This meant that as from September 2007 50% of the workload was taken by the vascular surgeon while the other 50% was shared between the three general surgeons with a vascular interest. In January 2014 another vascular surgeon was recruited to the service and all patients with vascular disease were treated by a vascular team. The three general surgeons with a vascular interest withdrew from the vascular on call rota and the vascular service. All diabetic foot related complications were treated by vascular specialists during this last period irrespective of whether the main pathology was ischaemia. Even cases where there was no significant peripheral arterial disease but where diabetic foot infection, usually in the context of peripheral neuropathy, was the main threat to the limb were cared for by vascular specialists.

The aim of this study was to assess the impact of the introduction of a specialist vascular service on lower limb major and minor amputation rates and open revascularisation procedures in a population with such a high prevalence of diabetes.

Materials and methods

This is a retrospective analysis of prospectively collected data over a period of 13 years between January 2002 and December 2014. Data was obtained from two main sources. The first source was the Annual Hospital Surgical Operation reports published by the Medical administrator's office for the main referral hospital for the years 2002-2014. The second source was the Vascular Database held by the vascular unit at the same hospital. The vascular unit was set up in late 2007 and complete data is available since the database was set up (2008-2014). The vascular database recorded all hospital activity performed by the vascular specialists.

The data collated from the Annual Hospital Surgical Operation reports included the total annual number of major lower limb amputations and the types of amputation (transfemoral, transtibial, other), the total annual number of minor amputations and the types of amputation (toe amputations or transmetatarsal and other foot amputations) and the total annual number of open revascularisation procedures (including aortofemoral, axillofemoral, common femoral endarterectomies, infrainguinal bypass procedures). The Annual Hospital Surgical Operation reports included procedures done by all surgeons working

in the hospital. The data is collected from the register kept in each operating theatre in the hospital which documents the case done and which is countersigned by the operating surgeon. The Annual Hospital Surgical Operation reports are based on this data which is anonymised and therefore information about mortality is not available. The data available relates to the number of each type of procedure performed. The data is inputted in real time including the time at which the patient enters and leaves theatre. The only possible inaccuracies in this data may relate to any errors in the type of procedure documented by the surgeon although the probability of errors in the type of procedure performed is low.

The data collated in the Vascular Surgical Database included all the procedures performed by the vascular specialists only. The data included the total annual number of major amputations and the type, the total annual number of minor amputations and the type as well as the total annual number of open revascularisation procedures performed by the vascular specialists. Data is also collated in this database on risk factors including diabetes, renal disease, smoking, hyperlipidaemia. cardiac disease and carotid status based on the recommended standards for reports dealing with lower extremity ischemia issued by the Society for Vascular Surgery.[12] Mortality data can be derived for the cohort of patients in this group but mortality data was not reported in this paper as this information was only available for data obtained through the vascular surgical database but not through the Annual Hospital Surgical Operation reports.

Data was analysed in two ways. Firstly the data was analysed by time period. Period 1 covered the six year period between 2002 and 2007 during which the vascular service in the hospital was provided by general surgeons with a vascular interest. Period 2 covered the six years between 2008-2013 during which half the workload was covered by the vascular specialist and the other half by the same general surgeons with a vascular interest. Period 3 covered between January to December 2014 when all patients with vascular disease were treated by a vascular team with minimal involvement of the general surgeons with a vascular interest. All the data collated in Period 1 was compared to the data in Period 2 irrespective of the type of consultant providing care. Data for period 2 (2008-2013) was also analysed according to the type of caring consultants providing care (vascular specialist or general surgeons with vascular interest).

All teams (whether vascular or general with a vascular interest) practised in the same institution and had equal access to all resources including endovascular interventions, access to interventional radiologists, multidisciplinary team meetings, imaging facilities, theatre facilities and patient bed availability. All conditions in both groups were identical (same institution, same facilities, same time period) with the only variable between the two groups being the type of consultant.

By comparing the data from the vascular database and the data from the Annual Hospital Surgical Operations reports it was possible to determine how many procedures were performed by the vascular specialists and how many by all other surgeons during the study period.

Independent t-test was used to compare means for the three study periods and Chi square test was used to analyse groups based on caring consultant (vascular surgeon or general surgeons with a vascular interest). SPSS version 22 statistical software package was used.

Results

Major amputations

Between January 2002 and December 2014 a total of 1366 major lower limb amputations were performed. Figure 1 shows the total number of major amputations performed each year during this time period. During Period 1 (2002-2007) 725 major amputations were performed giving an average of 120 major amputations/year. During Period 2 (2008-2013) the total number of major amputations was 577 giving an average of 96/year while in Period 3 (2014) 64 major amputations were performed. There was a significant reduction in major amputations between Period 1 and Period 2 ($p=0.008$). 218 less major amputations were performed during period 2 compared to period 1. There was an even more significant reduction between Period 1 and Period 3 ($p<0.001$).

The peak in major amputations performed was reached in 2003 when 133 were done. During the last year of the study (2014) 64 major amputations were performed, constituting a 51.8% drop in major amputations between 2003 and 2014.

***Figure 1**: Major amputations: number of total, transfemoral and transtitibial amputations performed between 2002-2013.*

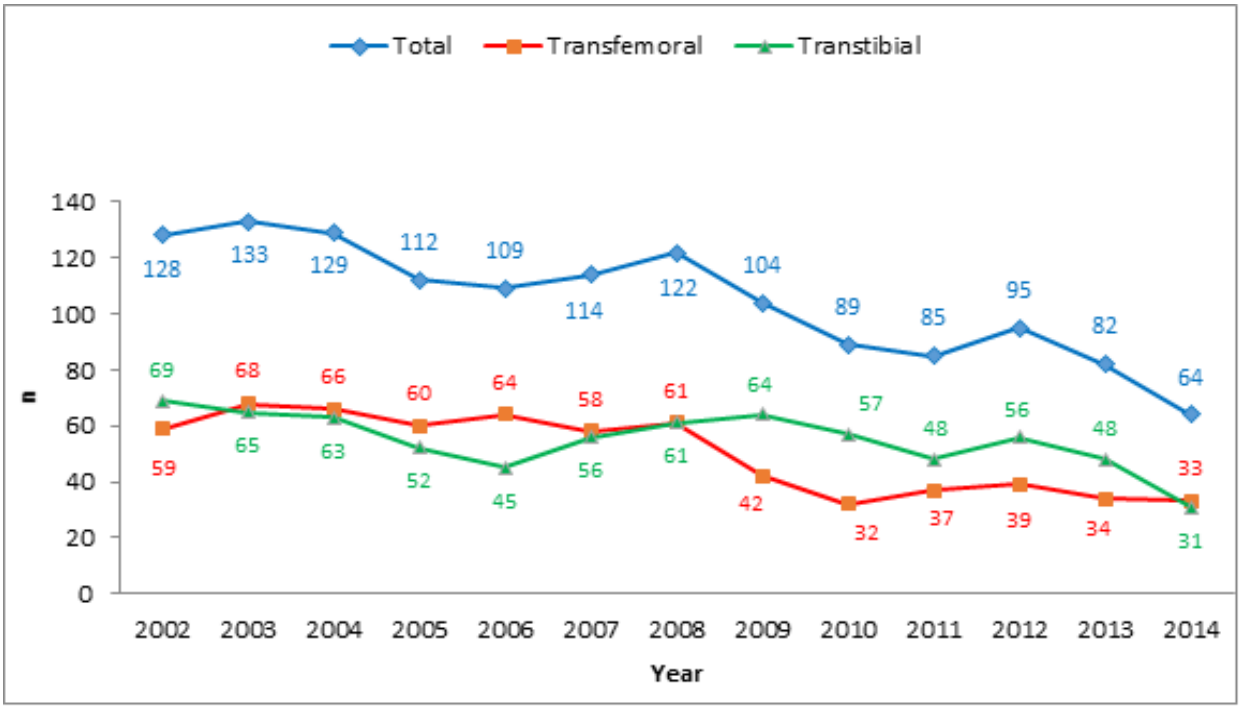
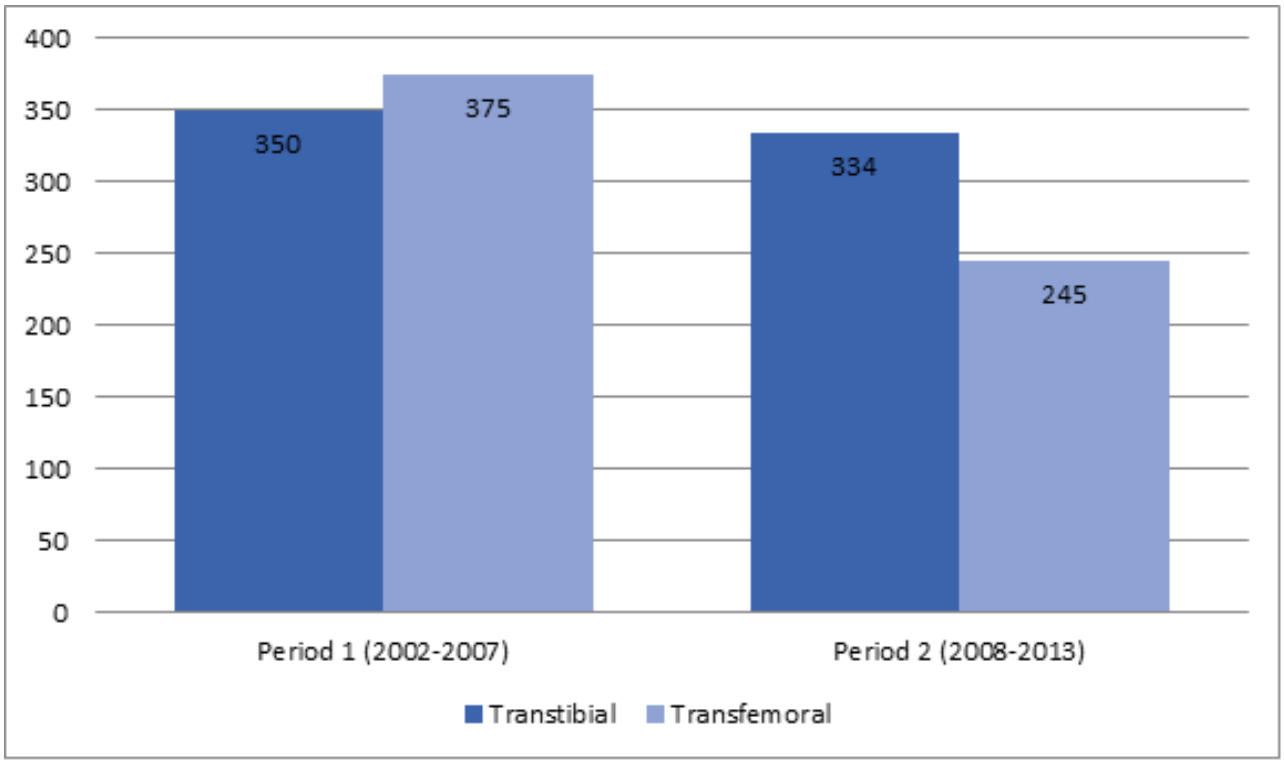


***Figure 2**: Major amputation levels during period 1 (2002-2007) and period 2 (2008-2013)*



The peak during period 1 reached in 2003 is equivalent to a rate of 33 major amputations per 100,000 population (based on 2005 census population figure). The trough reached in 2014 equates to 15.8 major amputations per 100,000 population (based on 2011 census population).

Figure 2 shows the types of major amputations performed during periods 1 and 2. During the whole period 653 transfemoral amputations and 713 transtibial amputations were performed. This equates to a transtibial to transfemoral ratio of 1.15 for the whole period. During period 1, 375 transfemoral amputations and 350 transtibial amputations were performed equating to a transtibial to transfermoral ratio of 0.93. During period 2, 245 transfemoral and 334 transtibial amputations were performed. This equates to a transtibial to transfemoral ratio of 1.36. The difference between the two periods in level of amputation was statistically significant (p<0.001).

Minor amputations

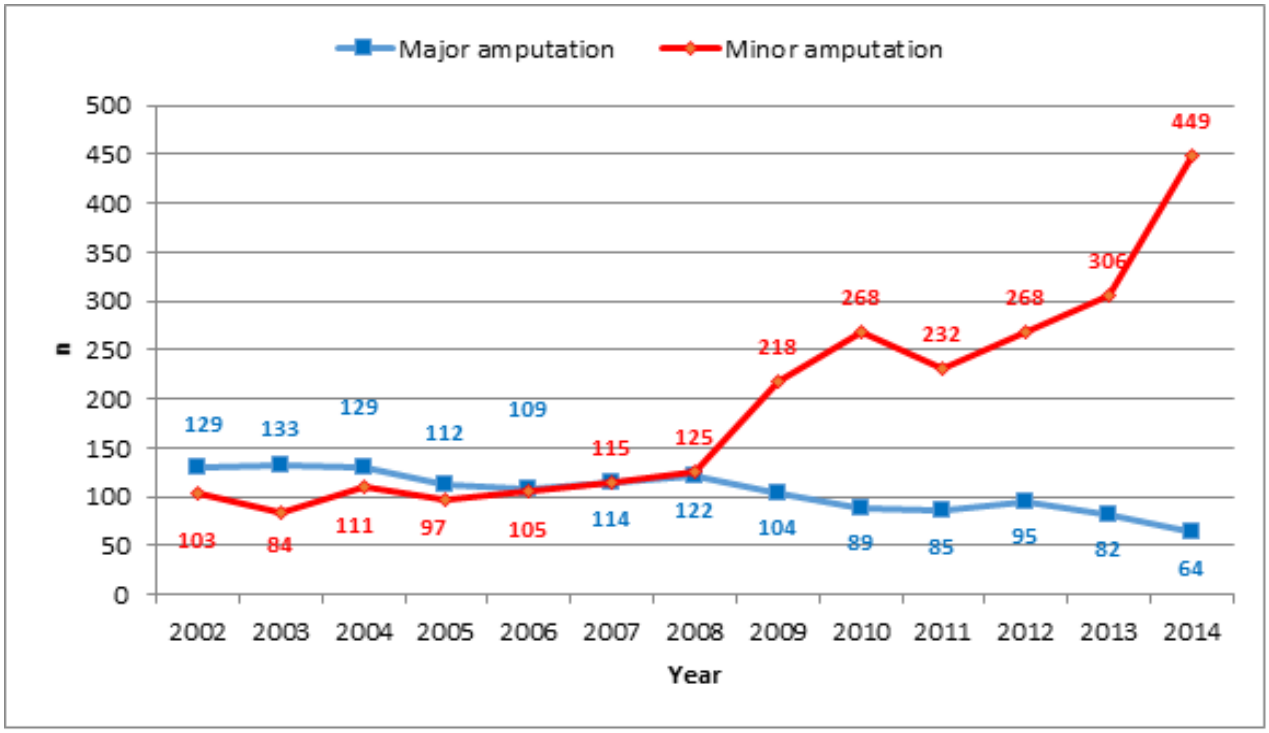
The total number of minor amputations during this period was 2521 with an average of 102/year during period 1 and 242/year in period 2 accounting for a 137% increase. In period 3, 449 minor amputations were performed constituting a 340% increase (p<0.001). The peak during period 1 was 115/year in 2007 while the peak in period 2 was 306/year in 2013 increasing to 449 in period 3.

The vast majority of foot amputations were toe amputations at the level of the proximal phalanx or metatarsal. Only a small proportion were transmetatarsal or higher foot amputations. During period 1 a total of 67 transmetatarsal or higher foot amputations were performed while in period 2 this increased to 142 (112% increase). The mean annual rate of transmetarsal amputations increased significantly from period 1 to period 2 (11.33 vs 23.5; *p=0.01*) and remained steady during 2014 (23/year)

The number of toe amputations in period 1 was 547 compared to 1316 in period 2 (140% increase). Again there was a significant increase in mean toe amputations performed annually between period 1 and period 2 (91 vs 219; *p<0.001*) and a further significant increase to period 3 (91 vs 449; p<0.001). The increase from period 2 to period 3 was also significant (*p=0.01*).

Figure 3 shows the inverse relationship between minor amputations (below ankle) and major amputations (above ankle) over the 13 years of the study.

***Figure 3**: Number of Major (above ankle) and minor (below ankle) amputations performed between 2002 and 2014*



Revascularisation procedures

712 open revascularisation procedures were performed in total. Of these 439 (61.6%) were performed during period 2. During period 1 a mean of 21.5 procedures were performed per year, during period 2 this increased to 73.2/year (240% increase; *p<0.001*) and increased further to 144/year in Period 3. Figure 4 shows the number of open revascularisation procedures during the study period.

Figure 5 shows the inverse relationship between revascularisation and major amputation rates.

Data analysed by type of caring surgeon Period 2 (2008-2013)

During period 2, 577 major amputations were performed of which 212 (36.7%) were performed by a vascular specialist while 365 (63.3%) were performed by the general surgeons with a vascular interest.

During period 2, 439 open revascularisation procedures were performed in total. Of these 359 (81.8%) were performed by the vascular surgeon compared to 80 (18.2%) by all 3 general surgeons with a vascular interest.

With regards to minor amputations a total of 1457 were performed during period 2 of which 1023 (70.2%) were performed by the vascular surgeon compared to 434 (29.8%) by the general surgeons with a vascular interest.

The total number of open revascularisation, minor and major amputations performed by the vascular surgeon in Period 2 were 1594 (64.5%) while for the general surgeons with a vascular interest this was 879(35.5%) during period 2.

Figure 6 shows the total number of major amputations and revascularisation procedures performed by caring consultant type. The ratio of major amputation to revascularisation for the general surgeons with a vascular interest was significantly higher than for the vascular surgeon (4.56 vs 0.59; *p<0.001*). The vascular surgeon performed 154 transtibial amputations and 58 transfemoral amputations during period 2 giving a transtibial to transfemoral ratio of 2.66. The general surgeons with vascular interest performed 180 transtibial and 187 transfemoral amputations giving a transtibial to transfemoral ratio of 0.96. (*p<0.001*)

Figure 4: *Open revascularisation procedures performed between 2002 and 2014 by General surgeons with a vascular interest and vascular specialists*

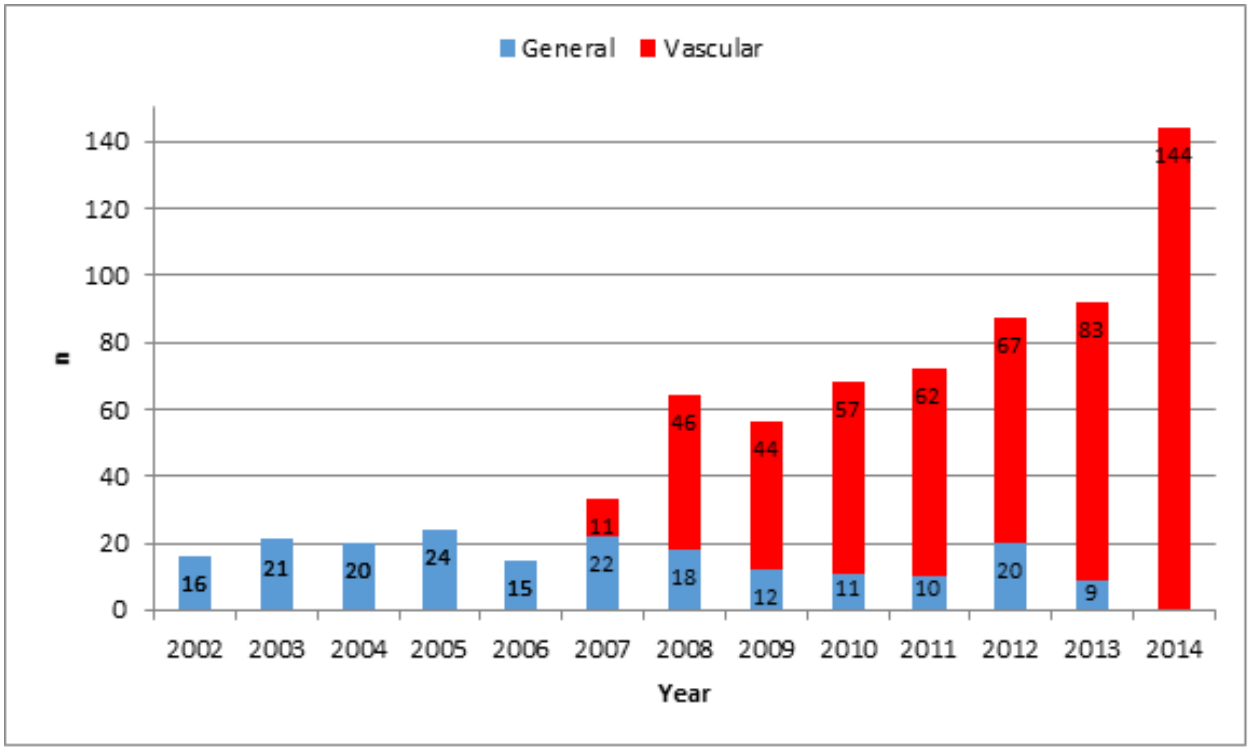


***Figure 5**: Relationship between major amputations and open revascularisation procedures between 2002 and 2013*

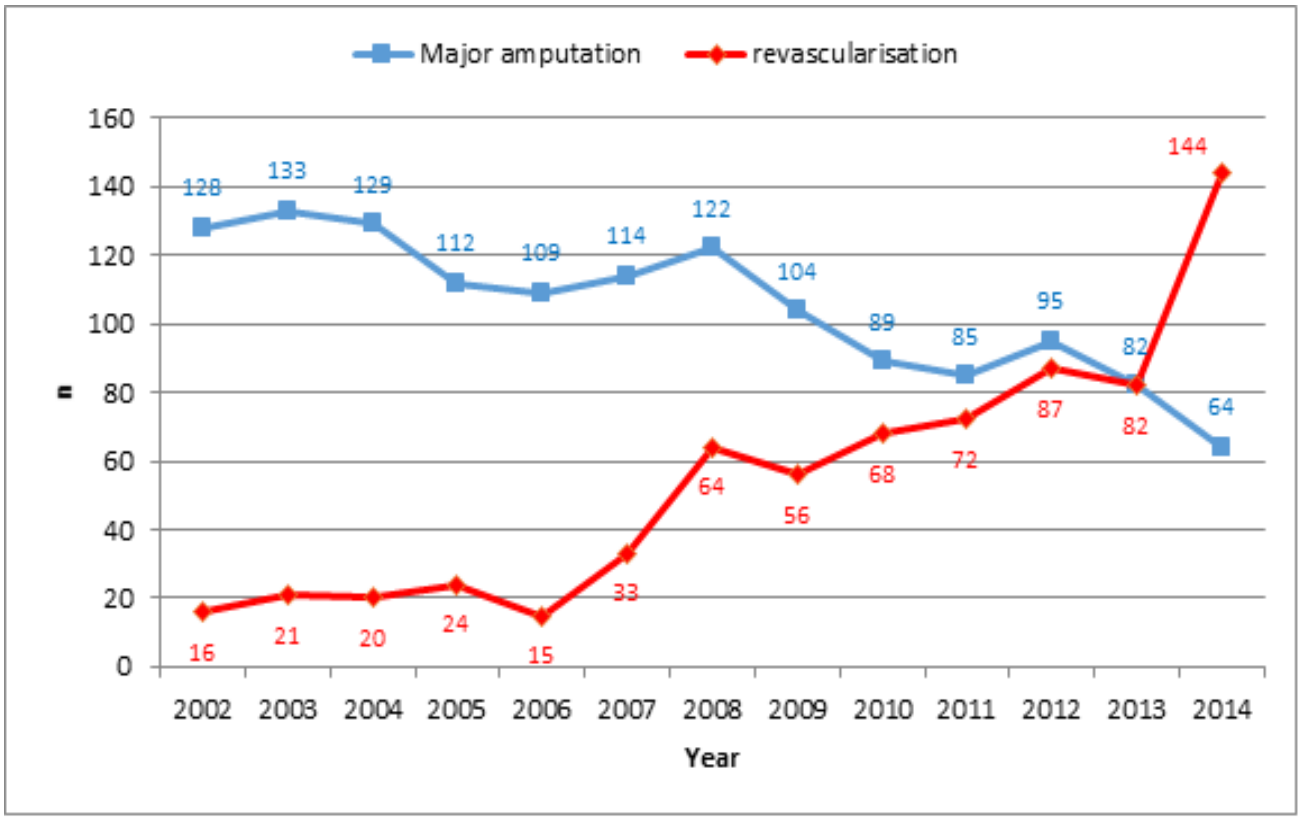
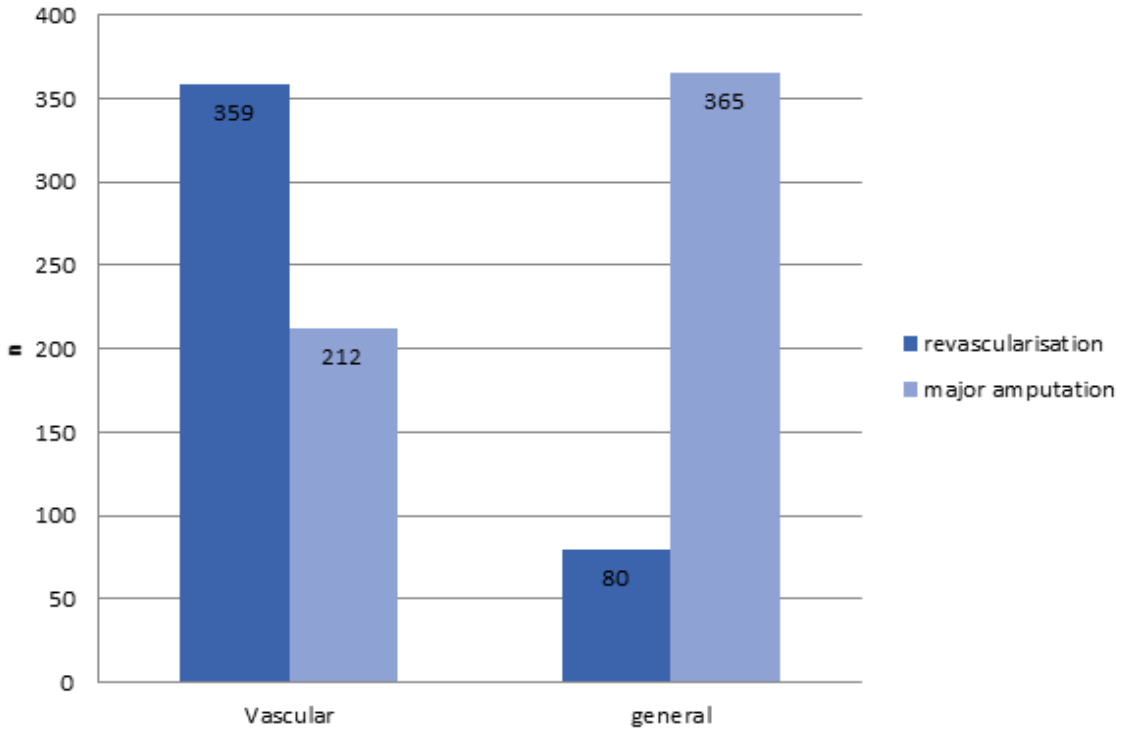


***Figure 6**: Open revascularisation and major amputations performed by vascular specialist and general surgeons with vascular interest during period 2 (2008-2013)*



Discussion

This study shows that the introduction of vascular specialists can have a very significant impact on major amputation rates and revascularisation rates. The data suggests that the addition of a vascular specialist to the existing consultant body led to a very marked increase in open revascularisation and minor amputation rates as well as a marked reduction in major amputations. The practice of the general surgeons with a vascular interest would necessarily include other surgical procedures limiting their time dedicated to vascular surgery.

Once the service was offered by vascular surgeons only there was a further significant increase in revascularisation and a significant reduction in major amputations. In this study a 51.8% reduction in major amputations occurred within 7 years of recruitment of vascular specialists. This is despite the fact that the size of the population increased significantly and the number of diabetics who are the main risk group for major amputation had also risen during the course of the study.

The level of major amputation shifted from a majority of transfemoral amputations during the period during which the general surgeons provided care, to a majority of transtibial amputations once vascular specialists started to contribute to the service. The total number of both transfemoral and transtibial amputations decreased but with a significantly bigger reduction in transfemoral amputations.

This study has also shown that the outcomes for patients cared for by vascular specialists differ from those of patients taken care of by general surgeons with a vascular interest. The revascularisation rate is significantly higher and the major amputation rate is significantly lower for those under the care of a vascular surgeon. In addition, for those requiring major amputation it is far likelier for patients to undergo a transtibial rather than a transfemoral amputation. This translates into significantly lower operative mortality rates and better rehabilitation rates although mortality data was not presented in this paper.

The differences observed between the outcomes of patients under the care of different types of consultant in this study is likely to be due to the type of caring consultant since there were no other obvious variables. The different teams worked in the same institution and cared for the same population during the same time period. The facilities available were identical for both groups. The selection of patients to the two groups was random as referrals of patients and acute admissions were on an alternate week arrangement between the vascular consultant and the 3 general surgeons with a vascular interest during Period 2. Most other studies have compared a study group with a historical group treated in a previous time period. The conditions for this study allowed a real time comparison of outcomes of patients cared for by different types of consultant within the same patient population during the same study period in the same institution.

The improvements noted in major amputation rates in Period 2 and again in Period 3 are likely to be due not only to the increase in revacularisation rates but also due to other developments during this period including an improvement in the endovascular revasularisation service, better organisation and access to clinics, development of multidisciplinary diabetic foot clinics, improvements in referral pathways and other changes brought about by recruitment of vascular specialists.

One of the limitations of the study is that no data was available about the total number of patients treated by both types of consultant. Having this data available would have given a clearer idea about the difference in approach (conservative vs interventional) between the two groups. Furthermore no overall mortality and morbidity figures were available for patients treated by both groups and hence outcomes for conservatively and actively treated patients cannot be surmised. This data would have been useful in comparing the composite endpoint of amputation free survival between the cohorts of patients treated by different consultant types. Another limiting factor is that no data is available about the risk factors of patients in the group treated by the general surgeons with vascular interest.

Conclusions

The cost of major amputations is significant and there is clear evidence that revascularisation is cost effective and results in cost savings to the health service.[13] The vast majority of patients requiring major amputations are often diabetics.

The projected increase in the prevalence of diabetes together with an aging population around the world suggests that the demand for vascular services is likely to increase. The evidence provided by this study, implies that training, recruiting and retaining vascular specialists particularly in geographical areas with a high prevalence of diabetes is a sound investment. The findings of this study indicate that recruitment of vascular specialists may be an effective way of increasing open revascularisation and reducing major amputation rates with the added benefits limb salvage provides to society.

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Original Article

Can the inevitable be prevented? – An analysis of loss to follow-up among grown-ups with congenital heart disease in Malta

Maryanne Caruana, Oscar Aquilina, Victor Grech

Abstract

Aims: To investigate the prevalence of loss to follow-up, factors predisposing to loss to follow-up and the outcome of recall into specialist care among grown-ups with congenital heart disease (GUCH) of moderate or severe complexity prior to the introduction of formal transition in Malta.

Methods: Medical documentation for all live patients with tetralogy of Fallot, aortic coarctation/interrupted aortic arch, partial and complete atrioventricular septal defect, Fontan-type circulation and transposition of the great arteries in our institutional database aged ≥16 years was analysed to determine follow-up status. Patients lost to follow-up were recalled through a postal appointment. Ordinal logistic regression was used to analyse the effect of gender, CHD complexity, consistency of paediatric cardiology follow-up during childhood, number of cardiac surgical/interventional procedures and use of long-term cardiac medications on loss to follow-up.

Results: Forty-one of 187 patients (21.9%) (27 males; 34 with moderate disease) had been lost to follow-up. Limited paediatric cardiology input (OR, 5.08; 95% CI, 1.77-14.63) (p=0.003), ≤1 surgical/interventional procedures (OR, 3.34; 95% CI, 1.09-10.26) (p=0.035) and no long-term cardiac medications (OR 7.34; 95% CI, 1.74-31.02) (p=0.007) were associated with higher risk of loss to follow-up. A positive response to recall was obtained from 33/41 (80.5%) patients. Significant cardiac morbidity was found in 5/33 (15.2%) patients upon reassessment.

Conclusions: Loss to specialist follow-up occurs even in health systems with little perceived barriers to medical care. Consistent specialist input during all stages and patient and family education through formal transition can help ensure a smoother transfer to GUCH care.

Keywords

Congenital Heart Defects; Lost to Follow-up; Transition to Adult Care

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Introduction

Major advances in cardiac surgery and transcatheter interventions have made it possible for most children born with congenital heart disease (CHD) to survive into adulthood.[1-3] However, complete cure is seldom achieved and lifelong specialist follow-up is required to allow early detection and timely management of significant recurrent or residual structural lesions and arrhythmias as these patients grow older.[4] Several lesion-specific guidelines containing indications on the nature and frequency of long-term follow-up for these patients have been published.[5-7] Lapses of care resulting from loss to follow-up represent a major set-back in this surveillance process and can have a negative impact on long-term outcomes.[8-9]

The incidence of CHD in Malta is 8/1000 live births, which is similar to that in other European

countries.[10] Transfer of care from paediatric to adult services across all specialties takes place at the age of 14-16 years. Virtually all congenital cardiac surgery on children and adults is carried out in overseas tertiary referral centres, in the United Kingdom, through a bilateral national health service agreement, while a number of structural cardiac interventions are carried out locally by visiting specialists. A structured paediatric cardiology service started operating in the main teaching hospital in the early 1990s. A Grown-Up Congenital Heart disease service was set up a few years later, while a formal transition process was instituted at the end of 2015. Up to the time of writing, there was no clinical nurse specialist cover for paediatric cardiology, transition or GUCH clinics.[11]

The aims of this study were (a) to determine the prevalence of loss to GUCH follow-up (b) to investigate potential factors predisposing to loss to follow-up and (c) to analyse the outcome of an exercise in recall into GUCH care in a cohort of Maltese adult patients with CHD of moderate or severe complexity in the period preceding the introduction of a formal transition process.

Methods

(a) Study cohort and prevalence of loss to GUCH follow-up

Five specific congenital cardiac lesions of moderate or severe complexity – (i) tetralogy of Fallot (TOF), (ii) aortic coarctation and interrupted aortic arch (CoA/IAA), (iii) partial and complete atrioventricular septal defects (AVSD), (iv) univentricular physiology with Fontan-type palliation (UVH-Fontan), (v) transposition of the great arteries (TGA) with arterial or atrial switch repair - were chosen arbitrarily for inclusion in this study, based on the well-established notion that all these lesions warrant regular long-term specialist follow-up.[5-7] A query for each of these lesions as the primary diagnosis was run in our institutional congenital cardiac database (MAPCAD)[3,12] at the end of 2013, among Maltese subjects born before end December 1997 (and thus aged 16 years or over by time of data extraction). Following this initial query, only live subjects whose complete medical documentation could be traced were subsequently included. Non-Maltese nationals that might have entered the congenital cardiac system upon relocating to the islands were purposefully excluded to avoid the potential bias introduced by differences in access to medical care. The study protocol was approved by the University of Malta Research Ethics Committee and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Clinical details and follow-up records were obtained from hospital paper notes and digital appointment systems in use at our institution. Loss to GUCH follow-up was defined as lack of written or digital documentation attesting to ongoing clinical encounters within the GUCH service as of the age of 16 years.

(b) Investigation of potential factors predisposing to loss to GUCH follow-up

The potential impact of five factors – (a) patient gender (b) CHD complexity (c) paediatric cardiology follow-up during childhood (d) number of cardiac surgical/interventional procedures (e) use of long-term cardiac medications – on loss to GUCH follow-up were investigated. CHD complexity was classified in line with the recommendations of Task Force 1 of the 32nd Bethesda Conference.[4] The term "paediatric cardiology follow-up during childhood" referred to significant input by a local or visiting paediatric cardiologist in the management of CHD up to the age of transfer to adult care, and was classified as 'limited' or 'regular'. "Surgical/interventional procedures" refers to any open surgical procedure or transcatheter intervention undertaken to repair or relieve the original congenital defect and any important residual or recurrent lesions related to it but excluded diagnostic cardiac catheter studies. This term also included electrophysiological procedures and the implantation of a permanent pacemaker or implantable cardioverter-defibrillator for the management of significant arrhythmias. "Long-term cardiac medications" refers to any medications being used for the management of ventricular systolic and/or diastolic dysfunction, antiarrhythmic drugs, antiplatelet and anticoagulant agents and antihypertensive medications.

(c) Analysis of exercise of recall into GUCH care

All subjects that had been lost to follow-up were recalled to GUCH clinic through a postal appointment as per our institution's outpatient policy, with a second appointment given in case of a negative initial response. The responses to recall and cardiac morbidity at time of reassessment were

obtained from the hospital digital patient management systems and medical notes. The term "reassessment" refers to the GUCH clinic visit and subsequent imaging, functional testing and arrhythmia assessment triggered by the cardiologist. "Significant cardiac morbidity" at time of reassessment refers to a significant structural lesion, impairment of functional status or arrhythmias requiring a prompt surgical, percutaneous or electrophysiological intervention or change in medical management.

(d) Statistical methods

Descriptive statistics included proportions for categorical variables and mean ± 1 standard deviation for continuous variables. Ordinal logistic regression was used to generate odds ratios (OR) for loss to GUCH follow-up based on patient gender (male vs. female), moderate vs. severe lesion complexity, limited vs. regular paediatric cardiology follow-up, ≤1 vs. >1 surgical/interventional procedure and no vs. on long-term cardiac medications. All analyses were performed using SPSS 21 (IBM® SPSS® 21, SPSS Inc., Chicago IL, USA). Statistical significance was defined as $p<0.05$.

Results

(a) Study cohort characteristics and prevalence of loss to follow-up

The initial database query returned 211 subjects with one of the above congenital cardiac lesions aged ≥16 years. Twenty-four subjects could not be traced or had died before the time of data extraction and were excluded. The study cohort consisted of 187 patients as follows: TOF = 70, CoA/IAA = 56, AVSD = 34, UVH-Fontan = 13, TGA = 14 (Figure 1). The main characteristics of these patients are summarised in Table 1. Forty-one of 187 patients (21.9%) (27 males; 34 moderate CHD) had been lost to GUCH follow-up: TOF = 10/70 (14.3%), CoA/IAA = 22/56 (39.3%), AVSD = 4/34 (11.8%), UVH-Fontan palliation = 1/13 (7.7%), TGA = 4/14 (26.7%).

(b) Factors predisposing to loss to GUCH follow-up

Ordinal logistic regression analysis identified the following factors to be associated with a significantly higher risk of loss to GUCH follow-up: limited paediatric cardiology follow-up (OR, 5.08; 95% CI, 1.77-14.63), ≤1 surgical/interventional procedure (OR, 3.34; 95% CI, 1.09-10.26) and no long-term cardiac medications (OR 7.34; 95% CI, 1.74-31.02). Patient gender and lesion complexity (moderate compared to severe complexity) had no statistically significant impact on loss to follow-up (Table 2).

(c) Analysis of recall into GUCH care

The mean age at time of recall for the 41 patients that were lost to GUCH follow-up was 34.73 ± 13.88 years. A positive response was obtained from 33/41 (80.5%) patients (21 males; moderate CHD = 28/34, severe CHD = 5/7). Significant cardiac morbidity was found in 5/33 (15.2%) patients upon reassessment in the GUCH service (Figure 2). Two patients with previous transannular patch TOF repair needed surgical pulmonary valve replacement (PVR) for severe pulmonary regurgitation (PR) and one patient with TOF and previous palliative open pulmonary valvotomy was offered balloon pulmonary valvuloplasty for severe recurrent valvular pulmonary stenosis (PS). One patient with unrepaired partial AVSD and severe left atrioventricular valve (LAVV) regurgitation underwent surgical defect closure and LAVV repair and one patient with Eisenmenger AVSD required optimisation of pulmonary vasodilator treatment.

***Table 1**: Characteristics of the 187 patients included in the study*

Characteristic	No. of patients (n (%))
Male gender	107 (57.2)
Moderate complexity	145 (77.5)
≤1 surgical/interventional procedure	111 (59.4)
No cardiac medications	103 (65.2)
Limited paediatric cardiology follow-up	60 (32.1)

Figure 1: Generation of study cohort. The term "missing" refers to subjects logged in the institutional congenital cardiac database (MAPCAD) that either died before the end of 2013 (time of data extraction) or who could not be traced on the institutional data information system. (AVSD = atrioventricular septal defect; CoA = coarctation of the aorta; IAA = interrupted aortic arch; TGA = transposition of great arteries; TOF = tetralogy of Fallot; UVH = univentricular heart)

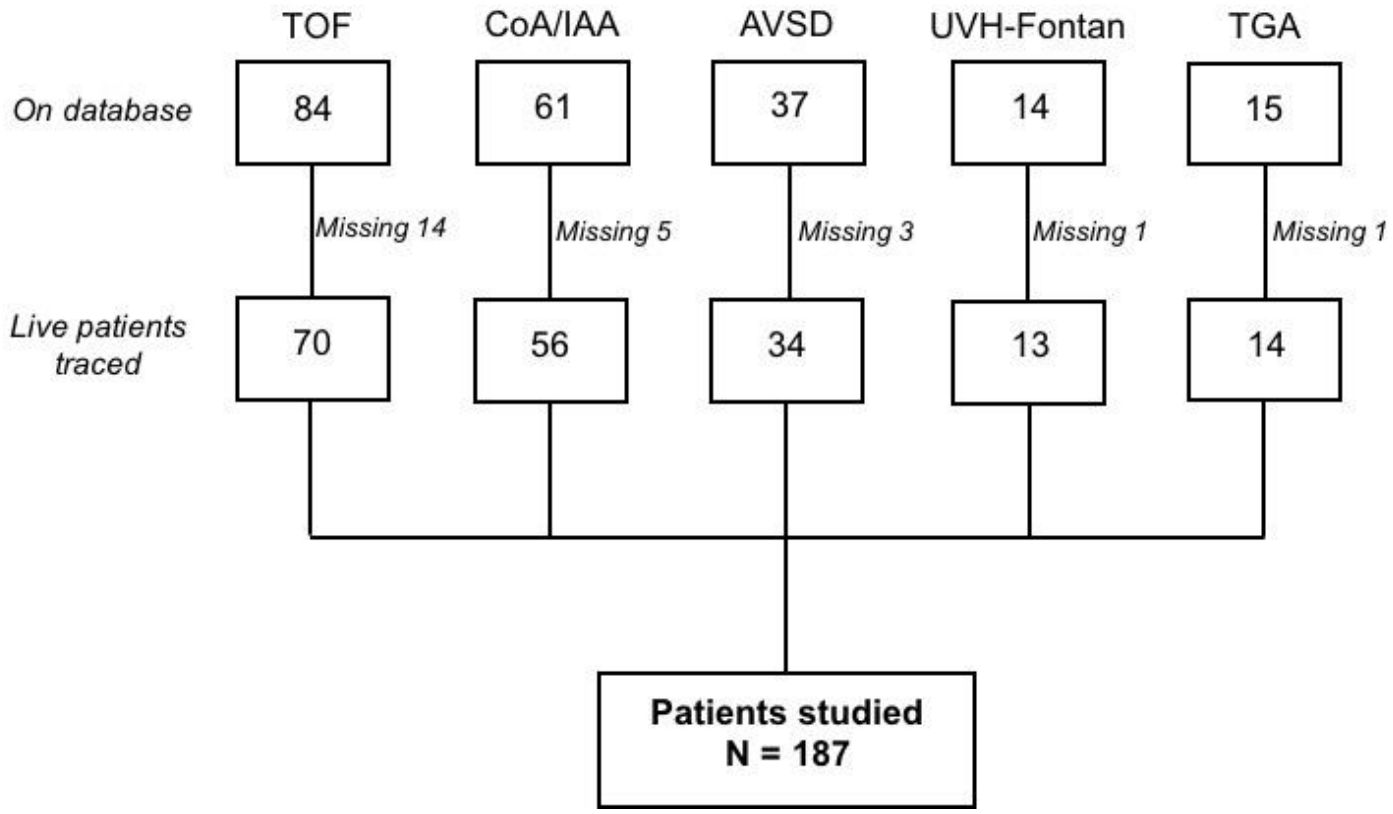
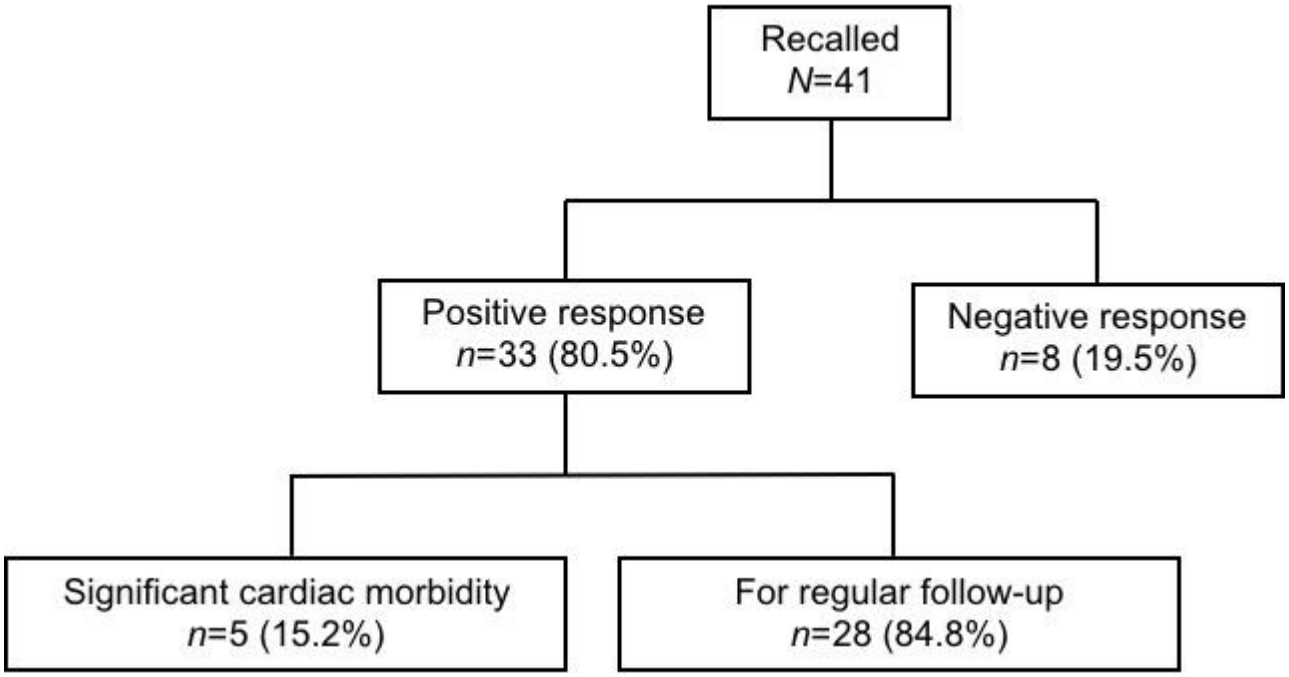


Table 2: *Outcome of ordinal logistic regression analysis of the impact of five studied factors on likelihood of loss to ACHD follow-up*

Factor	OR	95% CI lower, upper	*p* value*
Male vs. female gender	2.12	0.80, 5.65	0.132
Moderate vs. great complexity	1.60	0.32, 8.03	0.569
Limited vs. regular paediatric cardiology follow-up	5.08	1.77, 14.63	**0.003**
≤1 vs. >1 cardiac surgery/intervention	3.34	1.09, 10.26	**0.035**
No vs. on long-term cardiac medication	7.34	1.74, 31.02	**0.007**

* Significant p values are shown in bold

Figure 2: *Outcomes of recall exercise for the 41 patients lost to GUCH follow-up. Thirty-three of the recalled subjects attended an appointment in GUCH clinic, and 5/33 needed management of significant cardiac morbidity.*



Discussion

Nowadays, loss to specialist follow-up is recognised as an important stumbling block to the effective management of GUCH patients worldwide.[8-9,13-18] Ours is the first study to investigate this phenomenon among adult patients with CHD of moderate and severe complexity in the Maltese population.

(a) Prevalence of loss to follow-up and associated factors

The prevalence of loss to follow-up in our study cohort was 21.9%. There are wide variations in loss to follow-up rates in the published literature and ours appears to be one of the lowest reported. In their 2009 study on 643 subjects with CHD of all complexities in Quebec, Canada, Mackie *et al* [14] found that 61% of CHD patients were not being seen by a cardiologist by the age of 22 years, while the 2013 multi-centre North American study by Gurvitz *et al* [19] reported that 42% of the 922 patients with CHD of all complexities aged ≥18 years and attending their GUCH centre visit admitted to at least one >3-year gap in cardiology care. From their single-centre experience in Leuven, Belgium, Moons *et al* [18] reported that 54% of all CHD patients were not under active clinical follow-up. Yeung *et al* found a >2-year lapse in cardiology care in 63% of 158 patients with moderate/severe CHD in a centre in Colorado, US, and Reid *et al* [13] reported a rate of failure to transfer to GUCH care of 53% among 360 patients with complex CHD in Toronto, Canada. Wray *et al* [20] carried out a similar exercise to ours concentrating on repaired TOF in one main tertiary centre in the United Kingdom (UK) and found a 24% loss to follow-up rate. De Bono *et al* [21] documented a nearly 50% rate of loss to follow-up among patients with repaired aortic coarctation referred to a UK regional GUCH centre. It is likely that the small geographical area of the Maltese islands, the universal access to medical care and the concentration of specialist care in one main centre together contribute significantly to the relatively low rate of loss to follow-up documented in our study. All the other studies referred to earlier were conducted in countries far larger than Malta, and often where GUCH care is provided in multiple centres possibly different to those delivering paediatric care. At the same time, the fact that over one fifth of patients with moderate or severe CHD in our study were lost to follow-up despite this combination of favourable circumstances highlights the relative ease with which these patients can "slip through the net" and underlines the importance of implementing a robust infrastructure to ensure their

safe transfer from paediatric to adult care.

As expected, a lower number of cardiac interventional or surgical procedures was associated with a higher risk of loss to adult specialist cardiology follow-up in our study population. Similar findings were documented by Mackie *et al* [14] and Reid *et al* [13], in whose studies a higher number of cardiac procedures was associated with a better chance to transfer to adult care. In another study by Mackie and colleagues [15], cardiac catheterisation in the preceding 5 years was also found to be associated with a lower likelihood of loss to follow-up. It is likely that a higher number of cardiac procedures, especially if undertaken in older years, acts as a "reminder" to patients and family of their cardiac condition. In addition to this, a higher number of cardiac procedures leads to more encounters with specialists that are more likely to reiterate the importance of long-term follow-up and ensure its implementation. We found that the lack of regular cardiac medications was also associated with a higher risk of loss to follow-up. To our knowledge, ours is the first study to investigate the association between cardiac medication use and loss to GUCH follow-up. It can be postulated that the need for daily medications acts as another "reminder" to patients of a chronic condition that warrants specialist follow-up. Furthermore, the need to have prescriptions written from time to time, ensures patients' contact with medical professionals who can in turn ensure that such follow-up is in place.

The other factor with a significant association with loss to follow-up in our study cohort was a limited paediatric cardiology follow-up when compared to a more consistent input. Findings in several other studies reinforce our observation. In analysing the timing of loss to follow-up in their population, Mackie *et al* demonstrated that the greatest loss to follow-up happened during childhood and prior to the time of transfer to adult care.[14] Others showed that clear documentation in medical notes about the need for follow-up in a GUCH centre and recommendations on follow-up timeframes correlated with more successful transfer to adult care.[13,15] A number of interview-based studies featured the impression of the congenital defect being treated or of not knowing about the need for follow-up [8,15,19-20] as leading patient-reported responses for gaps in cardiology care. With their better understanding of the sequelae of repaired and unrepaired CHD, it would be reasonable to expect paediatric cardiologists to better convey the idea of need for long-term follow-up both in their written treatment plans and in their communication with patient and family from an early stage, thus ensuring better transfer to adult care.

We found no association between lesion complexity (moderate vs. severe) and likelihood of loss to GUCH follow-up. This contrasts with the findings by Yeung *et al* [8], who also restricted their study to patients with lesions of moderate or severe complexity and found those with moderate disease to have a significantly higher likelihood of >2-year gaps in cardiology care. Other studies that included patients with CHD of all complexities [14,19], found those with mild disease to be at highest risk of loss to follow-up or to experience gaps in care. Males often show an increased prevalence of risk-taking behaviour, and some authors found male gender to be associated with loss to follow-up before adulthood.[14] Although a previous study among Maltese GUCH patients had confirmed more risk-taking behaviours in male patients with respect to some lifestyle habits [11], our current study failed to show a significant association between gender and loss to follow-up.

(b) Recall of GUCH patients lost to follow-up

To our knowledge, there are only two other nationwide exercises aimed at recalling GUCH patients lost to follow-up reported in the literature to date: a Danish television and newspaper campaign in 2005 [16] and a national media campaign organised by the CONCOR project group in the Netherlands in 2009.[22] The exercise carried out in the Netherlands helped identify 593 patients aged 20-40 years that had previously been lost to follow-up, 85% of whom had mild disease, 14% had moderate CHD and 1% had lesions of severe complexity.[22] Of the 147 responders to the Danish campaign seen in one main institution, 71% had simple lesions and 29% had moderate CHD.[16] Our recall exercise differed by using hospital appointment letters and by concentrating on only five specific congenital lesions of moderate or severe complexity.

Our patients' turnout to recall was encouraging at 80.5%. Response rates to recall reported in other studies with a known patient denominator were all lower: 40% response rate from repaired atrial and

ventricular septal defects recalled in Belgium by Gabriels *et al* [23], 47% return to clinical care among the patients with moderate/severe CHD contacted for telephone interview by Mackie *et al* [15] and 38% of patients with operated TOF accepting to be referred to a GUCH service after a telephone interview in the study by Wray *et al*.[20] Although, at first glance, patient response to our exercise was better, it is difficult to compare considering the differences in congenital pathologies and means of contacting patients employed by different author groups.

(c) Consequences of loss to follow-up

The main risk of loss to follow-up is that patients find themselves living with residual or new structural lesions, arrhythmias or ventricular dysfunction for a protracted period of time and only present late with symptoms of decompensation, when it is either too late to get an optimal outcome from intervention or possibly too late to even contemplate one. Indeed, cardiac symptoms [8,19] and arrhythmias [8] were among the commonest reported reasons for patients not under active follow-up to seek clinical assessment.

Among patients in our cohort that returned to specialist care after recall, significant cardiac morbidity was found in 15.2%, with these patients needing some form of prompt intervention after their reassessment. Following their nationwide campaign in the Netherlands, Vis *et al* [22] diagnosed previously unknown residual lesions in 16% of patients that accepted a new cardiology review and, of these, 6% were found to warrant prompt intervention. Among the patients returning to care after the Danish recall exercise, Iversen *et al* reported moderate/severe PR in 55.6% of TOF patients, moderate/severe atrioventricular valve regurgitation in 75% of AVSDs and significant recoarctation in 20% of patients with repaired CoA.[16] De Bono *et al* [21] found 55% of the patients with repaired CoA referred to their regional GUCH centre to require the introduction of new medications mainly for better management of arterial hypertension and 22% of patients needed referral for specialist investigation or invasive treatment following their initial assessment. Yeung *et al* [8] made a new diagnosis of haemodynamic significance in 60% of their patients returning to cardiology care and were able to demonstrate a significant association between lapse of medical care and need for urgent cardiovascular intervention. Considering the early timing of interventions in a proportion of patients returning to care in these different studies, it is reasonable to postulate that some, if not all, would have been put forward for such treatment even earlier had they not been lost to follow-up. Furthermore, as Wray *et al* argue in their study on repaired TOF patients lost to follow-up [20], loss to follow-up could also increase the risk of premature cardiac-related death by denying patients access to procedures that could improve long-term outcomes if performed in a timely fashion.

Limitations

A main limitation of our study is the small number of patients included, which is in itself a result of the small Maltese population. In our study, patients with mild CHD were purposefully excluded as we aimed to concentrate on patients with moderate/severe disease where a consensus on need for regular follow-up is well-established. Automatically, this precluded us from analysing loss to follow-up among patients with milder disease compared to those with more severe forms as done in other studies referred to earlier. The authors recognise that the use of an interview or questionnaire for patients returning to specialist care would have helped shed a different light on reasons behind loss to follow-up so as to avoid it recurring in the future. Incomplete note keeping made it difficult to determine the age at last visit prior to loss to follow-up for some of the patients and thus this aspect was omitted during analysis.

Conclusions

Patients with CHD remain prone to loss to specialist follow-up even in health systems with little perceived barriers to medical care like the one in place in Malta. Loss to follow-up can delay the management of significant new or residual structural lesions, arrhythmias or ventricular dysfunction, which in turn can have a negative impact on outcomes. Effective transfer from paediatric to adult care requires consistent specialist input from the early stages, coupled with age-appropriate patient and family education highlighting the rationale for and importance of, long-term follow-up, even in the absence of symptoms. Non-congenital cardiologists and physicians should be made equally aware of the

importance of follow-up for CHD patients and be provided with an easy referral route to GUCH services. A formal transition process should help consolidate the process of patient empowerment [18,24-25], while also identifying patients with social and financial issues that might be at higher risk of defaulting future appointments.[8]

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Review Article

Informed Consent in Clinical Studies

Erica Cini

Abstract

Informed and voluntary consent are important aspects that should be considered when conducting human research. The importance of this has come to the forefront particularly since the atrocities of World War II. Since, there have been numerous legal additions to safeguard research volunteers and ethical approval applications also incorporate this process. Consent is therefore one of the nuts and bolts of research methodology.

This article looks at the informed consent process and at how this is obtained. It discusses how research informed consent varies from consent for a clinical procedure and looks at occasions when this important aspect can be waived.

Main Text

Informed and voluntary consent are important aspects to consider when conducting human research. The Nuremberg Code[1], The Declaration of Helsinki[16] and The Belmont Report[17] all support this key aspect.

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The Nuremberg Code[1] a set of 10 ethical principles, is laid out following the atrocities of World War II to protect fellow humans who take part in medical experimentation. The first principle of this code is about 'voluntary consent'. The Nuremberg Code[1] highlights that a person must have 'legal capacity to give consent'. This not only spells out that an assessment of capacity is necessary but also has implications in studies involving children, adolescents and vulnerable adults. Capacity is a time and decision specific assessment of the person's understanding, ability to retain, weigh and communicate the information and their decision. A capacity assessment is more complex in children as one must consider their level of psychological development, their understanding of the decision as well as the views of the parents.[2] Following the Gillick ruling, it must be noted that children, even under the age of 16, have the capacity to consent to treatment, even if their parents do not consent.[3] Whilst this is used in medical care, in most circumstances Gillick competency is not extrapolated to medical research.[4]

Another important aspect of The Nuremberg Code (1947)[1] is that a person must have the 'free power of choice'. This means that they are not to be constrained or coerced in any way to join the study. It expands on the meaning of obtaining informed consent - that is that a person must be given enough information to ensure that they can take 'an understanding and enlightened decision'.[1] This means that a person must know the nature of the clinical trial, expected length of time during which the research will be undertaken, the aims and objectives, the way in which the trial will be conducted, any adverse effects or risks as well as potential benefits and alternative therapies/treatment options to the one under investigation. All these aspects, form the basis of the Integrated Research Application System (IRAS) form. This is the form through which ethical approval is requested - and this must be obtained prior to the commencement of a clinical trial. Finally, The Nuremberg Code (1947)[1] also

stipulates that the process of ascertaining informed consent is the role of the chief investigator and emphasises that this role cannot be delegated.

The Declaration of Helsinki,[16] underwritten by the World Medical Association, further expands on The Nuremberg Code. It explains why human research is needed but emphasises that despite this, the person's health must remain the priority.[5] It acknowledges the patient's right to withdraw from a study and this may occur at any stage of the clinical trial. The Declaration of Helsinki also mentions the concept of assent, whereby participants who are not able to give informed consent (and therefore need a third party to do so on their behalf - this may include children and people with learning disability, amongst others) should still agree to participate in the clinical trial/research.[5]

The Belmont Report[17] emphasises the principles of beneficence, justice and respect.[6] Within this, it describes the participant as 'autonomous', meaning that they can choose whether they would like to be part of a trial or otherwise. This forms the crux of informed consent. Furthermore, it stipulates that people with diminished capacity should be given additional safeguards.

Informed consent should include information on premature termination of a clinical trial and this should only occur for efficacy, safety or feasibility reasons.[22] The informed consent process is usually evidenced with signed consent documentation. However, there are occasions when this may not be possible. This does not preclude that the person does not receive the necessary information to make the decision is given, but waivers the need for signed documentation. This may be necessary to safeguard the person if the research is about sensitive topics (such as domestic violence research) or in research whereby there is "no more than minimal risk of harm to subjects" [7] or when written consent is not usually required for such procedure. This usually encompasses telephone and web-based surveys.[7]

This begs the question - can informed consent be waived? There are some instances where some or all aspects of informed consent can be waived.[8] The Common Rule in the United States[9] identifies 4 main occasions where this can be waived, that is:

1. There is minimal risk;
2. The resulting waiver does not affect the rights or well-being of the people involved in the research;
3. The waiver is needed for the practicality of the research methodology;
4. Additional information is provided to the people involved in the research after this is carried out (where practical).

Minimal risk is basically day-to-day risk, that we all could face as we go about our daily living. These risks are so commonplace, that we don't usually think about these.[10] In research terms, educational/public health or routine care aspects are examples that would be included under this umbrella.[8] When thinking about methodology, certain modalities of data collection, such as surveys or reviewing medical notes, can also be regarded as minimal risk.[11]

On an aside, both healthy volunteers and patients may receive payments, incentives or expenses payments for their participation in the clinical trial. This should not be related to risk. All payment information should be given to the participants and included in the patient participation leaflet.[23] The Health Research Authority (UK) has issued specific guidance around payment and incentives in relation to research.[23]

The second aspect of when informed consent can be waived goes hand in hand with minimal risk. It relates to ensuring that the resultant waiver does not go against the laws of the state or affect the person's health, finance or legal aspects.[8]

Some research methodologies make obtaining informed consent difficult - such as studies involving cluster level interventions or with large cluster sizes.[8] Another possibility whereby gaining informed consent may be tricky is if the information disclosed during this process were to cause a bias either to the outcomes of the research or cause selection bias.

It is very important to treat the 'research subjects' as individuals and in a humane way. This therefore implies that even if approval is granted on the basis that informed consent is not possible, it is still important to make the information on the study available (e.g. through leaflets, website links) to the potential subjects.[8] Consideration should be made to ensure that this information is explained in a way that the persons involved in the study understand.

One of the functions of informed consent is to allow the people involved in the study (and those treated at a later stage – i.e. after the publication of

that study), to benefit from the study outcomes. This justifies their risk exposure for the benefit of the general population.[8]

So far we have talked about informed consent as a whole, but we must also consider the timeliness of that consent, that is, whether this should be done before or after the randomisation process. Good practice is for informed consent to be sought early on in the study.[8] During randomised control trials (RCTs) the earliest opportunity is before the randomisation process whereby information will be provided about the different arms of the study. Moreover information about the study and expected outcomes as a whole should also be given. It is of paramount importance that comprehensive, honest and accurate information is given.

However, if randomisation has taken place prior to consent being sought, as can be the case in cluster randomised controlled studies (C-RCTs), then the information given can be tailored to the relevant arm that the person has been allocated to.[8] In this case, it is thought justifiable to mention the generic study interventions and aims but not to give specific details about the study and the other arms as this lessens the likelihood of bias.[8]

In some C-RCTs obtaining informed consent prior to randomisation may be difficult[12] and this can raise ethical controversies.[13] Some researchers insist that if the C-RCTs are assessing routine care and are associated with minimal risk this may preclude the need for informed consent,[14] and others state that not obtaining consent prior to randomisation is ethical so long as this is obtained prior to the start of the study and the data collection.[8] The counter-argument to this is an ethical one, with some researchers insisting that the difficultly of obtaining informed consent in C-RCTs should be managed by improving the structure around obtaining informed consent.[12] The 1991 International Guidelines for Ethical Review of Epidemiological Studies state:

> *"When it is not possible to request informed consent from every individual to be studied, the agreement of a representative of a community or group may be sought… Approval given by a community representative should be consistent with general ethical principles… A leader may express agreement on behalf of a community, but an individual's refusal of personal participation is binding" (15: p. 225-226).*

In essence it is clear that the informed consent process is important. It ensures that participants have enough information and understanding to make a decision as to whether they want to enter a clinical study that is in line with their beliefs, values and culture. However as there are some exceptions when this can be waived, informed consent is not an absolute criterion. It remains however, a critical aspect that must be considered when conducting clinical studies.

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Review Article

Aetiology of thyroid autoimmunity

Carol Cardona Attard, Sandro Vella

Abstract

Autoimmune thyroid disease (AITD) is characterised by the development of thyroid autoantibodies, mainly anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies (primarily found in Hashimoto's thyroiditis [HT]) and thyroid stimulating hormone receptor antibodies (predominate in Graves' disease [GD]). While genetic factors provide 70 to 80% of the risk for the development of thyroid autoimmunity (TAI), environmental factors contribute about 20 to 30% to the immunopathogenesis of AITD. Such environmental factors include smoking (predisposes to GD but protects against HT), alcohol (moderate consumption protects against both HT and GD), stress (predisposes to GD) and iodine (possibly increases risk of AITD). Low selenium and vitamin D levels might increase the risk of TAI, although data remains indeterminate and selenium supplementation did not always improve TAI in clinical studies. Additionally, certain drugs, toxic chemicals, infections, birth in winter and autumn and radiation exposure have also been implicated in the development of TAI. Preventive interventions to decrease the risk of AITD are limited and not always feasible, though personal and public health interventions might help with smoking and iodine exposure.

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Introduction

Autoimmune thyroid disease (AITD) is a multifactorial disorder characterised by the development of autoantibodies against particular thyroid antigens in genetically predisposed individuals, facilitated by the exposure to particular environmental factors. Anti-thyroid peroxidase antibodies (TPO-Abs), anti-thyroglobulin antibodies (Tg-Abs) and thyroid stimulating hormone receptor antibodies (TSH-R Abs), are the main autoantibodies occurring in AITD.[1] While TPO- and Tg-Abs are mainly associated with Hashimoto's thyroiditis (HT), TSH-R Abs are the main anti-thyroid antibodies found in Graves' disease (GD).[1-2] Thyroid autoimmunity (TAI) in the absence of clinical autoimmune disease is identified by the presence of these antibodies.[2]

Primary hypothyroidism caused by HT forms the bulk of clinical disease. Its incidence rises with increasing age and is more common in iodine sufficient populations.[2] The incidence rates of autoimmune hypothyroidism are 80/100,000/year in males and 350/100,000/year in females. On the other hand, the incidence rates of autoimmune hyperthyroidism are 8/100,000/year in males and 80/100,000/year in females.[3] In the third National Health and Nutrition Examination Survey, TPO-Abs were observed to be three times less prevalent in African blacks than in white Caucasians.[4]

It has been observed in twin studies that genetic factors, including polymorphisms in major histocompatibility genes (human leukocyte antigen), thyroid specific genes (e.g. TSH-R and thyroglobulin genes) and immunoregulatory genes (such as the cytotoxic T lymphocyte antigen-4 gene), provide a contribution of about 79% to the development of GD.[5-6] Similarly, genetic factors account for about 73% of the risk to develop TPO- and/or Tg-Abs.[7] Thus, environmental factors contribute about 20 to 30% to the immunopathogenesis of AITD.[6]

Existential Factors

Existential factors include age, female sex and parity.[6] In epidemiological studies, prevalence of thyroid antibodies was noted to increase with age[2, 4] (although a peak of antibody positivity at around 45 to 55 years is demonstrated in a few studies).[2] GD incidence was seen to peak at an age between 20 and 49 years in two studies, between 60 and 69 years in Malmö Sweden, while it increased with age in Iceland.[8] AITD has a strong female preponderance, which may in part be explained by skewed X chromosome inactivation,[1] and in part by hormonal influences, as oestrogen appears to favour a T-helper 2 immune response, where antibody production is increased through activation of B-lymphocytes.[9]

Pregnancy is characterised by immunosuppression to protect the foetus. However, this amelioration in immunity disappears in the post-partum period, often leading to the onset/exacerbation of existing AITD.[10] In the prospective Amsterdam AITD cohort study, there were more hypothyroid cases in the postpartum period, while hyperthyroid cases were more frequent during pregnancy.[11] The reason for an association between parity and AITD might be explained by foetal microchimerism, since foetal cells have been identified in the blood and thyroid tissue of women with HT and GD. This might trigger a graft-versus-host maternal immune response, leading to autoimmune diseases.[12] However, other population-based studies contradict this hypothesis, where no association was found between previous pregnancies, parity or abortion and thyroid antibodies.[13-14]

Environmental Factors

1. Smoking

Smoking is a well-known risk factor for GD. A meta-analysis showed an odds ratio (OR) of 3.30 (95% confidence intervals [CI], 2.09, 5.22) for GD, with an even greater OR of 4.40 (95% CI, 2.88, 6.73) for Graves ophthalmopathy in current smokers when compared to never smokers. This effect is more marked in women and appears to be dose dependent. However, this risk is abolished a few years after smoking cessation, resulting in an insignificant OR of 1.41 (95% CI, 0.77, 2.58) for GD in ex-smokers compared to never smokers.[15]

On the other hand, current smoking protects against autoimmune hypothyroidism in a dose-dependent manner. This has been shown in several studies, including a population-based study by *Pederson et al*, where smoking was negatively associated with the presence of Tg-Abs more than TPO-Abs.[16] In contrast, discontinuation of smoking increased the risk for developing both TPO- and/or Tg-Abs,[17] with a 6-fold increase in overt autoimmune hypothyroidism in the first 2 years following smoking cessation, although this increased risk was transient (DanThyr study).[18]

2. Alcohol

Alcohol has been shown to protect against autoimmune hypothyroidism. In a population-based case-control study carried out in Denmark, moderate alcohol consumption (11–20 units/week) was mostly protective, irrespective of gender, smoking and type of alcohol consumed.[19] Moderate alcohol consumption (compared to abstinence/abuse) also protected against the development of GD with hyperthyroidism, thus indicating a dose-dependent relationship.[20]

3. Stress

Stress is known to be a triggering factor in the pathogenesis of GD, however, its effect on HT has been barely researched.[6] In a five-year follow-up prospective study, stress was not found to be associated with the development of TPO-Abs or with the development of hypo- or hyperthyroidism. Hypothyroid cases were in fact found to suffer from a less depressed mood than controls at the point of diagnosis, and thus the authors concluded that stress is not implicated in the development of AITD.[21]

However, in a population-based case-control study, stress and negative life events within the previous 12 months were found to be associated with the onset of GD.[22] Another case-control retrospective study confirmed a correlation between stressful life events (SLE) and the onset of GD, while no association was found between SLE and the onset of toxic nodular goitre, confirming that stress precipitates autoimmune rather than non-autoimmune hyperthyroidism.[23] Moreover, the prognosis of GD treated with antithyroid drugs appears to be worse, with higher relapse rates and TSH-R Ab titres following treatment withdrawal in individuals who suffer from mental disorders and significant stress.[24]

4. Selenium

Selenoproteins, mainly glutathione peroxidases, iodothyronine deiodinases and thioredoxin reductases are important enzymes involved with thyroid hormone metabolism, regulation of the redox state as well as protection of the thyroid gland from oxidative damage.[1] A recent large population-based study carried out in China demonstrated a higher incidence of autoimmune thyroiditis in individuals with low selenium.[25] Low selenium levels were also noted to be associated with AITD, especially GD, in another population-based study carried out in Denmark.[26]

However, the results of clinical trials testing the effect of selenium supplementation on TAI are equivocal.[1] A Cochrane database systematic review concluded that further randomized placebo-controlled trials are required to assess the effect of selenium supplementation on HT as the evidence so far is incomplete.[27]

5. Vitamin D

Although Vitamin D deficiency is associated with various autoimmune diseases including type 1 diabetes (T1D) and rheumatoid arthritis, its association with AITD is still uncertain.[1] Table 1 delineates a number of studies, where an association of AITD with vitamin D deficiency was either confirmed or refuted. Certain polymorphisms in the vitamin D receptor gene (mainly the BsmI or TaqI) were noted to confer an increased AITD risk.[28] Moreover, a recent trial has demonstrated that vitamin D supplementation causes significant TPO-Ab titre reductions.[29]

6. Infections

Several infections have been implicated in the development of AITD in genetically susceptible individuals including *Yersinia enterocolitica*, Hepatitis C virus, Coxsackie B virus, retroviruses, *Borrelia Burgdorferi* and *Helicobacter pylori* infection, particularly the cytotoxin-associated gene A strain. Infections may trigger AITD by several mechanisms, some of which may include release of sequestered antigens on cell apoptosis/destruction, molecular mimicry (an epitope on bacterium/virus is recognized as self), cryptic epitope exposure and activation of resident T-cells through inflammation and cytokine secretion.[30]

Table 1. *Association of Vitamin D deficiency with AITD in some clinical studies.*

Study	AITD associated with Vitamin D deficiency?
Effraimidis G et al. 2012[43]	NO
D'Aurizio F et al. 2015[44]	NO
Yasmeh J et al. 2016[45]	NO
Kivity S et al. 2011[46]	YES
Bozkurt NC et al. 2013[47]	YES
Wang J et al. 2015 (A meta-analysis)[48]	YES

7. Seasonality

Hamilton et al investigated the effect of month of birth and seasonality on AITD onset in northern European Caucasian and United Kingdom populations and found no impact of month of birth on GD development. However, slightly higher birth rates in autumn were detected in HT females from the OXAGEN AITD Caucasian family collection.[31] A previous Greek study showed that male GD birth rates peaked in winter, while females with GD had two birth peaks: spring and autumn. Conversely, HT female birth rates peaked in winter, while males with HT were mostly born in winter and summer. In the general population births peaked in summer for both males and females. Therefore, they argued that both GD and HT have a similar aetiology as T1D and multiple sclerosis i.e. seasonal bacterial/viral infections during the perinatal period may be the initial trigger, as most births of AITD individuals peaked in winter and autumn.[32]

8. Drug Therapy

Several drugs may induce TAI including interferon-α, interleukin-2, campath-1H and highly active antiretroviral therapy. Instead of causing *de novo* TAI, lithium and amiodarone (an iodine rich drug) appear to be key risk factors for the development of hypothyroidism in patients with pre-existing TAI. Amiodarone's iodine load is also responsible for inducing the onset of previously subclinical GD, resulting in autoimmune thyrotoxicosis.[10]

Oestrogen use (as the oral contraceptive pill

[OCP] or hormone replacement therapy [HRT]) was found to have varied effects on TAI in different studies. It was found to be negatively correlated to TPO-Abs and was associated with a lower risk of subclinical or overt hyperthyroidism (but not autoimmune hypothyroidism) in a cross-sectional analysis of the Amsterdam AITD cohort.[33] In a Danish population-based cross-sectional study, only the use of HRT was associated with a lower occurrence of Tg-Abs (but not of TPO-Abs),[13] while no difference in thyroid antibody frequency was noted in post-menopausal women with or without HRT in a different study.[34] Furthermore, oestrogen use was found to have no correlation with thyroid antibodies in a Japanese-Brazilian population-based study.[35]

9. Radiation exposure

AITD is connected to therapeutic radiation including radioactive iodine, as well as occupational and environmental radiation exposure. Increased AITD was initially seen in atomic bomb survivors in Japan and following the radioactive fallout in Chernobyl.[36]

10. Toxic chemicals

Polyaromatic hydrocarbons including polychlorinated biphenyls (PCB) and polyhalogenated biphenyls (PBB) are organic compounds found in water and air and are made from coal. An increase in antimicrosomal and Tg-Abs together with a higher occurrence of hypothyroidism was noted in workers exposed to PBBs.[37] A higher prevalence of thyroid antibodies and an increased thyroid volume was also noted in Slovakian workers exposed to PCB.[38] Bisphenol A, perfluorinated chemicals, phthalates,[30, 36] solvents, metals, other anthropogenic compounds and petrochemical complex-related pollution have also been associated with AITD. Chemical toxins might trigger AITD by disrupting the immune system and/or interfering with thyroid function or by altering the thyroglobulin structure increasing its immunogenicity.[39]

11. Iodine

Autoimmune hypothyroidism and thyroid antibodies tend to be more prevalent in iodine replete areas and in individuals with excessive iodine intake or following iodization programmes.[1] In a Danish study, TPO and Tg-Abs became more prevalent after iodine fortification of salt, especially in young women and at low concentrations of antibody.[40] A higher prevalence of hyperthyroidism, especially in young individuals, was also noted in two areas of Denmark with moderate and mild iodine deficiency after cautious iodine fortification of salt.[41] However, a large Italian study observed an absence of an association between iodine fortification and HT or iodine induced hyperthyroidism.[42]

Table 2. *The natural history of progression of AITD.*[1]

Stage	Clinical Thyroid status	Thyroid Abs	Other changes
1	Euthyroid	Absent	Evidence of immune activation including changes in chemokines, vascular adhesion molecules, GFs cytokines and tissue remodelling factors
2	Euthyroid	Present	TSH starts getting deranged
3	Subclinical hypo/hyperthyroidism	Present	Duration longer for subclinical hypothyroidism than subclinical hyperthyroidism
4	Overt hypo/hyperthyroidism	Present	

Abs – antibodies; GFs- growth factors; TSH- thyroid stimulating hormone.

Natural history of AITD

The natural history of AITD involves four stages which are delineated in table 2. In a prospective study, progression to overt autoimmune hypothyroidism from euthyroidism took several years unlike the development of overt autoimmune hyperthyroidism which occurred after a few months.[11]

Conclusion

In conclusion, several environmental factors can affect progression to TAI. While some factors appear to predispose to both GD and HT, others may predispose to GD but protect against HT.[1] Preventive measures might involve public health interventions such as monitoring iodine intake and providing education against smoking. Promoting alcohol consumption, which has its own adverse effects, is unlikely to be feasible, while stress avoidance is not always pragmatic. Whether selenium and vitamin D supplementation can improve or protect against TAI is still indeterminate and requires further research. Other risk factors such as seasonality of birth, age and gender are non-modifiable, while avoidance of pregnancy is non-realistic.[6]

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Historical Article

Doctors during the 1837 Cholera Epidemic in Malta: Unearthing the Truth

Joseph Galea

Abstract

Epidemic cholera devastated the population of Malta for the first time in the summer of 1837 affected almost 9,000 people and killing half of them. In the medical literature of the time there was a heated debate about its causation and transmission. Many Maltese doctors believed it was contagious while others such as Giuseppe Maria Stilon and Tommaso Chetcuti along with the British Services doctors deemed it was contracted from miasma in the air. The fear of contagion prevented a number of Maltese physicians from attending to the sick, however all the cholera hospitals in Malta and Gozo were run by Maltese doctors. In the beginning of the epidemic the Governor through the official Malta Government Gazette called for the doctors' help, offered payment, appealed to their honour and finally threatened them. He also wrote to the Commonwealth Secretary complaining that he was not getting enough response from Maltese doctors and that he had asked the Governor of Gibraltar to send doctors to Malta. The arguments about the contribution of the Maltese doctors during this epidemic spilled over into the newly born free press in Malta. John Stoddart, the Chief Justice at the time and Sarah Austin the wife of John Austin, one of the British commissioners who were reporting on the state of the island observed the lack of enthusiasm shown by many Maltese doctors during the epidemic although they both praised those Maltese doctors who were exemplary. However Maltese doctors although frightened, performed their duty towards their patients and at least two of them paid with their life.

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Introduction

Epidemic cholera reached Europe for the first time at the beginning of the nineteenth century. After devastating countries all over Europe, it reached Malta in June 1837 finding a poor and destitute population that was too fragile to withstand its onslaught. It attacked the old and weak inmates of the Ospizio and then spread to every corner of the archipelago. The Government, belatedly appointed Committees of Health to deal with the consequences of the epidemic and cholera hospitals were opened in the cities and villages, directives issued and health workers and priests mobilized. The malady wreaked havoc for 3 months attacking 8785 and killing 4252 from a population of just over 120,000.[1] This had significant effect on the native population of Malta (Figure 1).[2] Out of a military population (including dependents) of 3214 persons there were 313 (9.7%) cases of cholera with 71 deaths (mortality rate of 22.7%). In the civil population of Malta (103344), there were 7672 cases (7.4%) with 3784 deaths (mortality rate of 49.3%) and in Gozo (16,534) there were 818 cases (4.9%) with 368 deaths (45%).[3] The epidemic was also causing economic hardship because businesses such as the cotton industry closed shop and the Governor and the Bishop set up a fund to relieve the poor who were hit most by economic stagnation.[4]

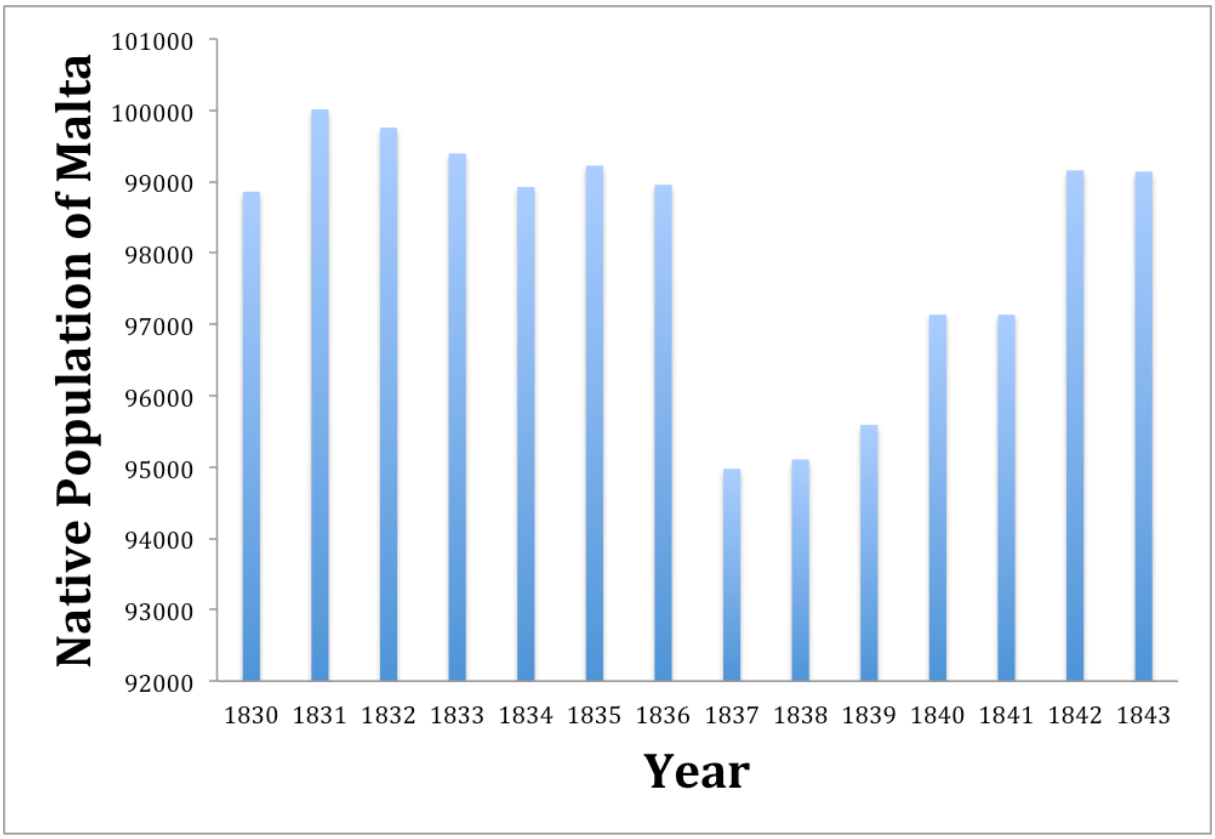
During most of the nineteenth century, through three cholera epidemics in Malta and before the discovery of the bacterium by Koch in 1884, argument raged over the mode of transmission of cholera. The medical profession was torn between those who believed that the disease was infectious and contracted from the environment and the few who believed it was contagious with the passage of the disease from one person to another. Arguments and copious persuasive evidence in favour of one hypothesis or the other pervaded the pages of nineteenth century medical literature.

By the spring of 1837, many Maltese physicians were aware of the epidemic that over the previous eight years had been ravaging one

European country after another. They were expecting its devastating arrival on our shores with trepidation even though there was official denial that it would ever find its way to Malta. Many physicians still had vivid horrifying memories of the 1813 visitation of the plague and the deaths including some of their own it left in its wake. The conflicting theories reaching Maltese doctors led to confusion and doubts about the transmission of this disease. Although the official medical line was that cholera was not contagious but occurs because of a miasma or infectious air in the environment, doubt lingered in many doctors' minds and uncertainty instilled fear. In a letter by the then Chief Justice of Malta Dr John Stoddart LLD to Dr Seth Watson DM, the translator to Dr Giuseppe Maria Stilon's book "The Cholera in Malta in 1837" wrote,

' It was scarcely possible to obtain medical assistance to the sufferers. With one or two exceptions (amongst whom there was Dr Arpa) the native Maltese physicians conceiving that cholera was a kind of plague, and communicable by contact, absolutely refused to approach a cholera patient'.[5]

Figure 1: *Native population from 1830 to 1843 showing the dip due to the cholera epidemic of 1837*



Dr Stoddart however stated that he must not be understood 'to impute to the medical gentleman of Malta, on all occasions, either physical or moral cowardice because there have been times when they have exhibited calmness and courage in the last extremity of danger'. Dr Stoddart then describes the courage shown by a Maltese police physician during the 1813 plague: 'This worthy man contracted plague in the discharge of his duty which disease was fatal.' An English surgeon, an acquaintance of Dr Stoddart, was present by his deathbed and to him the suffering physician said, 'with utmost coolness and resignation, "you see these black spots on my arm; they warn me of the near approach of death: in two hours, I shall be no more"'. Dr Stoddart wrote that the Maltese doctors' during the 1837 cholera 'backwardness arose less from timidity than from ignorance'. He puts their lack of knowledge squarely on the Government of the island who 'years and even months previously' should have employed 'the proper means to enlighten them on the nature of the disease, which

was so manifestly approaching' so that they would have undoubtedly 'been as ready as Dr Stilon to combat the malady, when it first appeared.'

The Medical Knowledge about Cholera at the Time

During this time, the germ theory of disease was shrugged upon. First proposed by Geralomo Fracastoro (1478-1553) in 1546[6] and further explained by Marcus von Plenciz (1705-1786) in 1762,[7] the germ theory only became an acceptable notion in the 1850s. Before then, Galen's miasma theory still dominated medical literature. As everywhere else in 1837 Malta, the physicians had divided opinions about the mode of transmission of cholera and the question of whether it was contagious or not was hotly debated. The non-contagionists were led by physicians from Britain, Germany and France and these doctors maintained that cholera was not communicable by contact with infected patients and their clothing (not even bed linen contaminated by their faeces). Therefore, they believed that its progression could not be controlled by quarantine and restrictive measures. They believed that the cholera epidemic came about when the susceptible person got the disease from air poisoned by miasma and emanations. On the other hand, the Italian medical intelligentsia was an advocate of the contagionist school where it was believed that cholera was spread by contact between the infected and the non-infected persons and their fomites. The Maltese medical profession of the time was largely influenced by Italian medical literature and by direct contact with Italian Universities and Italian physicians so it comes as no surprise that the theory of contagion took root in Malta and had an effect on the behaviour of Maltese doctors. The English doctors stationed and working in Malta were brought up with the non-contagionist theory in which they believed very strongly. Chetcuti writes *'I medici Inglesi, Clarke, Liddell, Sankey ecc. cercavano con esempio e colle persuasioni di toglier il timor del contagion, persuasi, come son quasi tutti l'Inglesi, della non contagiositá del choléra'*.[8] (The English medical doctors, Clarke, Liddell, Sankey etc. tried to remove the fear of contagion by example and by persuasion because like almost all the English were sure that cholera was not contagious). Most of the English doctors were military doctors and therefore trained to face life-threatening situations. This put the English doctors in a better mind frame psychologically to deal with the terrible calamity that was affecting our islands. The Maltese doctors who were in the thick of it and left us written accounts of the epidemic such as: Dr Giuseppe Maria Stilon, Dr L. Gravagna, and Dr Tommaso Chetcuti were convinced in the non-contagionist concept of transmission. This may help explain at least in part their fearlessness and the very active part they took in fighting the horrible disease. Dr Giuseppe Maria Stilon was of Italian origin but he had a doctorate from the University of Malta and had been practicing in Malta for 10 years. He was in private practice in Malta when the cholera epidemic reached Malta. In the context of this thesis he was in the same position as Maltese doctors. Dr Stilon scolded the contagionists for their verdict on how cholera had reached the inmates of the Ospizio and called their story 'a Shameless Fabrication*!*'[9] He added that in his experience, when the cholera patients were admitted into a temporary hospital which had been established in a normal school, they were 'treated with the most intimate familiarity, and yet out of sixty individuals, who were employed in the service of that establishment, only six were attacked, four of whom were persons notoriously addicted to the excess use of spirituous liquors'. It cannot be contagious he reiterated because 'attendants gathered together clothes of the cholera patients and laying them in a place covered with cloth reposed or slept on them when not on duty'. The medico-chirurgical assistants bled patients regularly and if the blood was hard to come, Stilon would bleed the other arm. In addition to this, he performed Caesarean sections on dead patients as necessary and assisted choleraic women in miscarriages without getting the disease. He recalled that during a post-mortem, when his assistant was helping him in 'laying open the smaller intestines, which were found full of a whitish pulpy matter, wounded one of his fingers, and yet there followed neither to him nor to any of us the least symptom of contagious cholera.'[10]

In his booklet '*Nel Ragguaglio sul Colera Morbus col modo di preservarsi'* Dr L Gravagna stated that 'cholera comes from miasma that infects the person and through the air in the atmosphere.' However, he adds that 'the miasmic principle does not explain the activity on the organism without finding a predisposition to it'.[11] He added that fear, the terror that one might get cholera, dirt, misery

and intemperance are important predisposing factors for the malady. Gravagna advised that the houses should be kept clean and any rotting matter that can cause foetid air should be removed. He advised the *capo di famiglia* to remove manure from cellars and courtyards and wash them well. [12]

Stilon divided the predisposition factors for cholera into physiological and pathological causes. Writing about the physiological cause he maintained that:

'among the different temperaments natural to the human body, the bilious is that which most predisposes to cholera. In fact, the greater part of the choleraic patients, who were admitted to hospital, were of that temperament; however, several were received who were of the scrofulous habit, and these were generally found the most difficult to cure. Vehement, and ill-regulated passions of the mind, such as terror, rage, anger, and that alarming fear, which often seizes persons at the first appearance of this terrible malady, are moral agents, which easily dispose the individual to be affected by it".[13]

He added that work that entails excessive exercise also predisposes to cholera because this tends to debilitate the body. This is attested to, by the large number of patients 'who belong to the class of the indigent, or those employed in very laborious occupations'.[14] The main pathological predisposing factors for cholera according to Stilon are:

'all acute or chemical inflammations of the mucous membrane lining the stomach and intestines – the presence of worms in the intestines – the effect produced by drastic purges, or by acids organic or inorganic, used in such a quantity as to keep up a continual irritation in the prima via, hypochondriasis, or any of those particular modifications of the gastro enteric viscera, which often remain after hepatitis, or chronic pulmonary disease.'

Dr Tommaso Chetcuti stated that the *miasma coleroso* (choleric miasma) waited for the high temperatures of 72°F, 74°F and 78°F on 8, 9 and 10 June 1837 respectively and a protracted hot wind from the south to hit old inmates of the Ospizio in Floriana, Malta.

Fear, Duty and the Polemic

Dr Constantino Giorgio Schinas also mentioned the reaction of doctors to the epidemic. Dr Schinas, a Greek doctor, studied at Pisa University, Italy, came to Malta in 1832, became Professor of Medicine in 1833[15] and published the first ever Maltese medical journal called *L'Ape Melitense – Giornale di Medicina* in the last quarter of 1838. It was published in Italian and contained translations of works from English, French and German. Dr Schinas wrote a monograph about the 1837 cholera epidemic in Malta divided in three parts and published it in the first 3 consecutive numbers of the *Ape Melitense.*[16] He gives a sincere and apologetic account in his periodical of his initial fear of the disease. He also reflects on the psychological conflict of the doctor who is called upon and expected to fight a dangerous foe when he is scared stiff for his own safety and in the full knowledge of his helplessness against a relentless enemy that might strike him down. Schinas confesses with pathos in the *Ape*:

'Doctors have certainly not been privileged by nature with the exemption of fear […] When the occasion for fear is real even the bravest man will feel afraid and nobody will deny that cholera is such an occasion […] If the physician believes in contagion he fears contact with others; and if he does not believe in contagion he is afraid of the air and noxious foods […] I cannot deny that I was afraid a little too much at the beginning […] but I must confess that the physician is in duty bound, in similar circumstances, to tender his aid and shows himself courageous; because although he believes himself to be weak, he is held to be omnipotent by the people; and when the people miss his help they get discouraged, and when they see him frightened they despair'.[17]

Sarah Austin (born Taylor, 1793-1867), the wife of the commissioner John Austin was very critical of the behaviour of many Maltese doctors. She stated that when the old, sick people were transferred from the Floriana Ospizio to Ricasoli at the dawn of the cholera epidemic of 1837, on the 13 and 14 June, a doctor did not examine them for four days. At Ricasoli 'two doctors stood at the doors and ordered medicine and the viaticum,'[18] wrote Austin. This version of events does strike one as being too simplistic as other documents have shown that the rate of the incidence of cholera in Fort Ricasoli soon after the mostly sick Ospizio inmates were ferried there was alarming and the medical staff could not cope with the increasing number of afflicted cases. The doctors were disheartened and

fearful and when two doctors contracted the disease themselves and had to leave the fort to be nursed at home, matters took an even worse turn.[19] There was an argument raging into the following year (1838) on whether the English or Maltese doctors cared more for cholera patients and Sarah Austin who was an eyewitness possibly took the English doctors' side. Of course, one might conclude that her opinion was biased given her nationality; however, one can hardly dismiss her account as a fabrication considering that throughout her writing she always defended the Maltese and spent a considerable amount of time interceding with the English authorities on their behalf. In a letter to Mr Victor Cousin, she wrote

'the Maltese are very docile, sharp and intelligent. How much there is to say about this little half-Arab nation – corrupted and degraded to the last degree by the worst government in the world, that of the Order; neglected and despised by the English, ignorant, superstitious, and devoured by every kind of prejudice! They must not be left in such a condition'.[20]

The editorial of the 10th issue of Harlequin stated that

'the conduct of the English medical men in *quel giorno di esperimento* was so exemplary, that the prayer of every person apprehensive of an attack of cholera was that he might have the good fortune of having an English attendant - while the dark and unchronicled deeds of Ricasoli, which had been confided to their own medical men remain to the present hour deeply impressed in the recollection of every honest Maltese, as a stain upon the native faculty amply calculated to justify the withdrawal of public confidence.[21]

This was rebutted by *Onesto Maltese* in the Mediterraneo where an insulted Maltese man denied the accusations and sarcastically asked if '*quel giorno di esperimento'* was 9 June when the English doctors misdiagnosed two cases of cholera at the Ospizio as not being such and persisted with their mistaken diagnosis for days despite the insistence by Maltese doctors that the patients were indeed suffering from cholera. [22] He argues that only one or two English doctors operated in Valletta and that they had only seen a few patients and were not trusted by the Maltese. Furthermore, the local population knew that the native doctors behaved properly in Ricasoli. The correspondent of the *Mediterraneo* reiterated that there was no stain on the Maltese profession with regards to the way doctors behaved during the epidemic, if anything, Maltese doctors did their very best to help their fellow human beings better than in other countries afflicted by this disease. All the cholera hospitals in Malta and Gozo were served by Maltese doctors '*con zelo, decoro e caritá'* and the Government had so much confidence in Maltese doctors that they were appointed to oversee the management of these hospitals.

The Government was harping on that cholera was not contagious but doctors and the higher classes did not seem to be buying this as their actions betrayed them:

'Four physicians were particularly mentioned as having done everything in their power to increase the alarm. With an ignorant presumption (never having seen the disease) only equalled by their abject cowardice, they confidently affirmed that it was contagious, and would not suffer anybody to touch them or even to touch any object they were to receive'[23]

These accusations brought to light by an indignant Austin are in line with the answer *The Curer of Phrenitis* gave to *Onesto Maltese* over two editions of the *Harlequin*.[24,25] He suggested that help for the cholera patients was not easily forthcoming because the Government had to issue a call for physicians on 20 June 1837 to 'aid in mitigating the unavoidable evils of the impending disease' promising payment and appealing to their honour. The letter continued that the Government had to flex its muscle and on 21 June 1837 threatened doctors by saying that if anyone had circulated the opinion that the epidemic was of a contagious nature and they persevered in such conduct, they would be 'disqualified for public situations.'[26] At the same time, 'one of the offenders' was turned out of his chair at the University. Austin had no doubt that this indignation was 'perfectly well founded and the punishment merited'.[27] The governor issued further invitations on 22 June[28] and 4 July[29] to the medical profession, which led *The Curator of Phrenitis* to come to the conclusion that not all Maltese doctors had been forthcoming in their help for cholera patients. Austin echoes this in her essay and writes that even though the Government reassured the physicians that the disease was not contagious as evidenced by the medical authorities of Gibraltar (Figure 2) and Paris (Figure 3), 'medical men either

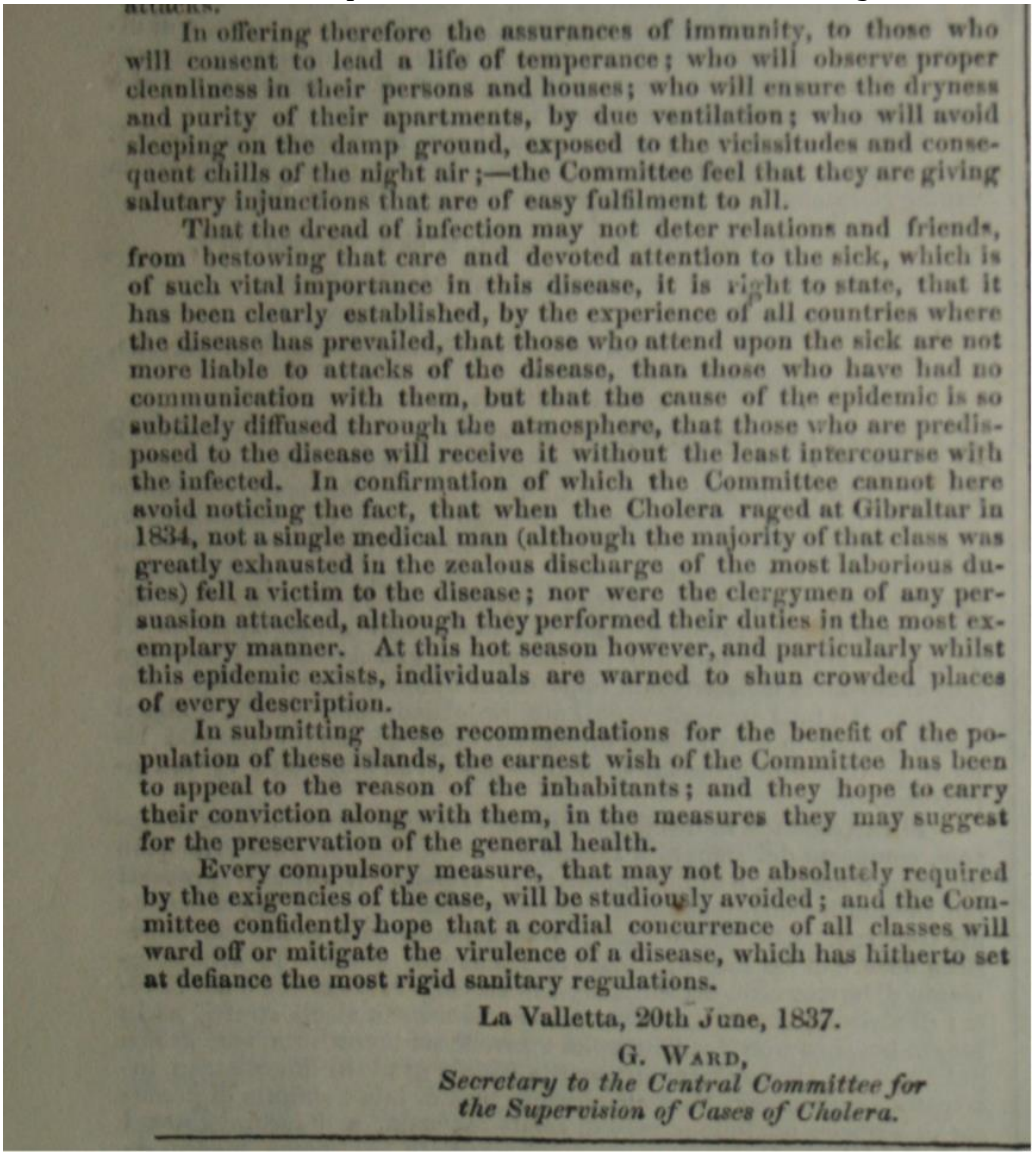
refused to attend, or, if they did attend, would not approach the patient.'[27] An invitation to the medical students and other members of the profession to visit the hospitals fell on deaf ears.[27] The *Harlequin* writer however contended that he was:

'far from intending to cast discredit upon the faculty of Malta; many of whom, under the unpropitious circumstances, as regards instruction, and information, in which they have so long found themselves placed, have arrived among their fellow citizens, at a grade of eminence which hardly anyone could have expected'.[30]

Sarah Austin accused one physician of 'turning his fears to better account in the first days of panic. He made 200 scudi by selling little packets of some specific against cholera; he pushed them across the counter or table with a stick and made the people throw their money into vinegar.' Austin concluded by writing the damning line: 'What is very certain is, that these physicians would do nothing for anybody.'

Austin wrote her article almost 30 years after the events and although she was present during the epidemic and stated she wrote from notes she had taken during the time, she would have most probably aided her memory from literature written at the time and her point of view is in fact that of the government of the time and her compatriots.[31]After the government call on 20 June 1838, the naval and military doctors responded unhesitatingly to the government's call for help but it seems that the Maltese doctors were less than enthusiastic.[32]

***Figure 2**: Notification in the Malta Government Gazette (28 June 1837) by G. Ward, Secretary to the Central Committee for the Supervision of Cases of Cholera dated 20 June 1837 stating that the evidence provided from the Gibraltar cholera epidemic shows that cholera is not contagious.*



In offering therefore the assurances of immunity, to those who will consent to lead a life of temperance; who will observe proper cleanliness in their persons and houses; who will ensure the dryness and purity of their apartments, by due ventilation; who will avoid sleeping on the damp ground, exposed to the vicissitudes and consequent chills of the night air;—the Committee feel that they are giving salutary injunctions that are of easy fulfilment to all.

That the dread of infection may not deter relations and friends, from bestowing that care and devoted attention to the sick, which is of such vital importance in this disease, it is right to state, that it has been clearly established, by the experience of all countries where the disease has prevailed, that those who attend upon the sick are not more liable to attacks of the disease, than those who have had no communication with them, but that the cause of the epidemic is so subtilely diffused through the atmosphere, that those who are predisposed to the disease will receive it without the least intercourse with the infected. In confirmation of which the Committee cannot here avoid noticing the fact, that when the Cholera raged at Gibraltar in 1834, not a single medical man (although the majority of that class was greatly exhausted in the zealous discharge of the most laborious duties) fell a victim to the disease; nor were the clergymen of any persuasion attacked, although they performed their duties in the most exemplary manner. At this hot season however, and particularly whilst this epidemic exists, individuals are warned to shun crowded places of every description.

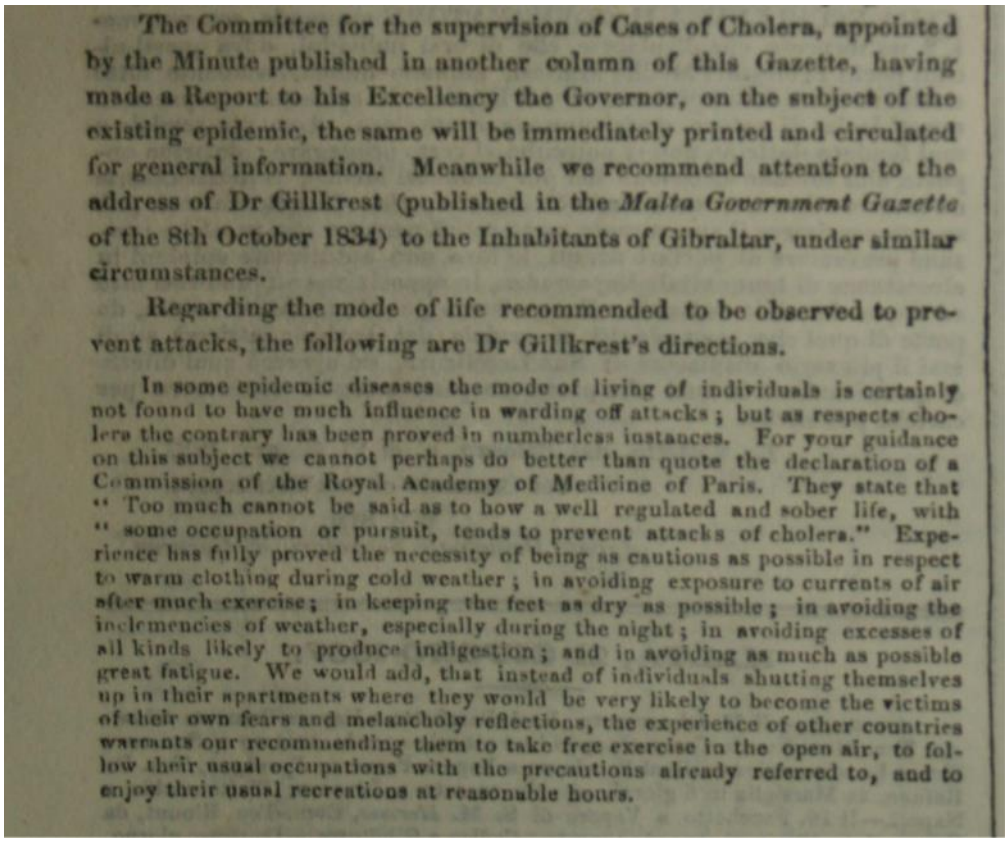
In submitting these recommendations for the benefit of the population of these islands, the earnest wish of the Committee has been to appeal to the reason of the inhabitants; and they hope to carry their conviction along with them, in the measures they may suggest for the preservation of the general health.

Every compulsory measure, that may not be absolutely required by the exigencies of the case, will be studiously avoided; and the Committee confidently hope that a cordial concurrence of all classes will ward off or mitigate the virulence of a disease, which has hitherto set at defiance the most rigid sanitary regulations.

La Valletta, 20th June, 1837.

G. WARD,
Secretary to the Central Committee for the Supervision of Cases of Cholera.

***Figure 3**: Contribution issued by the Central Committee for the Supervision of Cases of Cholera in the Malta Government Gazette (21 June 1837) quotes the Commission of the Royal Academy of Medicine in stating that isolation is not recommended for cholera patients because the disease is not contagious.*



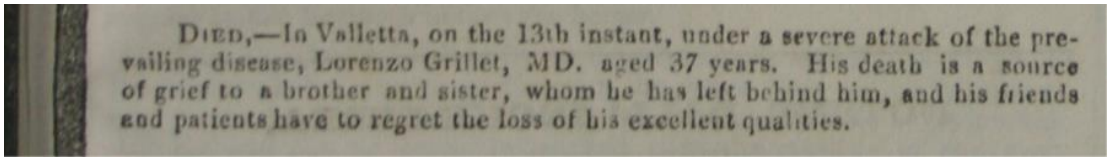
The Committee for the supervision of Cases of Cholera, appointed by the Minute published in another column of this Gazette, having made a Report to his Excellency the Governor, on the subject of the existing epidemic, the same will be immediately printed and circulated for general information. Meanwhile we recommend attention to the address of Dr Gillkrest (published in the *Malta Government Gazette* of the 8th October 1834) to the Inhabitants of Gibraltar, under similar circumstances.

Regarding the mode of life recommended to be observed to prevent attacks, the following are Dr Gillkrest's directions.

In some epidemic diseases the mode of living of individuals is certainly not found to have much influence in warding off attacks; but as respects cholera the contrary has been proved in numberless instances. For your guidance on this subject we cannot perhaps do better than quote the declaration of a Commission of the Royal Academy of Medicine of Paris. They state that "Too much cannot be said as to how a well regulated and sober life, with "some occupation or pursuit, tends to prevent attacks of cholera." Experience has fully proved the necessity of being as cautious as possible in respect to warm clothing during cold weather; in avoiding exposure to currents of air after much exercise; in keeping the feet as dry as possible; in avoiding the inclemencies of weather, especially during the night; in avoiding excesses of all kinds likely to produce indigestion; and in avoiding as much as possible great fatigue. We would add, that instead of individuals shutting themselves up in their apartments where they would be very likely to become the victims of their own fears and melancholy reflections, the experience of other countries warrants our recommending them to take free exercise in the open air, to follow their usual occupations with the precautions already referred to, and to enjoy their usual recreations at reasonable hours.

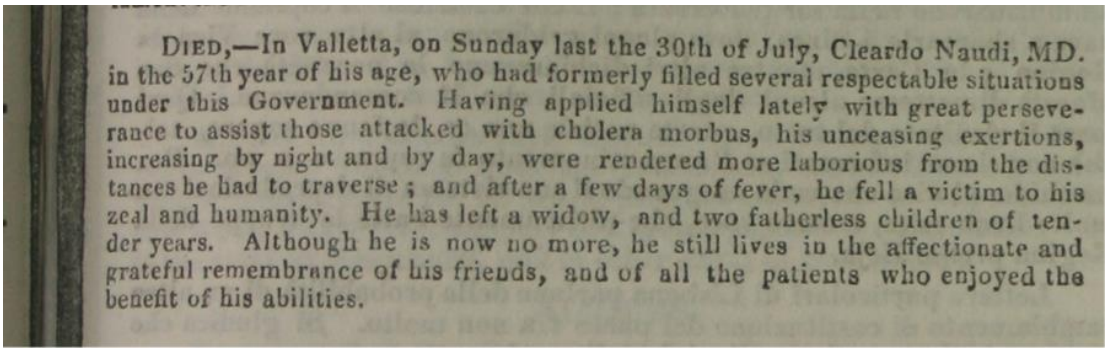
***Figure 4**:* Obituary of doctors dying from cholera during the 1837 cholera. (a) Lorenzo Grillet and (b) Cleardo Naudi.

a.



DIED,—In Valletta, on the 13th instant, under a severe attack of the prevailing disease, Lorenzo Grillet, MD. aged 37 years. His death is a source of grief to a brother and sister, whom he has left behind him, and his friends and patients have to regret the loss of his excellent qualities.

b.



DIED,—In Valletta, on Sunday last the 30th of July, Cleardo Naudi, MD. in the 57th year of his age, who had formerly filled several respectable situations under this Government. Having applied himself lately with great perseverance to assist those attacked with cholera morbus, his unceasing exertions, increasing by night and by day, were rendered more laborious from the distances he had to traverse; and after a few days of fever, he fell a victim to his zeal and humanity. He has left a widow, and two fatherless children of tender years. Although he is now no more, he still lives in the affectionate and grateful remembrance of his friends, and of all the patients who enjoyed the benefit of his abilities.

In his dispatch of 2 July 1837 to Lord Glenelg, Secretary of State for the Colonies, Governor Bouverie stated that on the 20 June 1837 he:

'invited all Medical Men to come forward and lend their professional assistance; this invitation was responded to at once, by every English medical man in the island, even by some who had retired from practice; but I regret to add that the Maltese practitioners showed no such alacrity in the cause of humanity, and they evinced, on the contrary, great backwardness, at the commencement, in offering their assistance; occasioned by a belief generally prevalent among them that the disease was of a highly contagious nature.' [33]

The Governor continued in this same dispatch: 'Finding that this dangerous doctrine of contagion was sedulously inculcated by some; perhaps who conscientiously believed it to be true and by others whose motives were less excusable', he issued another minute the following day.

The Governor continued in this report to Lord Glenelg that 'this measure followed by the commendable example set by the English medical men who fearlessly put themselves at once in contact with the dying and the dead, has had a most salutary effect, in allaying the general panic which from that moment began gradually to subside.' [33]

He also suggested to the Secretary of State to the Colonies that:

'Fearful that the malady may increase, in which case paucity of medical aid to be depended upon in this island, might lead to effects the most disastrous, it is my intention to solicit by the present packet, the assistance of some medical men from Gibraltar if it can be obtained. The admiral has kindly consented to detach from the squadron two or three professional Gentleman whose service will be of the greatest utility'.[34]

The Governor of Gibraltar, Sir Alexander Woodford obliged and immediately dispatched five medical men to help with the care of the cholera sufferers in Malta.[35]

The Governor concluded this 2 July 1837 dispatch by 'bearing testimony to the unwearied exertions of Dr Clarke, Assistant Inspector of Hospitals and Dr Liddell, Physician to the Naval Hospital, for whose valuable advice and assistance beyond the sphere of their respective official duties.'[36]

However, a number of Maltese doctors did look after patients with cholera and a few died during the exercise of their duty (Figure 4). The district police physicians in Malta and Gozo were Maltese (and Gozitan) and most of them looked after the afflicted with responsibility. The agreement of the doctors in Gozo to do their full duty was unanimous.[37]

Dr Tommaso Chetcuti looked after many cholera patients in the Rabat and Imdina area. He gave a very balanced and credible account of the behaviour of the doctors during this horrendous epidemic.[38]

'It is true that the first few cholera cases at the Ospizio that occurred on 9 June were correctly diagnosed by Drs Axisa, Gravagna and Portelli and incorrectly diagnosed as being another non well-defined illness by Drs Clark and Lawson and this is attested by a letter by Dr Axisa himself.'[39]

There were 700 old and frail people taken by boat from the Ospizio to Ricasoli accompanied by two Maltese doctors, Dr Giuseppe de Salvo (who had been looking after them at the Ospizio) and Dr Antonio Grech: 'How much intrepidity and courage can one expect from these two young doctors without expertise about this terrible disease and the two chaplains who were locked up with all these sick persons facing this horrible disaster?' Chetcuti asked. The English doctors Clarke, Liddell and Stankey tried by example and persuasion to convince the others that the disease is not contagious but by the 17 June, 133 cases had occurred, three-fifths of who were dead and two-thirds were dying.

Dr Gavino Portelli offered his services voluntarily and the physicians Michele Portelli, Luigi Pisani and Gaetano Mifsud joined him at Ricasoli to help with this mammoth task. The doors of the fort were locked to maintain order and they would not allow other doctors including Clark and Liddell to go in to treat the sick. The dead lay unburied, the place was not adapted to take the sick and the nurses and some doctors contracted cholera. The other doctors and the chaplains out of fear and in the throes of disease were offering very little help to the sick. On 21 June, Dr Gavino Portelli and Dr Giuseppe di Salvo had to leave the fort, sick from cholera, to be nursed at home. Mr Carlo Satariano who was in charge of the fort and Dr Gaetano Micallef also contracted cholera but they remained in the fort: 'One can imagine how devastated and disheartened the doctors and other carers were and how the cholera patients including Satariano and Dr Micallef were left to languish in desolation without any comfort except for the administration of water

and some calomel powder'.[40] Dr Sankey visited the cholera patients at the fort and tried to reassure Mr Satariano that he had gastric flu and not cholera. He did this to boost his morale. On the same evening, the administration of the fort passed on to Dr Anthony Speranza who reorganized the hospital, engaged more medical and nursing staff and persuaded the convicts to inter the 45 death corpses that had been left unburied. Governor Henry Frederick Bouverie visited Fort Ricasoli Hospital on Sunday 25 June and was satisfied with the medical and religious arrangements for inmates.[41] By this time, two hundred and seventy-five inmates had succumbed to the disease.

There were many doctors who had the courage to overcome fear even though they might have had doubts about the nature of cholera's transmission and who did their duty towards their patients and their fellow Maltese and most of them will remain forever unsung heroes who may even be damaged by the behaviour of others who did not find the moral and physical strength to put themselves forward to fight the horrible disease. A few doctors did however receive praise for their valour and dedication to their patients. John Stoddart the Attorney General at the time of the affliction wrote that Dr Stilon who was appointed head of the newly established cholera hospital in Valletta was 'skilful, and above all so energetic, zealous and persevering' He added that Stilon was a good man who was 'engaged in great work'.[42] At the time of cholera in Sliema there were about 450 inhabitants including 30 poor families employed in agriculture. A Dr Arpa was engaged and he was given a house in the village where he had a supply of 'medicines and utensils'. On the door was fixed a night bell and lamp shining on a board with an inscription saying, 'Advice and Medicine gratis (free) at all hours for the cholera'. Dr Arpa would also walk through the village morning and evening, enquiring into the state of health of every family and if any premonitory symptoms appear he would apply the proper remedy. Every morning, Dr Arpa would also supervise the 'distribution of bread to the poor families with a proportionate quantity of any kind of food they were accustomed to eat, taking care it was digestible, wholesome and sufficient.'[43] Sarah Austin mentions a Maltese physician Dr D. who was nearly worked to death during the epidemic. He became so ill during this time that he had to be supported at the bedside while he prescribed.[44] Some English doctors were also praised for their dedication to the patients; in his dispatch to Lord Glenelg, the Governor wrote that he was very grateful for the support of the British Naval Department and then commended Drs Clark and Liddell for their help beyond their call of duty.[45]

Conclusion

The mostly convinced non-contagionist doctors felt safe treating the cholera patients because they could not get the disease by contact with their patients, their fluids or their fomites and even if there was the poisonous miasma in the air, they were resistant to it because they did not exist in abject poverty and filth. They were strong and healthy with no debility and were not fearful or anxious, did not drink alcohol in excess and did not live a debased existence. The doctors who believed in the possibility of disease contagion were frightened but many of them performed their duties towards their patients. The fear of health care professionals of acquiring disease from their patients is still a very important issue in the management of patients with contagious diseases especially those carrying a bad prognosis such as ebola.

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