Volume 2, Issue 1, 2018

Malta Medical School Gazette

MMSG

University of Malta
Medical School

UNIVERSITY OF MALTA
L-Università ta' Malta

Table of Contents

Editorial: Transition of children to adult care
Simon Attard Montalto 1.

A Review of the National Adverse Drug Reaction (ADR) & Medication Errors Reporting System of Malta
John-Joseph Borg, Anthony Serracino Inglott, Dania Al-Haddad 4.

Did the introduction of high-sensitivity Troponin T for the assessment of suspected acute coronary syndrome in Malta result in reduction of hospitalization time? A retrospective review
Ahmed Chilmeran, Yahya Alwatari, Stuart Zintilis, Robert Xuereb 11.

Assessing the home management of hypoglycaemia in paediatric T1DM
Paul Torpiano, Karen Sapiano, John Torpiano 17.

An Audit on the Practice of Performing a Chest X–Ray in Infants with Bronchiolitis
Sarah Anne Caruana Galizia, Veronica Said Pullicino, Cecil Vella 25.

Rapidity of diagnosis and management of H. Pylori in the endoscopy unit at Mater Dei Hospital
Daniela Zammit, Thelma Xerri, Pierre Ellul 31.

Risk factors for adolescents developing substance use disorders; what should our prevention programs be targeting?
Nigel Camilleri, Andrea Saliba 39.

Incidence of Acoustic Neuroma in Malta
Ryan Grech, Kenneth Muscat, Joseph Attard 46.

Re-operation Rates in Breast cancer after Breast Conserving Surgery in Malta
Alexia Farrugia, Gordon Caruana Dingli 49.

User Satisfaction of Children and Young People's Service, Malta
Andrea Saliba, Nigel Camilleri 55.

Editorial

Transition of children to adult care

Simon Attard Montalto

Approximately 10% of young people aged 12-24 years suffer with a chronic condition, and most of these disorders will persist into adulthood [1,2]. The age when children are deemed to become adults, at least for health purposes, varies from country to country: the arbitrary cut-off in Malta was fourteen years but, in 2012, this was raised to a more realistic sixteen years. Nevertheless, this age is set artificially to accommodate health care practices and services and does not 'work' for all, particularly in those cases where adolescents may have associated problems of cognitive and developmental delay. A rigid cut-off and 'one-size-fits-all' transition process is unrealistic. Likewise, a totally unregulated free-for-all process that is solely decided by individual practitioners' whims is equally unworkable. A compromise position is required that respects the needs of individual adolescents, is cognizant of diverse medical conditions and differing time-frames, yet manages to accommodate all these variables within the prevailing healthcare service.

Simon Attard Montalto
Department of Paediatrics,
The Medical School,
Msida, Malta
simon.attard-montalto@gov.mt

The transition process should be designed on principles established on evidence-base and best practice although, in this regard, this is often lacking or of poor quality.[2-3] Moreover, few countries have well developed policies on transition, and fewer still monitor outcomes of such a policy.[3-4] Yet inadequate or non-existent transition is associated with poor measurable outcomes such as disease control, compliance, rates of hospitalisation, patient satisfaction, and is costly.[3-4] Transition needs to be accessible, practical and, ultimately, serves the patient such that a potentially difficult stage in their care is both as seamless as possible and functionally effective[5]. The latter can translate into better (or, at least, equivalent) quality of life, compliance and disease control, as well as integration and meaningful contribution to society.[1,3,5]

Patients who may require long term or specialised care into adulthood should be identified as early as possible (generally by their caring paediatric team) and plans toward transition set out [5,6]. This can take the form of a systematic formal process that is carefully co-ordinated (by a designated lead person(s), or team), that would require planning and an appropriate set-up, such as a dedicated clinic.[5-6] Ideally, these would be run jointly by both paediatric and adult physicians.[3] Hence, for example, a child with epilepsy in Malta could be introduced into this transition set up a year or two before their sixteenth birthday, and managed jointly for the interim period. Shared care can be extended earlier, such that jointly run clinics manage children from a much earlier age. In Malta, this concept has been pioneered with significant success for children with connective tissue diseases, whereby adult physicians with an interest in childhood rheumatology were invited to set up a joint clinic within the Paediatric Outpatient Department in 2008. Indeed, this service has now been in force in Malta for over ten years, and has worked extremely well with all parties benefitting from each other's knowhow. As patients within this joint Rheumatology clinic have got older, their care has naturally migrated from the paediatric side

toward adult colleagues. For these patients, the eventual 'final' transition at sixteen years to full adult care will be barely noticeable, with their management organised by physicians whom they have known for years. However, what works or is possible for Rheumatology where patient numbers are small, may be impractical for other specialties, and alternative options need to be found.

Any transition process needs to individualised as much as possible, and must involve the patient and their family.[5] Involvement of community services and support from family practitioners and, where appropriate, NGOs is crucial to the success of this process.[1,5,6] Timing may depend on disease-dependent issues as well as existing healthcare services,[5] but later transition and in line with social changes (e.g. school leaving, or official adulthood at 18 years) may be deemed more practical.[3] Transition at some arbitrary, rigid time point, particularly during mid-adolescence may be detrimental.[3,5]

Transition clinics with the entire team present may be difficult to create and sustain – yet, to a large extent, the template for this already exists in Malta in the form of visiting consultant clinics (VCC). These have been established for more than two decades in both Paediatrics and adult domains. With a little extra organisation, part of the VCC can be allocated to transition patients who can be seen by both respective visiting and local teams simultaneously. Indeed, this has been successfully introduced for several years in the paediatric respiratory VCC, in the main focusing on adolescents with cystic fibrosis, but the model is easily transferable to other conditions. The disadvantage with VCCs is that they occur infrequently and, for some patients, a more regular review may be required. The Grown Up Congenital Heart (GUCH) Disease model 7 established in Malta in is another extremely successful format of transitional care where multidisciplinary input is practiced *par excellence*. GUCH services commenced as a joint effort between paediatric and adult cardiology around 2001, and this clinic was joined by a visiting expert consultant three years later. A formal consultant post in GUCH was created in August 2015. Hence, for example, at present a pregnant twenty five year old would be managed routinely by an adult cardiologist GUCH consultant, a paediatric cardiologist with access to neonatal advice, an arrhythmia specialist if needed, an obstetrician, and in difficult/unusual cases, a visiting cardiologist.

Similar formats already exist in Malta or could certainly be envisaged for other sub specialties such as oncology, diabetes, epilepsy, other neuromuscular conditions, inflammatory bowel disease, renal disorders, etc., etc. Some specialties (e.g. orthopaedics, ENT, ophthalmology) routinely depend on consultants to treat and follow up both adult and paediatric cases and, for these patients, transition would appear to be automatic at the doctor-level. However, this ignores other important issues related to transition such as school related versus workplace related problems,[1,5,6] and these need to be addressed ideally within a designated transition clinic. For the most complex and/or totally unique cases (a real possibility in a country with a paediatric population of just 80,000), a one-on-one customised hand over would be recommended. This is not difficult to achieve in a small health service where everyone knows everyone else and most work on one hospital site. In our experience, a face-to-face handover together with the adolescent and with the parents present is entirely feasible and, in general, takes just a few phone calls to organise. An alternative, whereby a ticket of referral is simply posted through the internal mail system will probably result in a non-urgent outpatient appointment in an adult clinic several months, and in some cases, more than a year down the line. In the interim, these patients are technically orphaned and will recourse to their paediatrician for support, prescriptions, form renewal, etc., with problems arising in the event of approval required for repeat visits for shared care abroad, or during a crisis requiring acute hospitalisation.

Flexibility, tolerance, respect and common sense should be the order of the day. Intransigent rigidity that results in situations whereby staff are frightened (of repercussions from higher authorities!) to take blood from a sixteen and a half year old child with Down's syndrome in Children's Outpatients or, conversely, an adult higher specialist is told off by his/her consultant for giving advice on a fourteen year old with a condition that is more common in adult patients, is totally at odds with the spirit of transition and is certainly not in the patients' interest.

An effective transition process is not an optional extra but, in accordance with authoritative

bodies and patient feedback,[5,6,8] should be routine practice for all adolescents with a chronic condition. It requires commitment, both at an individual physician and health service provider level, planning and focused coordination.[5] Malta's greatest advantage is that expert support in the form of visiting consultant clinics are already established across almost all disciplines and access to colleagues is easy. In addition, very successful 'local' models have been established for decades and these can be used to model other, new transition clinics for other conditions. Whatever the format chosen for a particular subspecialty, family involvement and patient engagement [1-6] together with a degree of flexibility to cater for individual patient needs,[1,2,5,6] are key to the success of this essential process. Every discipline could set up this service according to their own requirements, but the initiation for transition almost always starts from the paediatric side. It may, therefore, be time to consider the creation of a dedicated service with a coordinator within this specialty (e.g. along the lines of a specialist paediatric nurse practitioner) with responsibilities for transitional care.

References

1. Key principles for transition of young people from Paediatric to Adult Health Care. NSW Agency for Clinical Innovation 2014.www.aci.health.nsw.gov.au
2. ML McPheeters, AM Davies, J Lounds Taylor, R Flowers Brown, SA Potter, RA Epstein. Transition care for children with special Health needs. Technical Brief 15; AHRQ Publication No.14-EHC027-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm
3. R Viner. Transition from paediatric to adult care: Bridging the gap or passing the buck? RCPCH Conference 2018; Archives Dis Childhood. 2018; 81 (3): 271-276. http://dx.doi.org/10.1136/adc.81.3.271
4. CM Hepburn, E Cohen, J Bhawra, N Weiser, RZ Hayeems, A Guttmann. Health system strategies supporting transition into adult care. Archives Dis Childhood. 2014; 100(6): 1-5. http://adc.bmj.com/content/100/6/559.short
5. NICE guidelines for Transition Care. NICE Guideline 43. http://www.nice.org.uk/guiidance/service-delivery--organisation-and-staffing/service-transition.
6. Building bridges: The transition from Pediatric to adult health care.Transition Care Network for young people with chronic childhood illnesses/disabilities. A Framework. NSW Agency for Clinical Innovation. ACI publications. 2015. https://health.usnews.com/health-news/patient-advice/articles/2015/10/05/building-bridges-the-transition-from-pediatrics-to-adult-health-care?page=2
7. J Sommerville. Near misses and disasters in the treatmentr of grown-up congenital heart patients. *J R Soc Med.*1997; 90: 124-7.
8. A Saliba, N Camilleri. User satisfaction of children and young people's service (CYPS) Malta. MMSG 2018; Volume 02 Issue 01 2018. p. 55

Cover Picture:
'Waterfront'
Acrylic
By Rosita Farrugia

Rosita Farrugia was born on 11th July 1952. She worked in Cardiac Lab and X-ray Dept. as a nurse. She worked in Italy with the Department of Peadiatrics for 12 years in Florence and Verona.
She went for missionary work for 2 years in Kenya and 2 years in Nigeria and also to Cosovo where they took 4 containers to the Red Cross. She is also a member in the Malta Council in the Voluntary sector and she is also a member of the Fraternity of Charles de Faoucauld.

Original Article

A Review of the National Adverse Drug Reaction (ADR) & Medication Errors Reporting System of Malta

John-Joseph Borg, Anthony Serracino Inglott, Dania Al-Haddad

Abstract

The overall objectives of Pharmacovigilance include early identification of potential safety hazards, evaluation, monitoring and where appropriate, implementation of regulatory action to maximise benefits and minimise risks associated with medicinal products. Reporting of an ADR associated with use of a medicinal product as well as medication errors is an essential source of necessary information that is required to achieve these objectives. Safety concerns that arise from spontaneous reporting contribute to assessment of the risk benefit balance and hence lead to a regulatory action which could be suspension or revocation of marketing authorization of the product or change in the product information. Furthermore, these safety concerns can be communicated to healthcare professionals through Direct Healthcare Professional Communications (DHPCs) and safety circulars and they form the basis of designing Risk Minimisation Measures (RMMs).

The establishment of a functional ADR reporting system by law since 2004, not only facilitates participation in the national and EU regulatory process, but also enables Malta to participate in the WHO Programme for International Drug Monitoring, both by contributing to and obtaining data from this extensive information resource.

John-Joseph Borg BPharm (Hons), MSc (Agric Vet Pharm), PhD*
Post-Licensing Directorate Medicines Authority,
San Gwann, Malta.
Course of Pharmacy,
Department of Biology,
University of Tor Vergata,
Rome, Italy
john-joseph.borg@gov.mt

Anthony Serracino Inglott PharmD,
Pharmacy Department,
University of Malta
Msida, Malta

Dania Al-Haddad B.S.c. Pharm.,
Post-Licensing Directorate Medicines Authority,
San Gwann, Malta

**Corresponding author*

Mesh Terms

Adverse Drug Reaction, Pharmacovigilance, Safety, Risk assessment

Introduction

All medicinal products in the EU including Malta are subject to strict testing and assessment of their quality, efficacy and safety before being authorised. Once placed on the market they continue to be monitored to assure that any aspect which could impact the safety efficacy profile of a medicine is detected and assessed and regulatory measures are taken as necessary. This continuous monitoring of the safety profile of a medicinal product is a core objective of Pharmacovigilance system. The ADR reporting system is an integral part of the Malta Medicines Authority's (MMA) Pharmacovigilance system through which post marketing data about medications are collected and processed to aid in the surveillance and regulation of medicinal products. The Aim of this review is to disseminate the science of pharmacovigilance amongst Maltese doctors and to encourage reporting.

The definition of ADR in the EU

Directive 2001/83/EC, defines an ADR as: A response to a medicinal product which is noxious and unintended, adverse drug reaction may arise from the use of the product within or outside the terms of the marketing authorisation or from the occupational exposure, conditions of use outside the

marketing authorisation include off-label use, overdose, misuse, abuse and medication errors. There are multiple synonyms for an ADR: suspected adverse (drug) reaction, adverse effect, and undesirable effect.[1]

A serious adverse reaction is an adverse reaction which either

- Results in death
- or is life threatening
- or requires in-patient hospitalisation
- or prolongation of existing hospitalisation
- or results in persistent or significant disability or incapacity or a congenital anomaly/birth defect. [1]

The ADR reporting system established in Malta is consistent with European and Maltese legislation for the regulation of medicinal products which directs competent authorities in member states to *establish a Pharmacovigilance system where this system shall be used to collect information useful for the surveillance of medicinal products, with particular reference to adverse reactions in human beings and to evaluate such information scientifically.*'[2-3]

In November 2003 the Maltese Medicines Act was published which established the regulatory framework for the MMA and lead further to the development of Pharmacovigilance subsidiary regulations.[3] As part of the EU network, the MMA actively participates in the EU fora (as Rapporteur) to carry out the necessary regulatory actions mandated by law to *suspend or revoke an authorization to place a medicinal product on the market where that product proves to be harmful in the normal conditions of use, or where therapeutic efficacy is lacking, or where qualitative and quantitative composition is not declared.*'[2]

The Role of Health Care Professionals

In all countries where Pharmacovigilance systems operate, the role of healthcare professionals is essential in recording and reporting suspected ADRs they observe in their practice in order to alert regulatory agencies to new or emerging safety concerns which facilitates timely and appropriate regulatory action to be taken. The Maltese legislation on Pharmacovigilance specifies that: *It shall be the duty of doctors and other healthcare professionals to report to the Authority any suspected serious or unexpected adverse reaction to a medicinal product.*[3] National competent authorities are also obliged to 'take *all appropriate measures to encourage doctors and other healthcare professionals to report suspected adverse reactions to the competent authorities*.'[2] To achieve this goal the MMA has adopted a 3 year (2016-2018) strategy plan to promote ADR reporting from healthcare professionals which involves the organisation of educational seminars and promotional materials to increase awareness of ADR reporting nationally.

How to Report

For the purposes of reporting, an ADR reporting form has been developed and validated. In 2015, a unified form was designed which combines reporting of ADRs and medication errors whether they were associated with an ADR or not. Submission of a report does not mean an admission of guilt, the information contained in reports are entered in the MMA's database in a secure manner and details of the reporter are destroyed following transmission to the European database (Eudravigilance).[4] ADR report forms can be downloaded from MMA's website: www.medicinesauthority.gov.mt/adrportal.

The minimum criteria for a valid ADR report is: an identifiable reporter (e.g. doctor, pharmacist, dentist), identifiable patient (initials or age or date of birth or sex); a suspected medicinal product and a suspected ADR. However, a report should provide as much information as possible in order to facilitate evaluation e.g. for biological medicinal products ADRs should be reported by brand names and batch number ensuring the traceability. During the process MMA might request further information regarding individual ADR reports as appropriate.

How to fill ADR form:

The ADR form is composed of three sections where each section has to be filled by the reporter. Section 1 is to be filled when reporting an ADR; section 2 to be filled only when reporting a medication error while section 3 is for the reporter's details that are requested for contacting the healthcare provider for further follow up. If a medication error resulted in an ADR then both sections 2 and 3 have to be filled in by the reporter. A detailed guidance and instructions on how to fill in each section can be found at the end of the report.

Submitting a report in a timely manner along with the best possible quality of data within the

report is essential for efficient causality assessment. The higher the accuracy of the provided data the more the results of an assessment will be valid. Therefore, including the start and stop dates of an ADR and the drug treatment in terms of dd/mm/yy is more granular than in terms of mm/yy. Furthermore, availability of relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, will facilitate decisions on the causal relation between an ADR and the suspected medications, e.g. a laboratory test measuring biochemical or an immunologic marker might be helpful to explain the suspected adverse drug effect.[5]

What and When to report

Healthcare professionals are encouraged to report all suspected ADRs to MMA. It is not necessary to be certain of the casual relationship between an ADR and a medicinal product to report, but by keeping vigilance for signs and symptoms that may enhance or exclude the possibility of a medicine-induced reaction as well as following up the patient enables the reporter to provide the necessary information for regulators and marketing authorisation holder (MAH) to interpret the case, evaluate the safety issues at hand and act accordingly if required.[6]

All suspected ADRs to all drugs and vaccines must be reported. Although it is highly significant to identify previously unrecognised side effects, it is also important to emphasise the fact that well-known ADRs (particularly serious or severe) of established medicines (e.g. gastrointestinal bleeding with non-steroidal medicinal products) are highly important to report as well.

Additionally, reporting can be made where there is lack of efficacy or when suspected pharmaceutical defects are observed. This aids in improving the quality of batch released medicinal products.

Management of reports

Once a report is received by the MMA, the ADR case is validated and the information is evaluated using a causality assessment method (French imputability method) and against the product's Summary of Product Characteristics (SmPC) to identify the expectedness or not of the ADR. Feedback is sent to the reporter by email or post and if necessary a request for follow up information is made. Reports are then inputted into Eudravigilance database and reporters' details are destroyed from the local paper-based form (to protect confidentiality of the reporter). Staff of the Authority will review safety issues arising from these received reports internally and with national experts/professional associations.

The MMA also requests modifications to be implemented to medicinal product information following safety signal detection activities by the EMA and the opinions adopted by its Committees.

How voluntary reporting of ADRs can affect the marketing authorization and labelling of medicinal products:

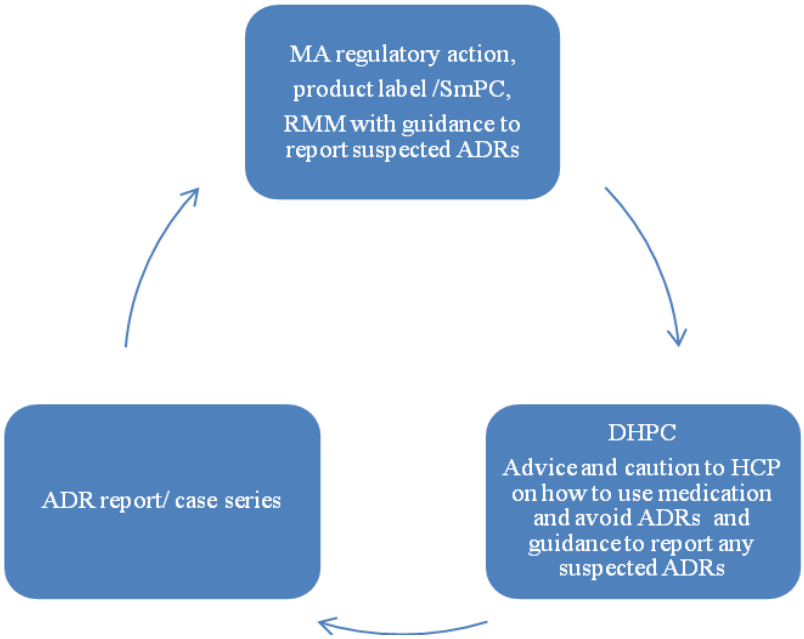
Spontaneous reporting is a system whereby case reports of adverse events are voluntarily submitted by healthcare professionals to the national Pharmacovigilance centre.[7] Once a signal is successfully detected and confirmed from spontaneous reporting; cumulative reviews are carried out by the regulatory authorities to propose any regulatory action deemed necessary (Figure 1).

Regulatory actions can be a change in the product information like in the case of Celecoxib (Celebrex®); where reported cases of severe serious skin reactions and hypersensitivity reactions lead to adding a general statement in section 4.4 of the SmPC regarding these ADRs and a warning to discontinue Celecoxib at the first sign of hypersensitivity reaction.[8] Or in other cases withdrawal from the market like suspension of Valdecoxib (Bextra®) -due to increased reporting of severe and unpredictable cutaneous adverse reactions- and the withdrawal of Fusafungin (Locabiotal®) in April, 2016 following reports of hypersensitivity reactions associated with its use.[9-10]

Risk minimisation measures (RMM) and ADRs

RMMs are a set of activities designed to guide optimal use of a medicinal product in medical practice with the goal of supporting the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring.[11] RMMs are often based on specific issues identified from the pre- or post-authorisation data and from pharmacological principles.[12]

***Figure 1**: How ADR reports influence product labeling and SmPC, RMMs, regulatory action of Medicines Authority and trigger circulation of DHPC*



Since 2009, the MMA has reviewed 505 RMMs.[13] The approved RMMs can be found from the MMA's website: www.medicinesauthority.gov.mt/safetyinf.[14]

RMMs may consist of routine risk minimisation or additional risk minimisation activities. Routine RMMs are those which apply to every medicinal product and they are: [12]

- Summary of product characteristics. [15]
- Package leaflet.[16]
- Product labelling.[16]
- Pack size.[12]
- Legal status: controlling the conditions under which a medicinal product is prescribed or the conditions under which it is administered. For example certain medications are available only by a special medical prescriptions e.g. medicines covered by the Dangerous Drugs Ordinance CAP 101.[17-18]

For some risks a routine approach is not sufficient and "additional measures" are warranted to improve the risk-benefit balance in the approved indications, these

measures come in several forms:

- Educational materials for healthcare professionals and patients such as brochures, checklists and patient alert cards.
- Controlled access programmes: these restrict how the medicines can be prescribed or dispensed, they can be used only when prescribed by a healthcare professional with specific expertise and patient has acknowledged that he is informed of a specific risk before receiving a medicine e.g Thalidomide Celgene.[19]
- Pregnancy prevention programme: These measures aim to ensure that women are not pregnant during treatment with medicinal products that are likely to cause harm to unborn child e.g Thalidomide Celgene Pregnancy Prevention Programme.[20]
- DHPC: These are letters sent directly to healthcare professionals who are likely to use the medicine, to warn them of a new safety concern and to inform them of the actions to mitigate the risk. This safety information may arise from studies, clinical trials or from spontaneous ADR reporting as well. Consequently, ADR reporting is valuable in contributing to the formulation of these advices. Furthermore, DHPCs increase awareness of healthcare professionals about their role and responsibility in reporting, as the final section of a DHPC is a reminder for healthcare professionals to report and how to report. A link to the ADR form is provided along with the contact details of the MMA and MAH to send the completed form. All archived DHPCs can be accessed from MMA's website: www.medicinesauthority.gov.mt/dhpc. To date the MMA approved 201 DHPCs (Table 2).

Table 1: *number of ADR reports received in the years (2010- Nov 2017)* [13,21]

Year	2010	2011	2012	2013	2014	2015	2016	Up to Nov 2017
Number of ICSR	194	150	153	150	169	122	118	228
Number of reported ADRs	403	273	300	349	741	615	613	416
% of Non-Serious ICSR	12.08%	10.7%	7.8%	7.33%	12.42%	4.88%	24.58%	27.89%
% of Serious ICSR	87.92%	89.3%	92.2%	92.66%	87.57%	95.12%	75.42%	72.11%
Most frequent system organ class	General disorders and administration site conditions	General disorders and administration site conditions	Gastrointestinal disorders	General disorders and administration site conditions	Infections and infestations	General disorders and administration site conditions	General disorders and administration site conditions	
Most frequent age criteria	18-64	18-64	12-64	20-64	20-64	20-64	18-64	18-64

When there is a potential safety concern relating to the safe and effective use of a medicinal product including warnings or alerts or product recalls, the MMA will issue a letter called safety circular to inform healthcare professionals. These safety circulars are available on MMA's website: www.medicinesauthority.gov.mt/safetycirculars.
The MMA operates a notification system where healthcare professionals can subscribe and be notified by SMS and e-mail regarding safety concern.[22]

Shared responsibility

It is the responsibility of the MAH to record all the suspected ADRs reported by healthcare professionals or patients and to submit them to "Eudravigilance" database. For these reports

Where the suspected ADRs occurred in Malta, the MMA may involve the MAH in the follow-up of the reports. Together the MAH and the MMA should collaborate to detect any duplicates of suspected ADR reports.

Conclusion

Since 2010 to date, MMA Pharmacovigilance system has received and processed 1284 of suspected ICRS reports. Through reporting, healthcare professionals make a positive contribution to the overall knowledge of the safety profile of medicines and to the national Pharmacovigilance system. All healthcare professionals are therefore encouraged to start reporting or continue to report to enhance and develop this process. MMA greatly appreciates the interest shown by healthcare professionals towards ADR reporting and acknowledges the contribution of busy healthcare professionals to the continued surveillance of the safety of medicines by contributing to the ADR reporting system.

***Table 2**: (Number of approved joint/DHPCs, RMMs in the period 2007- Dec 2017)* [21-22]

Publication / Year	DHPC	RMM	Safety Circulars
Dec 2017	18	103	6
2016	19	107	17
2015	11	88	15
2014	20	91	20
2013	40	94	28
2012	31	38	15
2011	26	22	19
2010	14	11	16
2009	8	21	12
2008	16	/	10
2007	11	/	19
2006	/	/	11
2005	/	/	15
2004	/	/	4
Total	201	505	205

References

1. European Medicines Agency and Heads of Medicines Agency. Guideline on good Pharmacovigilance practices (GVP) Annex I - Definitions (Rev 3). EMA/876333/2011[Internet]. London (UK): European Medicines Agency; 2011[Cited 2016 Aug 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf
2. The European Parliament and the Council of the European. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. OJ. 2012; L299: 1-3.
3. Laws of Malta. SL 458.35 Pharmacovigilance Regulations, 2012. Government Gazette of Malta 2012; 18985:12399.
4. Tanti A, Serracino-Inglott A, Borg JJ. Designing a national combined reporting form for adverse drug reactions and medication errors. East Mediterr Health J. 2015 Jan 1; 21(4):246-55.
5. Reidel MA, Casillas AM. Adverse drug reactions: Types and Treatment options. Am Fam Physician .2003 Nov 1; 68(9): 1781-1791.
6. Couper M. Safety of medicines- a guide to detecting and reporting adverse drug reaction- Why health professionals need to take action [Internet]. WHO; 2002 [Cited 2016 Sep 4].Available from: http://apps.who.int/medicinedocs/en/d/Jh2992e/
7. Brunner M. Pharmaceutical drug safety. In: Muller M, editor. Clinical pharmacology: Current topics and case studies .Vienna: Springer-Verlag Wien; 2010 .P. 268-274.
8. The European Agency for Evaluation of Medicinal Products. Committee for proprietary medicinal products (CPMP). Celecoxib -Article 31 referral –Annex I, II, III. EMEA/CPMP/1747/04A. [Internet]. London (UK) .European Medicines Agency; 2004. [cited 2016 Sep 11] Available from : http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Celecoxib/human_referral_000145.jsp

9. The European Agency for Evaluation of Medicinal Products. Post-authorisation Evaluation of Medicines for Human Use. EMEA public statement on the suspension of the marketing authorisation for Bextra (Valdecoxib) in the European Union. EMEA/358234/2005. [Internet] .London (UK): European Medicines Agency; 2005. [cited 2016 Sep 15] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/12/WC500018391.pdf
10. Les Laboratoires Servier. Direct Healthcare Professionals Communications. Fusafungine containing medicinal products will no longer be available on the market [Internet]. Nanterre (France): Les Laboratoires Servier; 2016 [cited 2016 Sep 16] Available from: http://www.medicinesauthority.gov.mt/dhpc
11. European Medicines Agency and Heads of Medicines Agencies. Guideline on good Pharmacovigilance practices (GVP) Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators. EMA/204715/2012 Rev 1 [Internet]. London (UK): European Medicines Agency; 2014 [cited 2016 Sep 20] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf
12. European Medicines Agency and Heads of Medicines Agencies. Guideline on good Pharmacovigilance practices (GVP) Module V – Risk management systems. EMA/838713/2011 Rev 2[Internet]. London (UK): European Medicines Agency; 2014 [cited 2016 Sep 20] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf
13. Malta Medicines Authority. Annual Reports (2004-2015). [Internet] Gzira: Malta Medicines Authority; 2016. [Cited 2016 Oct 5]. Available from: http://www.medicinesauthority.gov.mt/annual reports.
14. Malta Medicines Authority. Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations for Medicinal Products for Human Use 2015. Gzira (Malta); Malta Medicines Authority; 2015. Available from: http://www.medicinesauthority.gov.mt/safety?l=1
15. European Commission. Enterprise and industry directorate-general consumer good pharmaceuticals. A guideline on SmPC (Summary of product characteristics), September 2009[Internet]. Brussel: European Commission; 2008 [cited 2016 Oct 7].Available from: http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
16. European Commission. Enterprise and industry directorate general consumer good pharmaceuticals. Guideline on the readability of the labelling and package leaflet of medicinal products for human use, 2009. ENTR/F/2/SF/jr (2009) D/869 [Internet]. Brussel: European Commission; 2009. [cited 2016 October 11] Available from: http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf
17. Government of Malta. Medicines Act Subsidiary legislation 31.18 Drugs (Control) regulations: Legal notice 22 of 1985 Drug (control) regulations. Government Gazette of Malta 1985.
18. Government of Malta. Medicines Act Subsidiary legislation 31.18 Drugs (Control) regulations: Legal notice 34 of 1989 Drug (control) (amendments) regulations. Government Gazette of Malta 1989.
19. European Medicines Agency .Thalidomide Celgene-Annex I summary of product characteristics, Annex II.D Conditions and restrictions with regards to the safe and effective use of the medicinal product. EMEA/H/C/000712-PSUSA/2919/201510-3427. [Internet]. European Medicines Agency ; 2009 [cited 2016 Oct 12] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-._Product_Information/human/000823/WC500037050.pdf
20. Celgene Corporation: Risk Minimisation Measures. Thalidomide Celgene Pregnancy Prevention Programme; RMM L04AC02_EU108443001_21052015. [Internet]. Gzira(Malta): Malta Medicines Authority; 2014. [Cited 2016 Oct 12]. Available from : http://www.medicinesauthority.gov.mt/rmm
21. Tanti A, Benjamin M, Serracino-Inglott A, Borg JJ.A review of the national Pharmacovigilance system in Malta-implementing and operating a Pharmacovigilance. Expert opin Drug saf. 2016 Oct 10; 16(1): 65-76.
22. Malta Medicines Authority [internet]. San Gwann: Malta Medicines Authority; c2017 [cited 2017 Apr 3]. Safetyinformation. Available from: http://www.medicinesauthority.gov.mt/safetyinfo.

Original Article

Did the introduction of high-sensitivity Troponin T for the assessment of suspected acute coronary syndrome in Malta result in reduction of hospitalization time? A retrospective review

Ahmed Chilmeran, Yahya Alwatari, Stuart Zintilis, Robert Xuereb

Abstract

Aims: Troponins I and T are biomarkers used for diagnosing myocardial infarction. The recently developed high-sensitivity Troponin T assay can detect levels as low as 3 ng/L which gives the advantage of rapid diagnosis of acute coronary syndrome (ACS) allowing earlier intervention and theoretically earlier discharge. The aim of the study was to audit the hospital practice and its adherence to international guidelines in using Troponin for diagnosing ACS, and to assess the average hospital admission length when using Troponin T compared to the older Troponin I.

Methodology: A retrospective study that included all patients who had Troponin T taken between January 1st and January 31st, 2016 at Mater Dei Hospital (MDH), comparing them to patients who had Troponin I taken between November 1st and November 30th, 2015.

Results: Data collection yielded a total of 1,032 patients in the Troponin T group and 1,004 patients in the Troponin I group. The average length of stay when using Troponin T was 6.42 days whereas the average length of stay when using Troponin I was 7.16 days. Data analysis of those patients also showed that the average time interval between the first and second Troponin was in the region of 9 hours, which is not what the current guidelines recommend.

Conclusion: The use of the new highly sensitive Troponin T resulted in an average reduction in hospitalization time of 0.75 days per patient at MDH. Adherence to the "0/3 hours" guideline of the second Troponin is highly recommended.

Ahmed Chilmeran, MB BCh BAO*
Malta Foundation Programme trainee
ahmed.chilmeran@hotmail.com

Yahya Alwatari, MB BCh BAO
Malta Foundation Programme trainee

Stuart Zintilis, MD (Melit.), BSc (Hons)
Malta Foundation Programme trainee

Robert Xuereb MD FRCP(L) FRCP(E) FESC FACC
Chairman
Department of Cardiology
Consultant Cardiologist
Mater Dei Hospital
Msida, Malta

**Corresponding author*

Keywords

Acute coronary syndromes, High sensitivity cardiac markers, Malta, Troponin T, Myocardial infarction

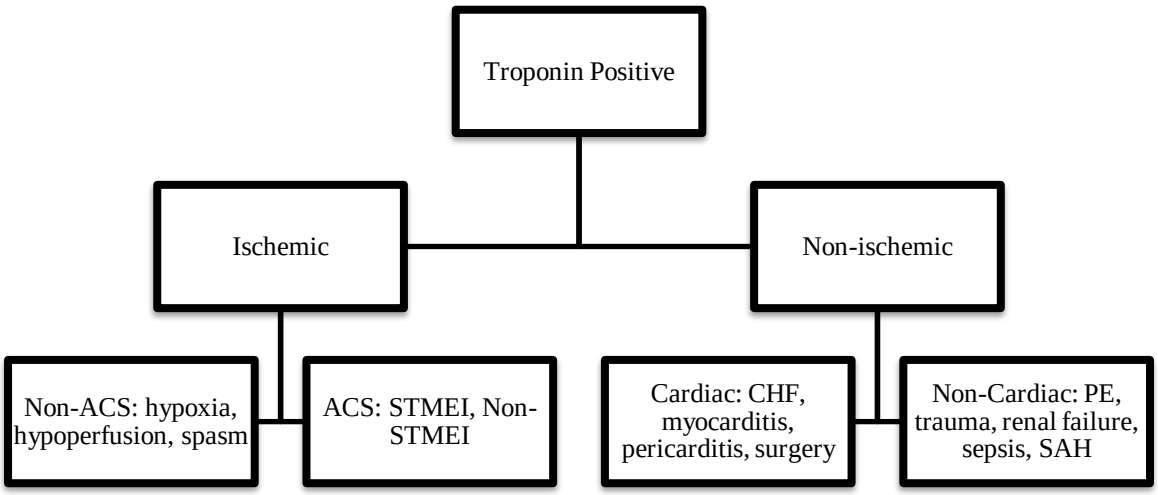
Introduction

Myocardial infarction (MI) is a leading cause of death and disability worldwide. Patients presenting with chest pain account for the second most common reason for emergency department visits in the United States, although only 20% of them are eventually found to suffer from acute coronary event.[1] Cardiac Troponin T (cTnT) and troponin I (cTnI) are enzymes used to confirm or rule out a diagnosis of myocardial infarction (MI) alongside a history of typical chest pain and ECG abnormalities. They are coded by specific genes and are deemed to be unique to the myocardium.[2]

The recent development of high sensitivity

cardiac troponin T (hs-cTnT) permits the detection of very low levels in the blood, which allows for a higher diagnostic accuracy in patients with suspected MI.[3] In addition, the early identification of individuals at risk for MI is vital because patients benefit the most from early and aggressive treatment.[4] In the past there were no set criteria on what a high sensitivity assay included, but this was resolved in 2012 after experts agreed on a definition: "high-sensitivity assays should have a coefficient of variance (CV) of <10% at the 99th percentile value in the population of interest. To be classified as high-sensitivity assays, concentrations below the 99th percentile should be detectable above the assay's limit of detection for >50% of healthy individuals in the population of interest".[5] Hs-cTnT is an extremely sensitive blood test for the diagnosis of MI but not as specific; several other conditions can cause a false positive result. This could create a challenge when trying to correlate a raised level of hs-cTnT and clinical findings, as illustrated in (Figure 1).[5] A meta-analysis involving 9 studies and 9186 patients estimated a sensitivity of 0.94 (95% confidence interval [CI] 0.89-0.97) and a specificity of 0.73 (95% CI 0.64-0.81) for hs-cTnT in diagnosing acute MI presentation to the emergency department.[6]

***Figure 1**: Illustrates causes of Troponin rise*



It is vital that a blood sample is drawn for cardiac troponin from all patients presenting with acute chest pain to the Emergency Department. According to the 2013 ESC guidelines for the management of non-ST elevation MI (NSTEMI), if hs-cTn is being used for the assessment of these patients, the time span between the first hs-cTn and the re-test hs-cTn should be 3 hours rather than the previously adhered to 6 hour time span. This facilitates an earlier rule in and rule out of ACS which leads to earlier intervention if necessary, or earlier discharge.[7]

In Malta, hs-cTnT was introduced to Mater Dei Hospital in December 2015. Prior to this date, cTnI was the cardiac enzyme used to diagnose or rule out MI.

Methods

This study had two aims: the first was to compare hospitalization time between patients admitted with suspected MI before and after the introduction of hs-cTnT, and the second was to audit the time span between the first cardiac Troponin and the follow up Troponin, and whether the ESC guidelines were being adhered to in Malta's main public hospital.

This research was conducted as a retrospective study with inclusion criteria encompassing all patients attending Mater Dei Hospital between November 1st 2015 and November 30th 2015 who had two or more cTnI samples taken. These were subsequently compared with patients attending between January 1st 2016 and January 31st 2016 who had two or more hs-cTnT samples taken. Patients who only had one troponin taken were excluded from this study.

The data was gathered from the Mater Dei Hospital medical computer records system (iSoft).

Exclusion criteria were applied manually by the authors during data analysis.

Results

In the cohort of patients between 1st November and 30th November 2015 there were 1005 patients. 566 were male (age range 10-95 years) and 439 were female (age range 16-100 years). In the cohort of patients between 1st January and 31st January 2016 there were 1031 patients. 571 were male (age range 14-97 year) and 460 were female (age range 18-98 years). Figure 2 compares the gender differences between both populations, while figures 3 and 4 compare the age differences.

The average time span between Troponin I tests that were taken was 9.26 hours (approximately 9 hours and 15 minutes) while the average time span between Troponin T tests that were taken was 9.14 hours (approximately 9 hours and 8 minutes). This resulted in an average reduction of 7 minutes (*P value 0.0001*).

The average length of stay for patients being investigated for suspected Acute Coronary Syndrome whilst using the Troponin I assay was 7.16 days, with a median length of 3 days, and this was reduced to 6.42 days with a median length of 2 days after the introduction of the new high-sensitivity Troponin T assay. This was an average reduction in length of stay of 0.74 days per hospital patient admission (18 hours approximately).

***Figure 2**: Illustrates the gender differences between both populations*

***Figure 3**: Illustrates the age groups in the first group (Troponin I population)*

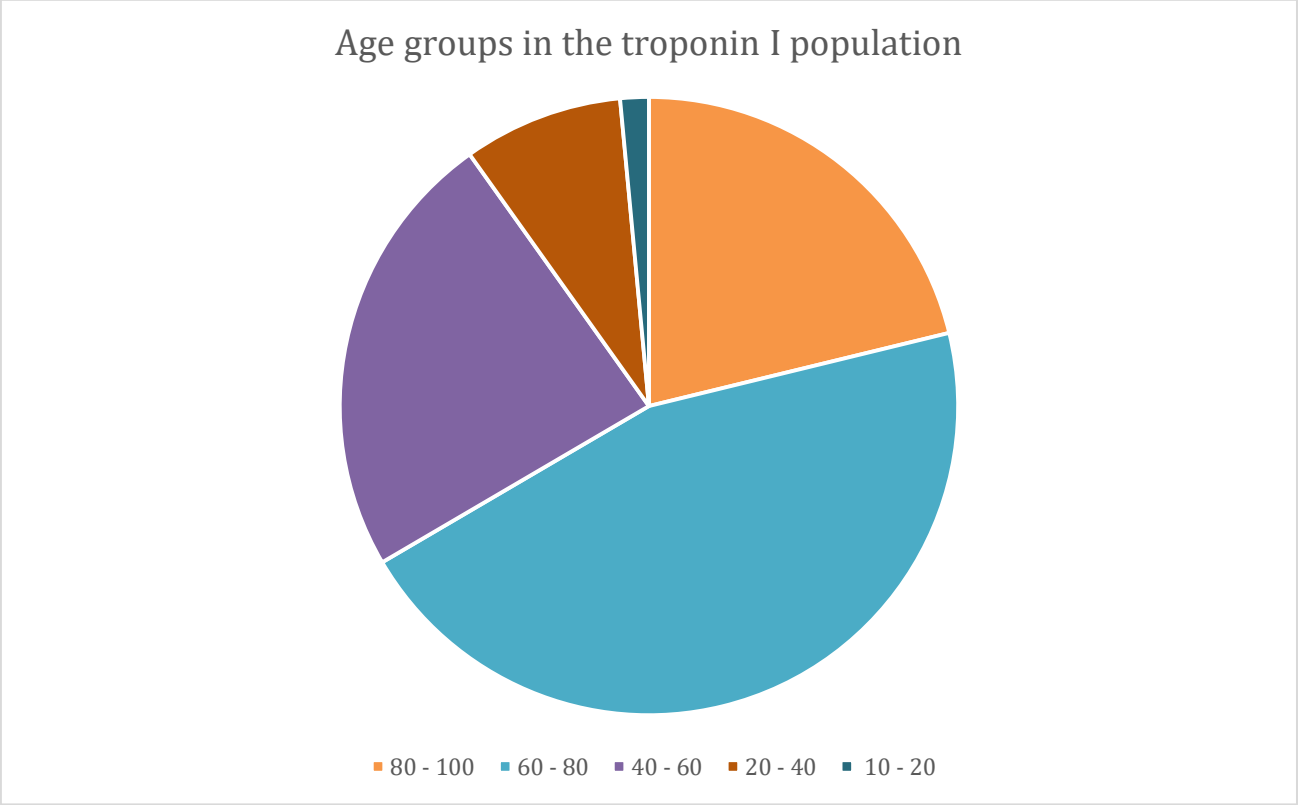
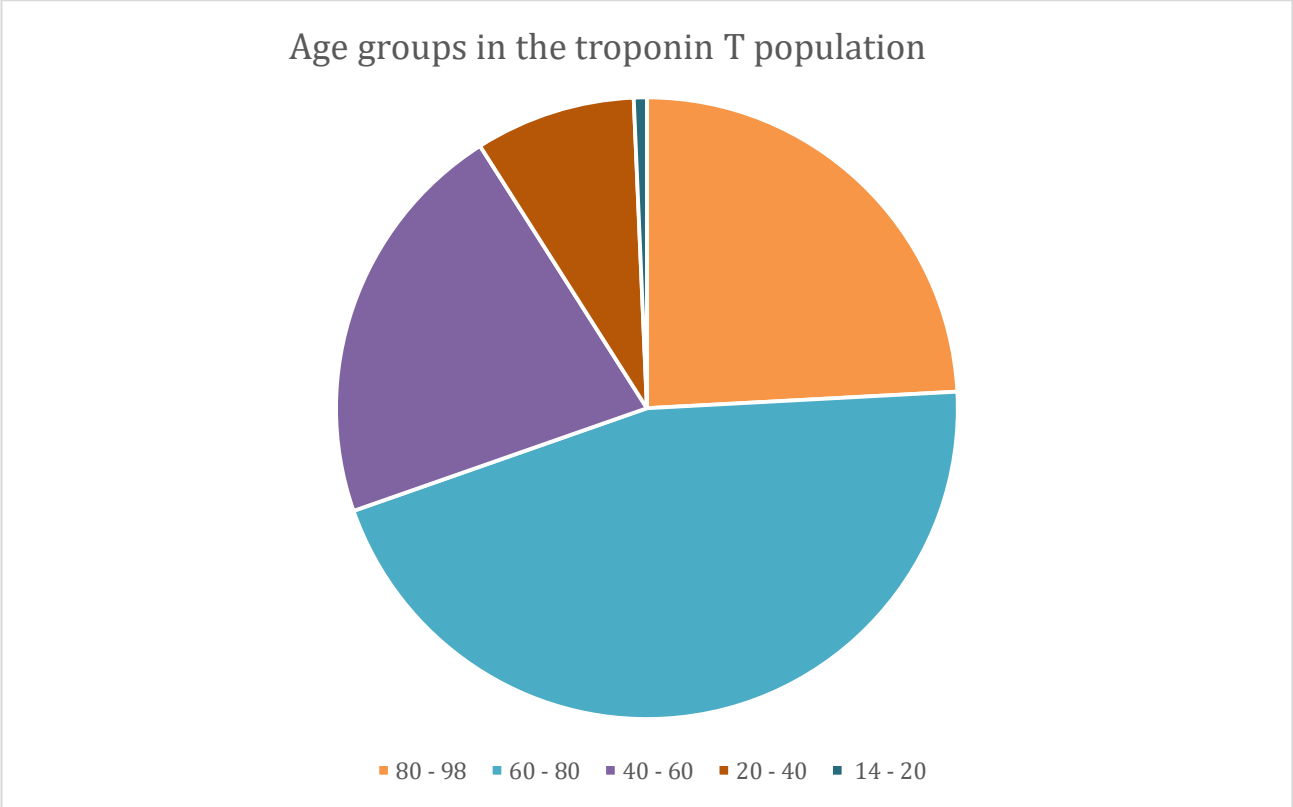


***Figure 4**: Illustrates the age groups in the second group (Troponin T population)*



Discussion

In Malta there is no single, consistent guideline to define the time period between taking serial Troponin T tests in the setting of a suspected Acute Coronary Syndrome. The current UK and European Guidelines state that the time period between Troponin 1 and 2 should be three hours. As can be seen from the results, before the introduction of the new high sensitivity Troponin T test the average time between Troponin I tests was 9.26 hours. After the introduction of the Troponin T tests, a small but significant impact on this time delay was observed, reducing it to 9.14. The reason why there wasn't a significant difference in the interval between the two tests could be attributed to the hospital policy at the time which still recommended a repeat test to be done after a six hour, rather than a three hour, window. We strongly recommended the implementation of change in this policy and repeating the 2nd hs-cTnT in three hours rather than six.

Prior to the introduction of the Troponin T high sensitivity assay, the average length of stay at hospital for patients being investigated for suspected Acute Coronary Syndrome was 7.16 days. With the introduction of the high sensitivity assay this length of stay reduced to 6.42 days. An average reduction of 0.74 days (18 hours approximately) was achieved with *P value less than 0.018*. Based on 2012 national figures published in the Times of Malta, the average cost of a bed in a Medical/Cardiac ward varied from 164.68 Euros to 278.87 (mean 221.78).[8] The reduction in time scale of 18 hours with regards to length of admission with the introduction of the Troponin T assay therefore equates to an average saving of 164.12 Euros per patient admission. Taking into account the fact that during January 2017 the number of patients admitted or already an in-patient but having serial Troponin tests taken was 32.23/day, if each of these patients spent an average 18 hours less as an in-patient, this equates to 23.85 days per month of bed-time saved. This would save an average of 5,289.50 Euros per day to the local health service; equating to 63,473.97 Euros per year. It is, however, too early to tell whether the introduction of hs-cTnT had an impact on mortality rates. This could be a potential aim for a future study.

Some randomized controlled trials have demonstrated the safety and the high efficacy of early patient discharge in accelerated 2-hour protocols when compared to standard care. If we are to standardize such protocols in the Malta health casualty service, the number of admissions will be expected to further decrease with significant economic benefits.[9]

Limitations

The design of our study does not come without a few limitations. The first of those was that other factors were noted to come into play when analyzing the length of stay of patients presenting with chest pain. Some patients in our cohort had a prolonged length of stay due to having multiple co-morbidities and having other diagnoses than ACS, making it necessary in their cases to prolong the length of their inpatient stays. In a few cases it was not possible to attribute differences in length of stay to the different Troponin assays. Another factor which might have confounded the interpretation of our results is the fact that overcrowding of hospital beds in January might have influenced an earlier discharge date for patients presenting the same way as those who presented in November, where less pressure for beds was present.

Another limitation was that in many cases a clear "clinical reason for request" was not adequately provided by the clinician requesting the Troponin blood test, in many cases sufficing with a simple "follow-up". For that reason it was not understood why a Troponin was taken in patients as young as 10 years, for example.

We did not include the diagnosis of patients included in this study or their outcomes as we did not deem it consistent with our scope and aims. We also did not look into time to intervention for patients who ended up being diagnosed with acute MI, although that could be a promising discussion point for another paper.

Conclusion

Based on our study, the introduction of high-sensitivity Troponin T for the assessment of acute coronary syndrome in Malta did result in a statistically significant reduction of hospitalization time and was thus cost effective. Further steps are advised to be taken to ensure adherence to the recent European guidelines of the second Troponin timing. We advise that patients presenting with symptoms suggestive of ACS have their first Troponin taken at the triage stage during the first encounter, which allows the second Troponin to be

taken 3 hours later. This will facilitate either earlier discharge and, if needed, earlier intervention.

Acknowledgments

Acknowledgements to Mr Ian Brincat for his help in collecting the study data

References

1. Alhamaydeh, M., Rivero, D., Alrawashdeh, M., Martin-Gill, C., Callaway, C. and Al-Zaiti, S.S. Electrocardiographic Characteristics of Patients Evaluated at the Emergency Department for a Chief Complaint of Chest Pain. American Heart Association. 2016; 134(1).
2. S Sharma, P G Jackson, and J Makan. Cardiac troponins. Journal of Clinical Pathology. 2014;57(10)
3. Xu RY, Zhu XF, Yang Y, Ye P. High-sensitive cardiac troponin T. Journal of geriatric cardiology: JGC. 2013 Mar;10(1):102.
4. Superko HR, Roberts R, Agatston A, Frohwein S, Reingold JS, White TJ, Sninsky JJ, Margolis B, Momary KM, Garrett BC, King SB. Genetic testing for early detection of individuals at risk of coronary heart disease and monitoring response to therapy: challenges and promises. Current atherosclerosis reports. 2011 Oct 1;13(5):396.
5. Matthew W. Sherwood, L. Kristin Newby. High-Sensitivity Troponin Assays: Evidence, Indications, and Reasonable Use. Journal of the American Heart Association 2014 Feb; 3(1)
6. Al-Saleh A, Alazzoni A, Al Shalash S, Ye C, Mbuagbaw L, Thabane L, Jolly SS. Performance of the high-sensitivity troponin assay in diagnosing acute myocardial infarction: systematic review and meta-analysis. CMAJ open. 2014 Jul;2(3):E199.
7. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2011;32(23):2999-3054.
8. Cassar J. Costs of beds at Mater Dei [Internet]. Times of Malta; [cited 2012 Nov 21]. Available from: https://www.timesofmalta.com/articles/view/20121121/local/Costs-of-beds-at-Mater-Dei.446233
9. Than M, Aldous S, Lord SJ, Goodacre S, Frampton CM, Troughton R, George P, Florkowski CM, Ardagh M, Smyth D, Jardine DL. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. JAMA internal medicine. 2014 Jan 1;174(1):51-8.

Original Article

Assessing the home management of hypoglycaemia in paediatric T1DM

Paul Torpiano, Karen Sapiano, John Torpiano

Abstract

Objectives: The home management of hypoglycaemia is an essential part of diabetes care. All carers of children with T1DM in Malta receive education on managing hypoglycaemia at the time of initial diagnosis. While this education is often revisited at subsequent appointments, it is not always retained and put into practice. We conducted a survey to assess Maltese carers' knowledge of how to manage suspected episodes of hypoglycaemia in their children, as well as identify areas where carers feel least confident.

Methods: All Maltese patients under the age of 16 years with T1DM were included. A questionnaire was formulated to assess various aspects of hypoglycaemia management that any carer of a child with T1DM might be expected to know. The carer of each patient with T1DM was contacted a minimum of 6 months following the diagnosis of T1DM.

Results: 117 carers of children with T1DM were interviewed by telephone or in person. While most correctly described appropriate first-line management of suspected hypoglycaemia, only 21% recognised the need to place an unconscious child in the lateral recumbent position, and only 53% suggested they would avoid giving anything by mouth in such an event. Over 80% felt confident in managing hypoglycaemia, but 78% feared using intramuscular glucagon.

Conclusions: This survey highlights areas of knowledge that parents of children with T1DM lack despite regular education. Doctors taking care of children with T1DM should regularly assess carers' knowledge, and discuss specific areas of concern.

Key words

Patient education, paediatric, T1DM, glucagon, hypoglycaemia

Paul Torpiano*, M.D., M.R.C.P.C.H., M.R.C.P.
Higher Specialist Trainee in Paediatrics
Mater Dei Hospital
Msida, Malta
paul.torpiano@gov.mt

Karen Sapiano, M.D.
Basic Specialist Trainee in Anaesthesia
Mater Dei Hospital
Msida, Malta

John Torpiano, M.D., M.Sc.(Lond), F.R.C.P., F.R.C.P.C.H.
Consultant Paediatric Endocrinologist
Mater Dei Hospital
Msida, Malta

**Corresponding author*

Introduction

Type 1 Diabetes Mellitus (T1DM) is common in Maltese children, occurring at an incidence rate of 21.8/100,000 children/year. This incidence rate appears to be rising.[1] Recurrent hypoglycaemia limits optimal glycaemic control in T1DM, and may cause high glycosylated haemoglobin (HbA1c) values when repeatedly over-treated or when carers maintain the blood glucose concentration in a higher-than-ideal range in an attempt to avoid hypoglycaemia.[2] Recurrent, severe episodes of hypoglycaemia in children are also associated with altered cognitive function, and may influence learning and attention levels as the child grows.[2] Furthermore, hypoglycaemia can be expensive: in an Italian study, 58 work-days per 100 person-years were lost by patients or their family members because of hypoglycaemia. Hypoglycaemic episodes cost €91 per person-year, while the total annual cost of hypoglycaemia in T1DM in Italy was over €26 million per annum.[3] The burden of hypoglycaemia in T1DM is both direct and indirect. Direct costs include medications used to treat

hypoglycaemia (glucose/glucagon), ambulance services, hospitalization for severe episodes, family doctor contact, and additional blood glucose testing required during periods of hypogylcaemia.[4-5] Indirect costs include working time lost due to hypoglycaemic episodes and additional food needed to treat hypoglycaemia. [4-5]

All patients under the age of 16 years in Malta are followed by a single paediatric diabetes team at Mater Dei Hospital. Patient education about the various aspects of T1DM and its care is provided at diagnosis, and this includes the management of hypoglycaemia. Printed information sheets are given, additional to meetings with the patients and their carers. All information is delivered by paediatric diabetes specialists, with support by the specialist diabetic nursing team. The patients are followed up at least every 3 months, and diabetes education is opportunistically revisited on these occasions.

The aim of this survey was to assess the knowledge retained by carers of paediatric and adolescent T1DM patients taught how to manage episodes of hypoglycaemia appropriately outside hospital, and identify the impact of the current paediatric education offered to carers of children with T1DM at Mater Dei Hospital in Malta.

Methods

All Maltese patients with T1DM under the age of 16 years, under the care of the paediatric endocrinology team at Mater Dei Hospital, were included. This is the main national hospital in Malta and the only one providing specialist paediatric diabetes care. A questionnaire was formulated, written in both English and Maltese. This questionnaire asked about various aspects of hypoglycaemia management that any carer of a child with T1DM might be expected to know, as based on the information sheet given to every family at the time of diagnosis. Questions were of two types: open-ended questions aimed to assess carers' awareness of how to generally handle a hypoglycaemic episode, while close-ended questions were asked at the end to assess carers' knowledge of specific areas of hypoglycaemia management. Each carer was contacted a minimum of 6 months following the diagnosis of T1DM. This was done to avoid interviewing carers of children with recently-diagnosed diabetes, who might not have had the opportunity to absorb the taught information, and who might not have had much experience yet in the management of hypoglycaemia. Furthermore, if questioned too close to the date of diagnosis, the carers' knowledge might reflect a lecture they had received recently, rather than retained information they would apply to the real-life scenario of hypoglycaemia.

For each patient, the carer was contacted on telephone numbers available on hospital records. The answering carer was asked if he or she would ordinarily take responsibility for the child's diabetes management. It is often one of the two parents who specifically takes charge of a child's medical care: questioning the parent who would ordinarily not be expected to manage the hypoglycaemia might have given an unfairly poor representation of the management the patient would receive in real life. The questionnaire was piloted on 20 carers to ensure that they were easily understood. The remainder of the study population was then questioned over a period of 4 months.

RESULTS

130 patients fulfilled the inclusion criteria, and 117 (90%) carers were successfully interviewed. 82 (70.1%) correctly identified 4 mmol/L as the recommended cut-off capillary blood glucose to define hypoglycaemia (Table 1). 55 (47%) could give 3 or more causes of hypoglycaemia, while 65 (55.6%) could mention at least 3 possible symptoms of hypoglycaemia to look out for.

107 (91.5%) said they would confirm a suspected episode of hypoglycaemia by testing the capillary blood glucose, while 10 (8.5%) said they did not feel the need to do this once hypoglycaemia was suspected (Table 2). 111 (95%) said that in the event the carer suspected a hypoglycaemia, and their glucose meter was unavailable, they would assume the diagnosis of hypoglycaemia and treat as such. 3 carers said they would seek medical attention in such a situation. 110 (94%) knew that hypoglycaemia should be treated with a sugar-containing product given by mouth, while 97 (83%) identified the recommended amount of sugar to administer. When asked what they would do if their child developed decreased level of consciousness, 96 (82%) specified they would avoid putting anything in their child's mouth.

Table 1. *Results: Recognising a hypoglycaemic episode.*

Recognising a hypoglycaemic episode		
i. Knowledge of the lower limit of CBG (4mmol/L)		
Response	**No. of carers**	**%**
<7mmol/L	1	0.9
<5mmol/L	5	4.2
Correctly identified as <4mmol/L	**82**	**70.1**
<3mmol/L	17	14.5
<2mmol/L	10	8.5
<1mmol/L	1	0.9
Does not know	1	0.9
ii. Knowledge of causes of hypoglycaemia		
Causes known	**No. of carers**	**%**
0	1	0.9
1	8	6.8
2	53	45.3
3	47	40.2
≥4	8	6.8
iii. Knowledge of the symptoms of hypoglycaemia		
Symptoms known	**No. of carers**	**%**
0	1	0.9
1	12	10.3
2	39	33.3
3	49	41.9
4	13	11.1
≥5	3	2.6

111 (95%) identified the need to re-check the CBG after giving oral sugar for hypoglycaemia, while 66 (57.4%) said they would wait 11-15 minutes before doing so. If the CBG remained below 4 mmol/L on re-testing, 100 (85.5%) said they would give a second oral dose of sugar, a further 28 (24%) saying they would check the CBG once again 15 minutes afterwards. 101 (86.3%) knew that a snack or meal should be given after successful correction of hypoglycaemia. 114 (97.4%) confirmed they would record an episode of hypoglycaemia on their diabetes diary to discuss with the doctor at the next available clinic visit.

Concerning the management of severe hypoglycaemia (Figure 1), 113 (96.6%) recognized the need for glucagon by intramuscular injection in this situation. Fifty-eight (49.6%) said they would call an ambulance immediately, and only 25 (21.4%) emphasised the importance of placing the child in a lateral recumbent position. 102 (87.2%) said they would call emergency services if the child failed to show signs of a response within 10 minutes of glucagon administration, and 95 (81.2%) understood the need to give oral sugar to the child once he or she recovered consciousness following glucagon administration. 85 (72.6%) could correctly recall the free phone number to call emergency services.

43 (36.8%) and 52 (44.4%) of carers felt ‘very good’ or ‘quite good’ respectively when asked about how confident they felt in managing hypoglycaemia (Figure 2). Only 1 (0.9%) felt ‘quite bad’ at this, while 4 (3.4%) felt ‘very bad’. 91 (77.8%) of carers said that using glucagon was the main aspect of hypoglycaemia management that they did not feel confident about.

Table 2. *Results: Managing a hypoglycaemic episode (HC = Health Centre: A&E = Accident and Emergency).*

Managing a hypoglycaemic episode		
i.	**Knowledge of the need to confirm suspected hypoglycaemia**	
Response	**No. of carers**	**%**
Checks CBG	107	91.5
Does not check CBG first-line	10	8.5
ii.	**Knowledge of what to do in case glucose monitor is unavailable/not functioning**	
Assumes it is a 'hypo' and treats as such	111	95
Calls Doctor	1	0.9
Goes to HC or A&E	3	2.6
Does not know	1	0.9
Other	1	0.9
iii.	**Knowledge of administration of oral sugar as first-line treatment for hypoglycaemia**	
Response	**No. of carers**	**%**
Yes	117	100
No	0	0
iv.	**Knowledge of administration of oral sugar – appropriate choice of sugar (fast-acting)**	
Response	**No. of carers**	**%**
Yes	110	94
No	7	6
v.	**Knowledge of administration of oral sugar – appropriate amount of sugar (15g)**	
Response	**No. of carers**	**%**
Yes	97	83
No	18	51.3
Not specified	2	17
vi.	**Knowledge of need to keep patient nil-by-mouth in case of loss of consciousness**	
Response	**No. of carers**	**%**
Yes	96	82
No	21	8
vii.	**Knowledge of need to re-check CBG after administering oral sugar**	
Response	**No. of carers**	**%**
Yes	111	95
No	6	5
viii.	**Knowledge of how long to wait before re-checking CBG after administering oral sugar**	
Response	**No. of carers**	**%**
0-5 minutes	7	6
6-10 minutes	14	12
11-15 minutes	66	56.4
16-20 minutes	8	6.8
21-30 minutes	9	7.7
31-45 minutes	2	1.7
46-60 minutes	4	3.4
>60 minutes	4	3.4
Does not know	1	0.9
Does not check again	2	1.7
ix.	**Knowledge of what to do if CBG remains low on re-checking**	
Response	**No. of carers**	**%**
Repeats oral dose of sugar	100	85.5%
Re-checks CBG after further 15 minutes	28	24%
Repeats 1) and 2) until CBG>4mmol/L	19	16.2%
Re-checks CBG after 15 minutes without giving oral sugar	1	0.9%
Gives snack/lunch/carbohydrates	10	8.5%
Does not know	4	3.4%
Administers glucagon	1	0.9%
x.	**Knowledge of need to give carbohydrates/snack/meal after hypoglycaemic episode**	
Response	**No. of carers**	**%**
Yes	101	86.3
No	16	3.7
xi.	**Knowledge of need to record hypoglycaemic episodes**	
Response	**No. of carers**	**%**
Yes	114	97.4
No	3	2.6

***Figure 1**: Results: Managing an episode of severe hypoglycaemia (IM = intramuscular).*

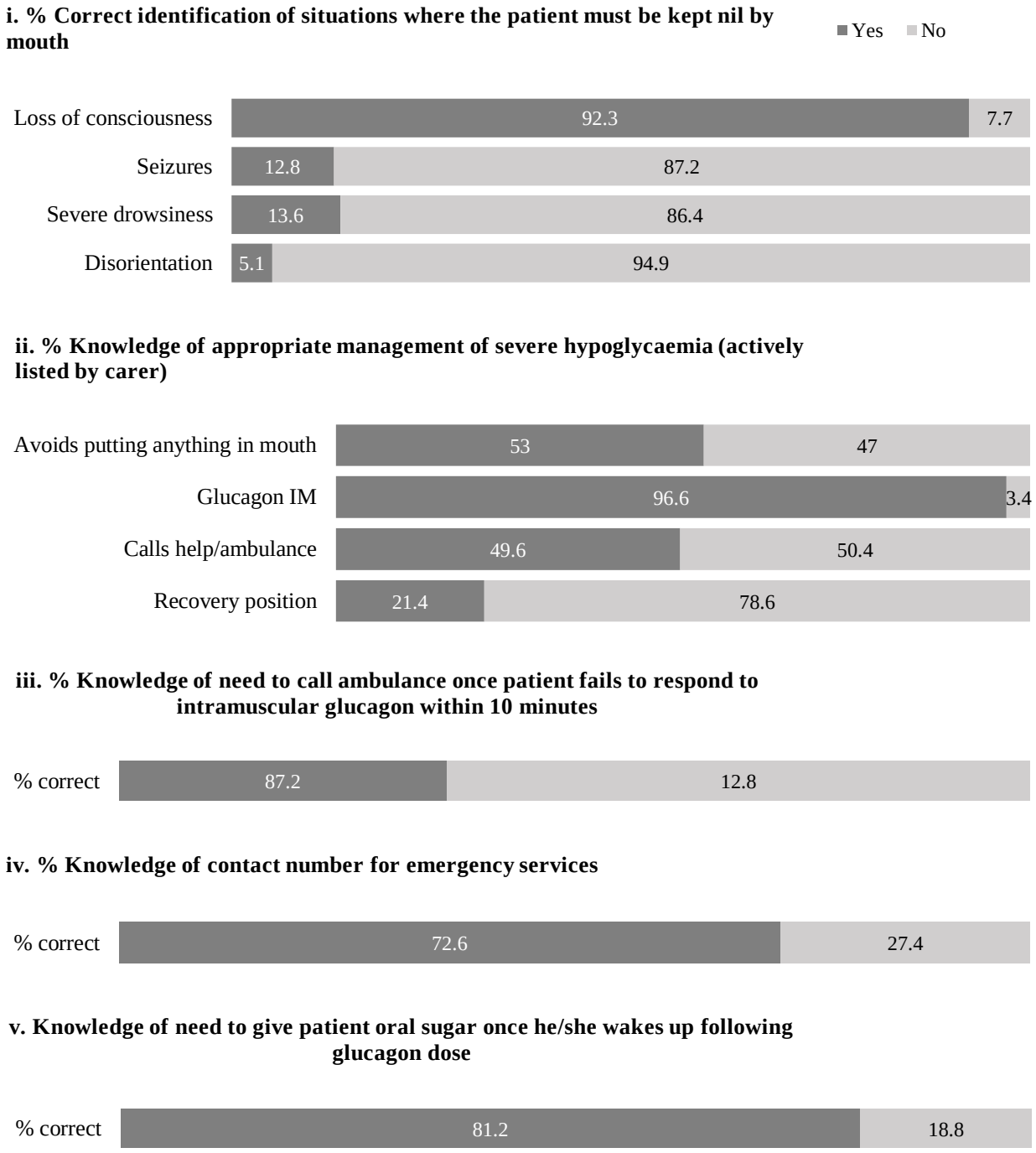
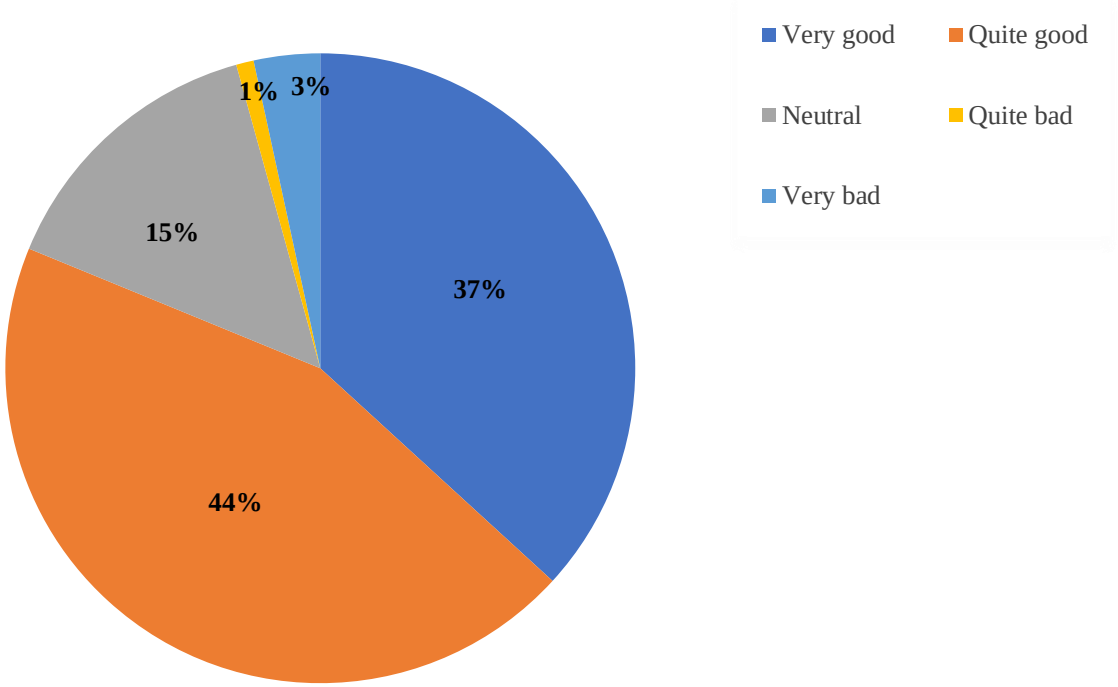
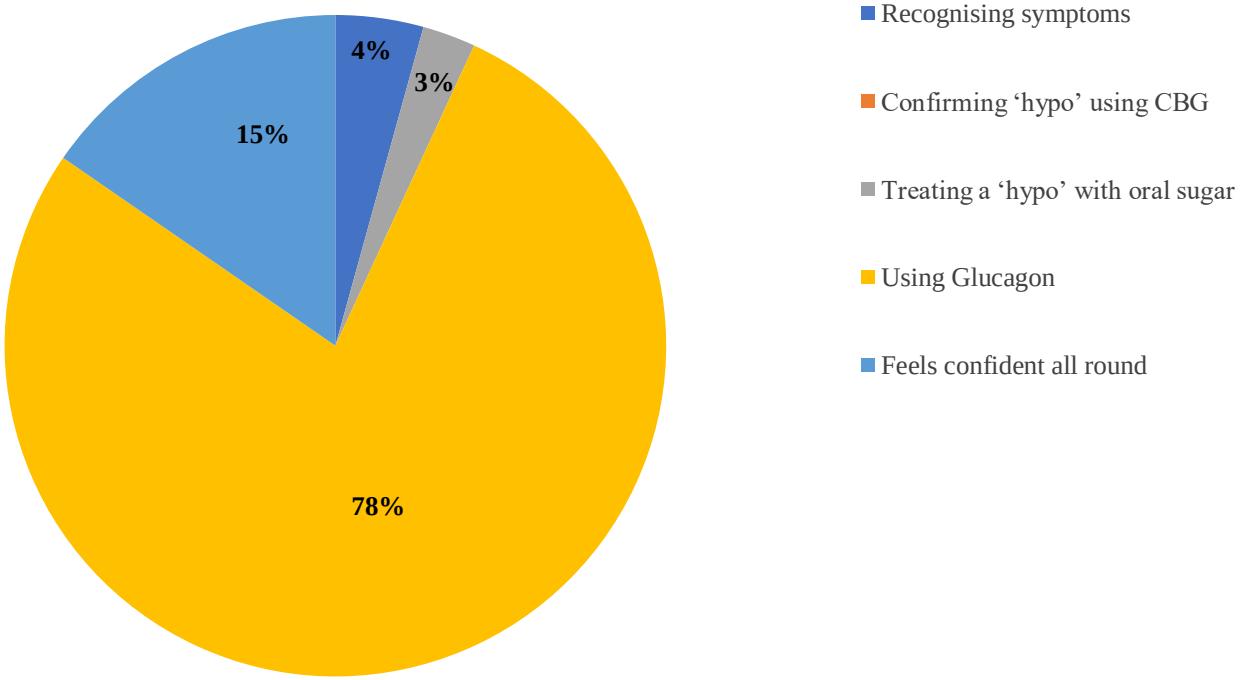


Figure 2. *Results: Assessing parental confidence in managing hypoglycaemia.*

i. How confident do parents feel in managing hypoglycaemia?



ii. Where do parents feel least confident?



Discussion

We present an assessment of the knowledge retained by carers of children and adolescents with T1DM, pertaining to the management of hypoglycaemic episodes. The data obtained covers the whole paediatric population with T1DM in Malta, and is the first of its kind in our country. It provides insight into the approach that doctors who see children with T1DM take regarding patient education. In Malta, carers of children with T1DM receive several one-to-one teaching sessions at initial diagnosis, covering most aspects of home care, including management of hypoglycaemia. This teaching is revisited opportunistically at subsequent outpatient visits, though there is no structured follow-up programme to assess carer knowledge retention and reinforce points that may have been forgotten.

Maltese carers fared worst in the section investigating their knowledge of managing an episode of severe hypoglycaemia. It was worrying that only 53% actively suggested they would avoid putting anything in their child's mouth in this situation, and although 96.6% appropriately mentioned intramuscular glucagon as the treatment of choice here, 77.8% said they did not feel confident in administering this drug. Furthermore, only 21.4% suggested they would place their child in the recovery position. These lacunae in their knowledge could put a hypoglycaemic child at increased risk of aspiration and other complications of severe hypoglycaemia. Just under 50% suggested they would immediately resort to emergency services in the event of a severe hypoglycaemic episode. This approach may lead to considerable inconvenience for the family of a child with T1DM, and will contribute to the patient load and thus overall waiting times at the hospital paediatric emergency department.

What may be the reasons for these specific failings in the knowledge of carers of patients with T1DM? Little emphasis may have been placed on the management of emergencies within T1DM, particularly at follow-up outpatient encounters, when the child in attendance is often alert and well. Education is often focused on theoretical aspects of T1DM and its care, rather than practical scenario-based sessions placing the carer in a situation where he or she must act out the management of hypoglycaemia. The same is true for the use of glucagon, and practical teaching sessions on the use of intramuscular glucagon, particularly for those carers with little experience in managing severe hypoglycaemia, would probably be useful. Another potential problem is that carers might receive conflicting information and advice from different health care professionals they meet in various settings, including the emergency department, hospital wards, school, outpatients' department, health centres, family doctor and private paediatrician. A consistent understanding of the recommendations made to carers on how to manage hypoglycaemia would be beneficial.

The study has several limitations. As carers were asked about what they remembered of what was taught to them, as well as questions relating to their own experience in managing hypoglycaemia, a degree of recall bias was inevitable. Secondly, a robust knowledge of the guidelines provided to parents might not necessarily reflect appropriate application of this knowledge in a real-life scenario of a child with hypoglycaemia. In these settings, panic might understandably take over, causing carers to forget the necessary steps to take. On the other hand, carers who struggled to respond correctly might find that they perform reasonably well in a real-life situation. The study considered the national picture, and has not investigated the influence of differing levels of education on the degree of retained knowledge. Furthermore, the telephone questionnaire was made opportunistically over a four-month period, meaning that the length of time that had elapsed since the last meeting with the paediatric diabetes team varied from one carer to another. This variation in time may have had a bearing on which carers responded correctly to the questionnaire. Lastly, although carers might be expected to have a robust knowledge of what to do in the circumstances of a hypoglycaemic episode, their knowledge might be influenced by their individual experiences. Some carers may never have had to deal with hypoglycaemia, while others might have had repeated experience with this. This experience may either make carers more proficient in the appropriate management of hypoglycaemia, or might have the opposite effect: leaving them more accepting of deviations from the target range of CBG.

In conclusion, appropriate training and education of carers of children and adolescents with T1DM is an essential part of their long-term care, not least in the management of hypoglycaemia.

Medical professionals responsible for the care of children with T1DM should include regular assessments of carer knowledge and concerns in the routine follow-up of these patients, as well as structured re-education. Failure to do this may potentially put the child at risk during an episode of severe hypoglycaemia.

References

1. Formosa N, Calleja N, Torpiano J. Incidence and modes of presentation of childhood type 1 diabetes mellitus in Malta between 2006 and 2010. Pediatr Diabetes. Denmark; 2012 Sep;13(6):484–8.
2. Cryer PE. Hypoglycemia risk reduction in type 1 diabetes. Exp Clin Endocrinol Diabetes. Germany; 2001;109 Suppl:S412-23.
3. Giorda CB, Rossi MC, Ozzello O, Gentile S, Aglialoro A, Chiambretti A, et al. Healthcare resource use, direct and indirect costs of hypoglycemia in type 1 and type 2 diabetes, and nationwide projections: Results of the HYPOS-1 study. Nutr Metab Cardiovasc Dis. Netherlands; 2016 Nov;
4. Brod M, Hojbjerre L, Bushnell DM, Hansen CT. Assessing the impact of non-severe hypoglycemic events and treatment in adults: development of the Treatment-Related Impact Measure-Non-severe Hypoglycemic Events (TRIM-HYPO). Qual Life Res. Netherlands; 2015 Dec;24(12):2971–84.
5. Heller SR, Frier BM, Herslov ML, Gundgaard J, Gough SCL. Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. Diabet Med. England; 2016 Apr;33(4):471–7.

Original Article

An Audit on the Practice of Performing a Chest X–Ray in Infants with Bronchiolitis

Sarah Anne Caruana Galizia, Veronica Said Pullicino, Cecil Vella

Abstract

Introduction: Bronchiolitis is one of the most common medical emergencies in infancy. One in three infants will develop bronchiolitis in the first year of life. 2 - 3 % of these require hospitalisation.

Aims: To assess the local practice of performing a chest X-ray in infants aged less than 6 months presenting with viral bronchiolitis and to compare this practice with the recommendations of the National Institute for Health and Care Excellence (NICE)[1] and American Academy of Paediatrics (AAP) clinical practice guidelines for bronchiolitis[2]. The secondary aim was to quantify how many of the chest X-rays performed were abnormal, and whether these were indicated or not.

Methodology: Approval was obtained from the Audit Committee and Data Protection Act Committee. Data was collected on infants aged less than 6 months who presented to the Paediatric Accident and Emergency department, Mater Dei Hospital, Malta between January - April 2016 and October 2016 - February 2017, with symptoms of bronchiolitis. The data was retrieved retrospectively from medical records and compared to a set of indications from NICE and AAP guidelines. Picture Archiving and Communication System was utilised to view chest X-rays and obtain radiologists' reports.

Results: 148 patients satisfied the inclusion criteria for bronchiolitis. 81 (54.7%) had a chest X–ray performed. Only 28 (34.6%) of the chest X-rays were indicated according to the guidelines. Overall percentage compliance to the guidelines was 64.2%. 67 (82.7%) of the chest X-rays performed were normal. 8 (57.1%) of the 14 abnormal chest X-rays were performed according to the guidelines.

Conclusion: There is room for improvement in abiding to the AAP and NICE guidelines with regards to the practice of performing chest X-rays in patients presenting with bronchiolitis. Abnormal chest X-rays, whether indicated or not, should be interpreted with caution. Adhering to the guidelines would result in a decrease in patient radiation exposure.

Keywords

Chest x-ray, bronchiolitis, compliance, guidelines

Sarah Anne Caruana Galizia M.D.*
Department of Paediatrics
Mater Dei Hospital
Msida, Malta
Sarah.caruana-galizia@gov.mt

Veronica Said Pullicino M.D., M.R.C.P.C.H.
Department of Paediatrics
Mater Dei Hospital
Msida, Malta

Cecil Vella M.D., M.R.C.P. (UK), F.R.C.P.H.
Consultant Paediatrician
Department of Paediatrics
Mater Dei Hospital
Msida, Malta

**Corresponding author*

Introduction and Aims

Bronchiolitis is the most common disease of the lower respiratory tract during the first year of life and one of the most common medical emergencies in infancy. 1 in 3 infants develop bronchiolitis in the first year of life and 2 - 3 % of all infants require admission to hospital.[1] Consequently, it is a burden for the child and respective families and is very costly for the

healthcare system.[3-4]

The diagnosis of bronchiolitis is a clinical one. The condition occurs in infants less than 2 years of age and is characterised by a viral upper respiratory tract prodrome followed by increased respiratory effort and is commonly associated with decreased feeding.[1-2]Apnoea may be the presenting symptom particularly in those infants with a history of prematurity.[5] Several viruses are responsible for causing bronchiolitis, respiratory syncytial virus (RSV) being the most common. In vulnerable children, such as those with underlying chronic conditions, bronchiolitis may cause significant morbidity and mortality.[2] However, the number of deaths from respiratory failure in bronchiolitis remains low.[6-7]

Clinicians should diagnose bronchiolitis and assess disease severity based on history and physical examination.[2] Chest X–rays should not be taken indiscriminately as they carry a small but significant exposure to radiation and are rarely useful in the diagnosis.

The NICE and AAP Guidelines on bronchiolitis have specific indicators on when to perform chest X-rays, as shown in Table I. According to the NICE Guidelines 'Fever in under 5s: assessment and initial management' a chest X-ray is indicated in children aged < 3 months presenting with fever if respiratory signs are present.[8] The latter was included as an indication for performing a chest X-ray in this audit.

The aim was to assess the local practice on performing a chest X-ray in infants aged less than 6 months presenting with viral bronchiolitis and compare this to the recommendations of the National Institute for Health and Care Excellence (NICE)[1] and American Academy of Paediatrics (AAP)[2] clinical practice guidelines for bronchiolitis. The secondary aim was to quantify how many of the chest X-rays performed were abnormal, and whether these were indicated or not.

Table I: *Indicators for performing a chest X-ray in infants with bronchiolitis according to the NICE[1] and AAP guidelines.[2]*

Indicators for performing a Chest X-ray	**NICE Guidelines[1]**	**AAP Guidelines[2]**
Fever $\geq 39^0$C	✔	
Persistent focal crackles	✔	
Signs of airway complication		✔
Signs of unexpected worsening disease		✔
Need for NPICU admission	✔	✔
Respiratory signs and fever in infant aged < 3 months	✔	

Methodology

Approval was obtained from the Audit Committee and Data Protection Act Committee. All patients aged less than 6 months attending the Paediatric Accident and Emergency Department between January to April 2016 and October 2016 to February 2017, with bronchiolitis, were included in the audit. The data was retrieved retrospectively from the patients' medical records and compared to a set of indications from the aforementioned NICE and AAP guidelines.

For the purpose of this audit, a diagnosis of bronchiolitis was based on a coryzal prodrome lasting 1 - 3 days followed by persistent cough, tachypnoea and/or chest recessions and the presence of wheeze and/or crackles. Patients aged less than 6 weeks presenting solely with apnoea were also included.[1]

Picture Archiving and Communication System was utilised to view chest X-rays and obtain radiologists' reports.

The overall percentage compliance to the guidelines was calculated using the following formula:

Percentage Compliance = (Number of patients for whom chest X-ray not taken and not indicated + Number of patients for whom Chest X - ray taken and indicated/ Total number of patients) x 100.

Results

A total of 148 patients had the necessary inclusion criteria for the diagnosis of bronchiolitis. 81 (54.7%) had a chest X–ray performed. Only 28 (34.6%) of the chest X-rays were indicated according to guidelines[1-2] (Figure I). Out of the 67 patients who did not have a chest X-ray performed, 2 had a fever $\geq 39^0$C. The overall percentage compliance to the guidelines was 64.2%.

The main indications for imaging were the need for a chest X-ray as part of a sepsis screen in febrile infants below the age of 3 months, the presence of signs of an airway complication and severe respiratory distress requiring admission to the Neonatal Paediatric Intensive Care Unit (NPICU) (Figure II). Table II demonstrates the number of indications present for those chest X-rays that were taken as per guidelines.

67 (82.7%) of the chest X-rays performed were normal or reported as showing peribronchial cuffing and 14 were abnormal. From the latter, 13 showed the presence of consolidation and 1 showed an incidental finding of dextrocardia. 8 (57.1%) of these 14 abnormal chest X-rays were performed according to the guidelines.

Figure I: *Percentage of chest X–rays indicated.*

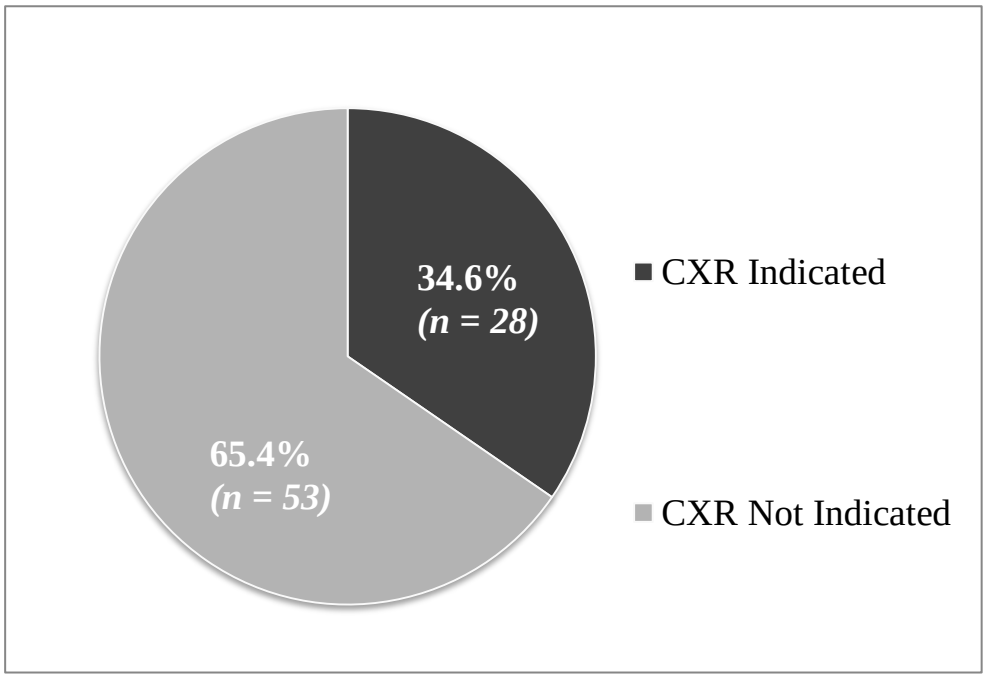
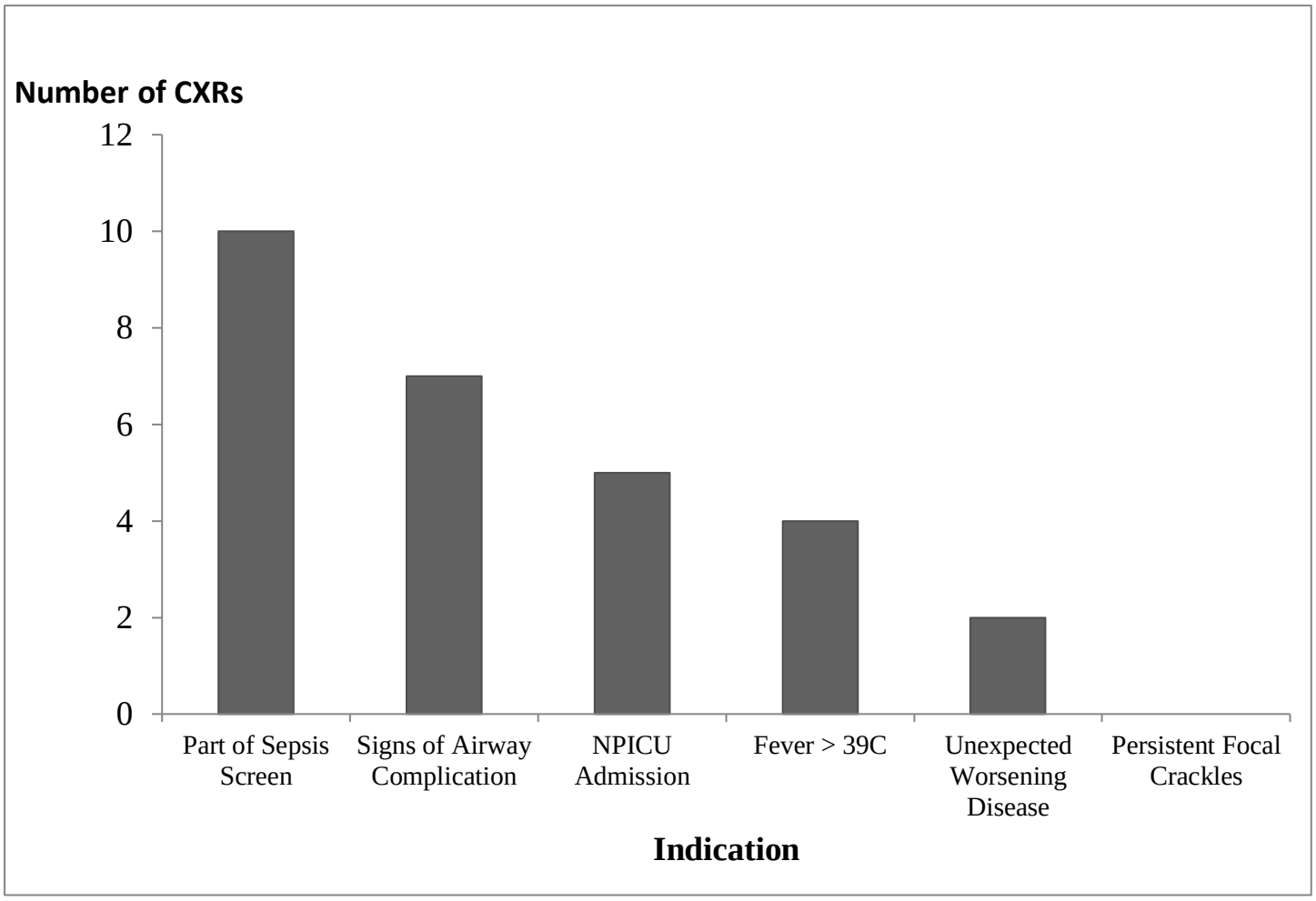


Table II: *Number of indicators present in the patients for whom a chest X-ray was performed according to guidelines.*

Number of Indicators for CXR	Number of Patients
1	24
2	4
≥ 3	0

Figure II: *Hierarchy of indications for chest X-ray.*



Discussion

During the study period, 82.7% of the chest X-rays performed for infants presenting with bronchiolitis were reported as normal or as showing peribronchial cuffing, in keeping with a diagnosis of bronchiolitis. A study by Nazif et al, showed that 84% out of 553 chest X-rays taken on infants with bronchiolitis were normal, a figure which is comparable to the results of this audit.[9]

This highlights the importance of clinicians diagnosing bronchiolitis and assessing disease severity based on history and physical examination.[2] Recent guidelines and evidence-based reviews suggest that no diagnostic tests are used routinely, as they do not have a substantial impact on the clinical course of bronchiolitis.[2-10] There is no correlation between chest X-ray changes and disease severity in infants presenting with bronchiolitis.[2]

81 chest X-rays were performed in this audit but 65.4% of these were not indicated. Clinicians must keep in mind the harmful effects of ionizing radiation associated with imaging procedures such as chest radiography. These may result in high cumulative effective doses of radiation.[12] In a 5 year old child, a single PA film chest X-ray is equivalent to 3 days of natural background radiation. The typical effective dose is that of 0.02 millisieverts. The risk of developing cancer from low-level radiation such as with diagnostic imaging procedures is uncertain. It is assumed that a linear relationship exists between exposure and cancer risk, and that there is no threshold value below which this risk is zero. As a result of these assumptions, the probability of developing cancer is presumed to increase with radiation dose even for low dose medical imaging procedures.[13-18] A precautionary approach should be taken so as to assure that the radiation dose used to perform the procedure does not exceed the dose required to obtain an image of adequate diagnostic quality.[19] Imaging modalities such as chest X-rays should therefore be used sparingly in children.

In addition to the adverse effects of radiation,

performing chest X-rays that are not indicated also unnecessarily delays patient transition from the emergency department to the inpatient ward and is an extra financial burden on the health service.

Parental requests and anxiety, as well as relative unfamiliarity of the foreign guidelines, are possible reasons for the low adherence to NICE and AAP recommendations. Despite guidelines, the clinician's acumen must be taken into consideration and performing a chest X-ray, if justified, supersedes the aforementioned drawbacks.

In this audit, 6 of the 14 abnormal chest X-rays were not indicated. These were all reported as showing a consolidation. The NICE guideline on bronchiolitis states that findings on chest X-ray may mimic pneumonia and lead to the unnecessary use of antibiotics, thus increasing antimicrobial resistance, without improving outcomes.[1]

In a study by Breakell R. et al, a simple educational intervention in the form of sessions to raise awareness of appropriate and inappropriate management of bronchiolitis amongst clinicians and nursing staff, held after the publication of the NICE bronchiolitis guideline, led to a fivefold reduction in the number of chest radiographs and enhanced compliance with the NICE guideline.[20]

A retrospective cohort study by Parikh K. et al showed that there was a statistically significant decrease in the use of diagnostic tests including chest X-rays following the publication of the AAP guidelines and that this may have reduced costs associated with bronchiolitis.[21] In another similar study which compared the use of diagnostic imaging in patients presenting with bronchiolitis before and after publication of the AAP practice guidelines, it was found that the use of radiography decreased from 65.3% to 48.6% after publication of the guidelines. Patient visits after publication of the guidelines had 59% lower odds of receiving a chest X-ray than those visits occurring before.[22]

Some studies suggest that local clinical guidelines are what truly drive change at the local level and that these have been found to be effective in increasing adherence to the bronchiolitis guidelines. Nationally developed guidelines may also reduce variations in care and unnecessary financial costs.[21]

The main limitation of this audit was the dependence on clear and reliable documentation in the patients' medical records. Inaccuracies may have led to underestimations of indicated chest X-rays.

Conclusion

The results of this audit indicate that there is room for improvement in abiding by the AAP and NICE guidelines with regards to the practice of performing chest X-rays in patients presenting with bronchiolitis. 53 out of 81 chest X-rays taken in this audit could have been avoided. Out of these non-indicated chest X-rays, 6 showed a consolidation. It is, however, debatable whether these radiographs were ultimately useful, since bronchiolitic changes on imaging may mimic a consolidation and thus lead to inappropriate antibiotic prescription. Hence abnormal chest X-rays in bronchiolitic patients should be interpreted with caution. In practice, it is difficult to eliminate all 'extra' chest X-rays and the clinician's acumen must be taken into consideration. Knowledge of the guidelines may be increased amongst medical staff from juniors up to consultants by means of simple educational sessions. Development of a local guideline on the diagnosis and management of bronchiolitis may also improve adherence to the NICE and AAP recommendations as local guidelines have been shown to be more effective in driving changes in local practice. These recommendations may help to decrease unnecessary radiation exposure and its adverse effects, reduce the financial burden of bronchiolitis on the health services and avoid unnecessary administration of antibiotics and the subsequent development of antibiotic resistance.

References

1. National Institute for Health and Care Excellence (NICE). Bronchiolitis in children: diagnosis and management. [NG9] [Internet] 2015 Jun [cited 2016 Sept 25]. Available from: https://www.nice.org.uk/guidance/ng9
2. Shaun LR, Allan S, Lieberthal H, Cody M, Brian KA, Jill E.B. et al. Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis. Pediatrics [Internet]. 2014 Nov [cited 2016 Sept 25];134 (5). Available from: http://pediatrics.aappublications.org/content/134/5/e1474
3. Wainwright C. Acute viral bronchiolitis in children - a very common condition with few therapeutic options. Paediatr Respir Rev. [Internet]. 2010 Mar [cited 2017 Jun 15];11(1):39–45. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20113991

4. Nagakumar P, Doull I. Current therapy for bronchiolitis. Arch Dis Child. [Internet]. 2012 Sep [cited 2017 Aug 1];97(9):827–830. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22734014
5. Zorc JJ, Hall CB. Bronchiolitis: recent evidence on diagnosis and management. Pediatrics [Internet]. 2010 Feb [cited 2017 Aug 2];125(2):342-349. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20100768
6. Fleming M, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. J Epidemiol Community Health [Internet]. 2005 Jul [cited 2017 Aug 2];59(7):586–590. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1757088/
7. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA [Internet]. 2003 Jan [cited 2017 Aug 4];289(2):179–186. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12517228
8. National Institute for Health and Care Excellence (NICE). Fever in under 5s: assessment and initial management. [CG160] [Internet]. 2013 May [cited 2017 Aug 5]. Available from: https://www.nice.org.uk/guidance/cg160/chapter/1-recommendations
9. Nazif JM, Taragin BH, Azzarone G, Rinke ML, Leiwehr S, Choi J et. Al. Clinical Factors Associated With Chest Imaging Findings in Hospitalized Infants With Bronchiolitis. Clin Paediatr (Phila) [Internet]. 2017 Oct [cited 2018 Feb 7];56(11):1054-1059. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28871880
10. Øymar K, Skjerven HO, Mikalsen IB . Acute bronchiolitis in infants, a review. Scand J Trauma Resusc Emerg Med. [Internet]. 2014 Apr [cited 2017 Aug 2]; (22)23. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4230018/
11. Choi J, Lee GL. Common pediatric respiratory emergencies. Emerg Med Clin North Am. [Internet]. 2012 May [cited 2017 Aug 4];30(2):529–563. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22487117
12. Fazel R, Krumholz HM, Yongfei Wang, Ross SJ, Chen J, Ting HH, et al. Exposure to Low-Dose Ionizing Radiation from Medical Imaging Procedures. N Engl J Med [Internet]. 2009 Aug [cited 2017 Aug 4]; 361(9):849-857. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa0901249
13. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. Am J Roentgenol [Internet]. 2001 Feb [cited 2017 Aug 6]; 176(2):289-96. Available from: http://www.ajronline.org/doi/abs/10.2214/ajr.176.2.1760289
14. Brenner D. Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. Pediatr Radiol [Internet]. 2002 [cited 2017 Aug 7]; 32:228-231. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.327.3681&rep=rep1&type=pdf
15. Brenner D, Doll R, Goodhead DT, Halla EJ, Land CE, Little JB, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci U S A [Internet]. 2003 Nov [cited 2017 Aug 7];100(24):13761-13766. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC283495/
16. Brenner D, Hall EJ. Computed tomography – an increasing source of radiation exposure. N Engl J Med [Internet]. 2007 Nov [cited 2017 Aug 8];357:2277-2284. Available from: http://www.nejm.org/doi/full/10.1056/NEJMra072149#t=article
17. Chodick G, Ronckers CM, Shalev V, Ron E. Excess lifetime cancer mortality risk attributable to radiation exposure from computed tomography examinations in children. Israel Medical Association Journal [Internet]. 2007 Aug [cited 2017 Aug 7]; 9(8):584-587. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17877063
18. Johnson JN, Hornik CP, Li JS, Benjamin DK, Yoshizumi TT, Reiman RE, et al. Cumulative radiation exposure and cancer risk estimation in children with heart disease. Circulation [Internet]. 2014 Jun [cited 2017 Aug 8];130(2):161-167. Available from: http://circ.ahajournals.org/content/130/2/161
19. Communicating Radiation Risks in Paediatric Imaging. Information to support healthcare discussions about benefit and risk. World Health Organization [Internet]. 2016 [cited 2017 Aug 8]. Available from: http://apps.who.int/iris/bitstream/10665/205033/1/9789241510349_eng.pdf
20. Breakell R, Thorndyke B, Clennett J, Harkensee C. Reducing unnecessary chest X-rays, antibiotics and bronchodilators through implementation of the NICE bronchiolitis guideline. Eur J Paediatr [Internet]. 2017 Oct 28 [cited 2018 Feb 7]; 177(1):47-51. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29080051
21. Parikh K, Hall M, Teach SJ. Bronchiolitis Management Before and After the AAP Guidelines. Pediatrics [Internet]. 2014 Jan [cited 2018 Feb 7];133(1) 1-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24298006
22. Johnson LW, Robles J, Hudgins A, Osburn S, Martin D, Thompson A. Management of Bronchiolitis in the Emergency Department: Impact of Evidence-Based Guidelines? Pediatrics [Internet]. 2013 Mar [cited 2018 Feb 7];131 Suppl 1: S103-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23457145

Rapidity of diagnosis and management of H. Pylori in the endoscopy unit at Mater Dei Hospital

Daniela Zammit, Thelma Xerri, Pierre Ellul

Abstract

Introduction: H.pylori infection has been associated with various gastric pathologies and its prevalence varies between different countries. Furthermore, there is an increasing antibiotic resistance and the eradication rates have declined. There is clinical and administrative pressure as to provide the Rapid Urease Test (RUT) result as quickly as possible and ideally prior to discharge from the endoscopy unit.

Results: A total of 542 patients fulfilled the inclusion criteria. The patient`s mean age was 54.6 years and 52.4% were female.

The main clinical indications for an Oesophago-Gastro-Duodenoscopy (OGD) were dyspepsia (44.7%) and GORD (24.5%). The overall positivity rate was 15% of which 8.7% were early positive and 6.3% were late positive. Analysis of patients' age with RUT positivity revealed that patients above the age of 60 years were more likely to have a positive result (p=0.013). There was no statistical significance between the H.pylori results and smoking (p= 0.6).

In this study, there was a variety of 10 different eradication regimes prescribed, the most popular being the use of a PPI 20mg BD + Amoxicillin 1g BD + Clarithromycin 500mg BD for 10 days (total of 27 cases) versus 14 days (23 cases).

Conclusion: This study demonstrates the importance of checking the RUT taken at endoscopy at 24 hours as this has given a 42% increase in the yield for H.pylori. It also demonstrates that various regimens are used in clinical practice. In view of the relatively low prevalence of H.pylori, especially amongst young patients, maybe it is prime time that treatment of H.pylori is specifically managed by culture and sensitivity to avoid worsening clarithromycin-resistance.

Keywords

Helicobacter pylori; triple therapy; OGD; Proton Pump Inhibitor; eradication regime.

Abbreviations:

- CLO: Campylobacter-like organism test
- CT scan: computerized tomography
- GI: Gastrointestinal
- GORD: Gastro-oesophageal Reflux Disease
- H.pylori: Helicobacter pylori

Daniela Zammit M.D.*
BST Psychiatry,
Mount Carmel Hospital
Attard, Malta
daniela.c.zammit@gov.mt

Thelma Xerri M.D.
BST Medicine,
Mater Dei Hospital
Msida, Malta

Pierre Ellul M.D., PhD, FRCP, MSc
Consultant in Gastroenterology and Internal Medicine,
Mater Dei Hospital
Msida, Malta

**Corresponding author*

- MALT: Mucosa-associated lymphoid tissue lymphoma
- OGD: oesophago-gastro-duodenoscopy
- PET scan: Positron Emission Tomography
- PPI: Proton Pump Inhibitor
- RUT: Rapid Urease Test

Introduction and Aims

Helicobacter pylori (H.pylori) is a gram-negative bacterium found in the stomach of more than 50% of the population worldwide.[1] It is linked to chronic gastritis, gastric and duodenal ulcers and stomach cancer.[2] Up to 85% of patients infected with H.pylori are asymptomatic;[3] therefore a 'test-and-treat' approach is adopted and is most effective in a population with a high prevalence of H.pylori infection (defined as a prevalence of more than 20%), especially in patients under the age of 50 years without any alarm symptoms.[4] There are various methods of testing; these can be divided into minimally-invasive (blood antibody test, stool antigen test or using the carbon urea breath test), and invasive (analysis of gastric biopsies through Rapid Urease Test (RUT test), histology and culture). None of the methods are 100% specific and sensitive. One of the most commonly used is the RUT test upon performing an oesophagogastroduodenoscopy (OGD).[5]

This gastric biopsy test is based on the activity of the H. pylori urease enzyme. This splits the urea test reagent to form ammonia. Ammonia, being alkaline, increases the pH. This is detected by a colour indicator. Tests that produce rapid reliable findings have been shown to reduce the overall cost of management of these patients by decreasing the need for telephone calls to be made to patients after 24 hours.

The standard first-line treatment option for H.pylori eradication is a 7-10 twice daily (b.d.) triple therapy of proton-pump inhibitor (PPI) together with amoxicillin and clarithromycin or metronidazole.[6] Unfortunately, such a regime is becoming increasingly ineffective worldwide due to clarithromycin resistance, with data showing that eradication rates have declined to less than 80% in both the United States and Europe.[7]

Several alternative regimes for eradication have been proposed, including the extension of the treatment duration to 10 or 14 days; using a different PPI; quadruple therapy with the use of bismuth with a PPI and two antibiotics; concomitant and sequential regimes; use of probiotics-supplemented triple therapy or using other antibiotics such as levofloxacin [8-11]. Despite such antibiotic regimens, a 100% eradication rate is rarely achieved. [13] The success of eradication therapy depends on patient compliance and bacterial factors such as antibiotic resistance.

Various studies have demonstrated different results on the correlation of smoking and prevalence of H.pylori infection. It is proposed that smoking is negatively associated with H.pylori infection due to an increase in gastric acidity following smoking,[9] whilst other studies showed a positive relationship in view of damage to gastric mucosal protection [10] and reduced efficacy of eradication therapy.[11-12] Others studies have demonstrated that there is no statistically significant difference in the rate of positive infections in relation to current or previous smoking status.[14] While most of the recent studies have concentrated on the choice and prescription of antibiotics there is minimal recent data on the timing of the interpretation of the RUT after an oesophago-gastro-duodenoscopy (OGD).

The primary aims of this study were:

1. To assess the diagnostic accuracy of the RUT by assessing it at 4 hours and 24 hours.
2. To determine whether there is a correlation between smoking and H.pylori infection.
3. To identify the different treatment regimes prescribed at our local hospital.

A secondary aim of the study was to determine the prevalence of positive H.pylori infections among patients undergoing an OGD..

Methodology

This was a prospective study performed between January 2016 and July 2016. Approval was obtained from the Malta University Research Ethics Committee. Ninety-five percent (95%) of the endoscopists who perform OGD's at Mater Dei Hospital agreed to participate. The following data was obtained and entered into the database: date of procedure; patient`s age; gender; clinical indication; RUT; treatment regime prescribed and smoking status. The exclusion criteria were: (1) patients had already been tested and/or treated for H.pylori (2) use of proton pump inhibitors in the 2 weeks prior to the test and (3) the use of antibiotics in the preceding 4 weeks.

The RUT used in each case by all endoscopists involved was the Kimberly-ClarK

CLOtest Rapid Urease Test. The test was defined as either negative, early positive or late positive.

The patients' OGD reports were checked on the same day of the procedure and the following day by two investigators. If the RUT test showed a colour change up to 4 hours after the procedure, it was marked as "early positive". If the RUT test demonstrated a positive test more than 4 hours later and within 24 hours, it was marked as "late positive".

Results

A total of 580 consecutive patients who performed an OGD at our centre were recruited. Thirty – eight (38) patients were excluded as 31 patients had been previously tested and/or treated for H. Pylori and another 7 patients did not have a CLO test taken during the OGD. From the 542 eligible patients, 52.4% were female (284 patients).

The minimum age was 15 and the maximum was 88. The patient`s mean age was 54.64 years (median age: 58 years; range 15 - 88 years). Figure 1 demonstrates the age distribution of the patients' cohort.

The main clinical indication was dyspepsia (44.7%). Other main indications were gastro-oesophageal reflux disease (GORD) (24.5%) and in the investigation of anaemia (10.1%). The other clinical indications are demonstrated in Table 1.

From the cohort, 85% of the RUTs were negative for H.pylori. The rest were positive and were classified into early positive (8.7%) and late positive (6.3%). Analysis of patients' age with RUT positivity revealed that patients above the age of 60 years were more likely to have a positive result (p=0.013). Figure 2 demonstrates the percentage of positive RUT tests for every age group.

Figure 1: *Age distribution of patients who underwent OGD*
The minimum age was 15 and the maximum was 88. The patient`s mean age was 54.64 years (median age: 58 years; range 15 - 88 years).

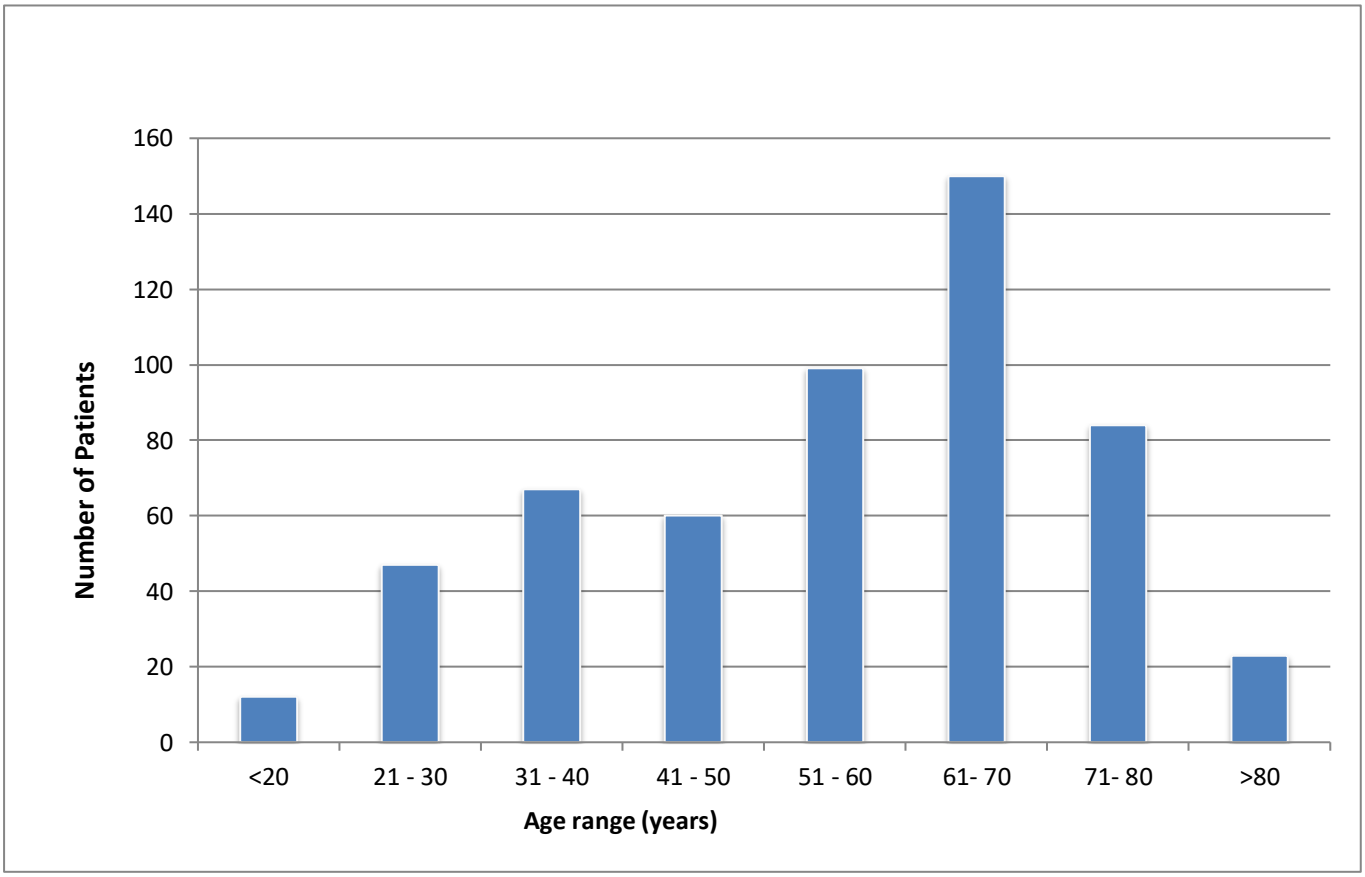


Table 1: *Clinical indication for OGD*

The main clinical indication was dyspepsia (44.7%). Other main indications were gastro-oesophageal reflux disease (GORD) (24.5%) and in the investigation of anaemia (10.1%).

Clinical Indication	Percentage (%)
Dyspepsia	44.7
GORD	24.5
Anaemia	10.1
Weight loss	2.2
Variceal Screening due to cirrhosis	2
Dysphagia	1.1
Not specified	3
Screening for upper GI cancer	6.5
Work-up for coeliac disease	2.2
Suspected upper GI bleeding	2
Gastric mass on CT scan and/or increased uptake on prior PET scan	1.7

Figure 2: *Percentage of Positive RUT in each age group*

From the cohort, 85% of the RUTs were negative for H.pylori. The rest were positive and were classified into early positive (8.7%) and late positive (6.3%). Analysis of patients' age with RUT positivity revealed that patients above the age of 60 years were more likely to have a positive result (p=0.013).

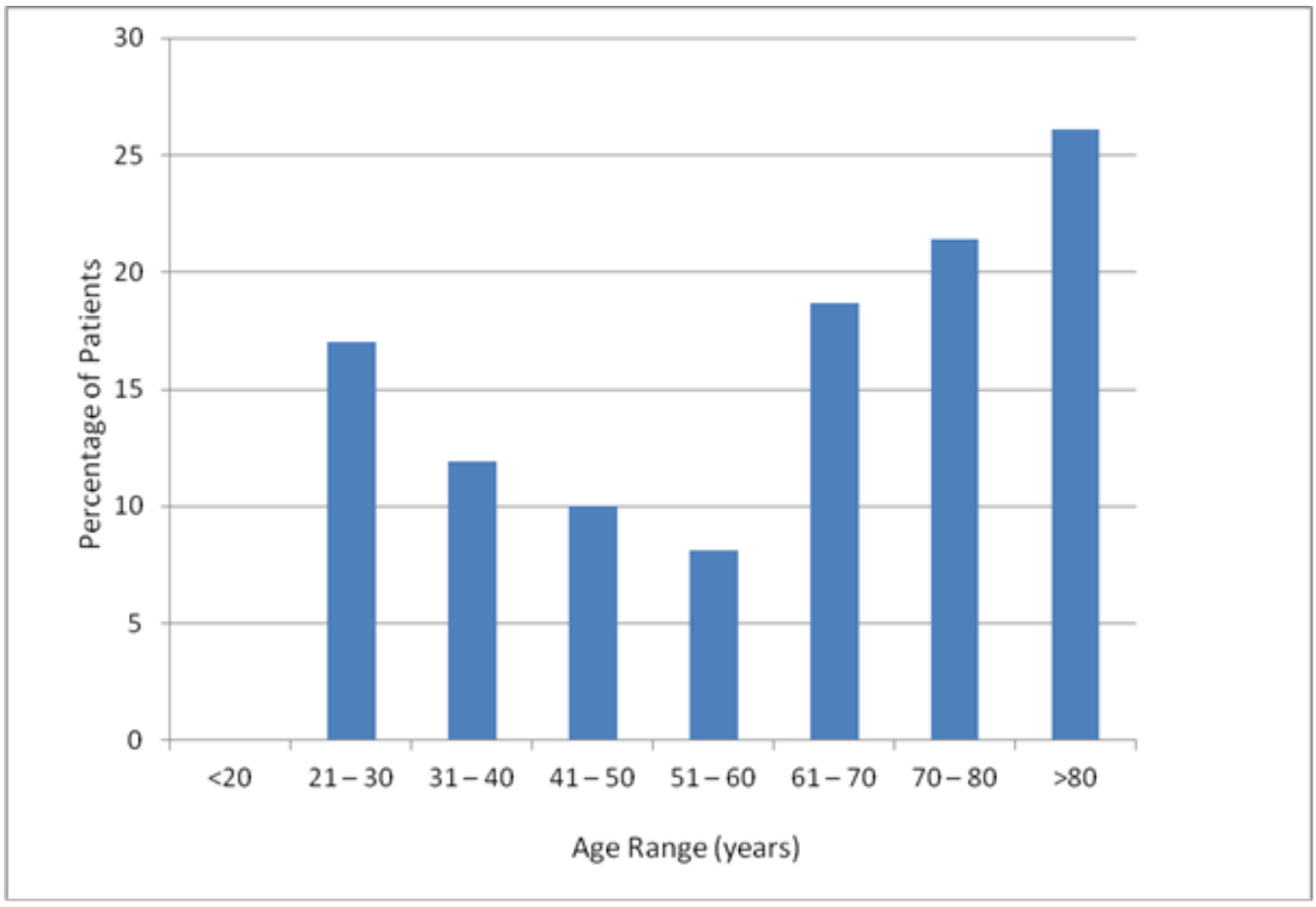
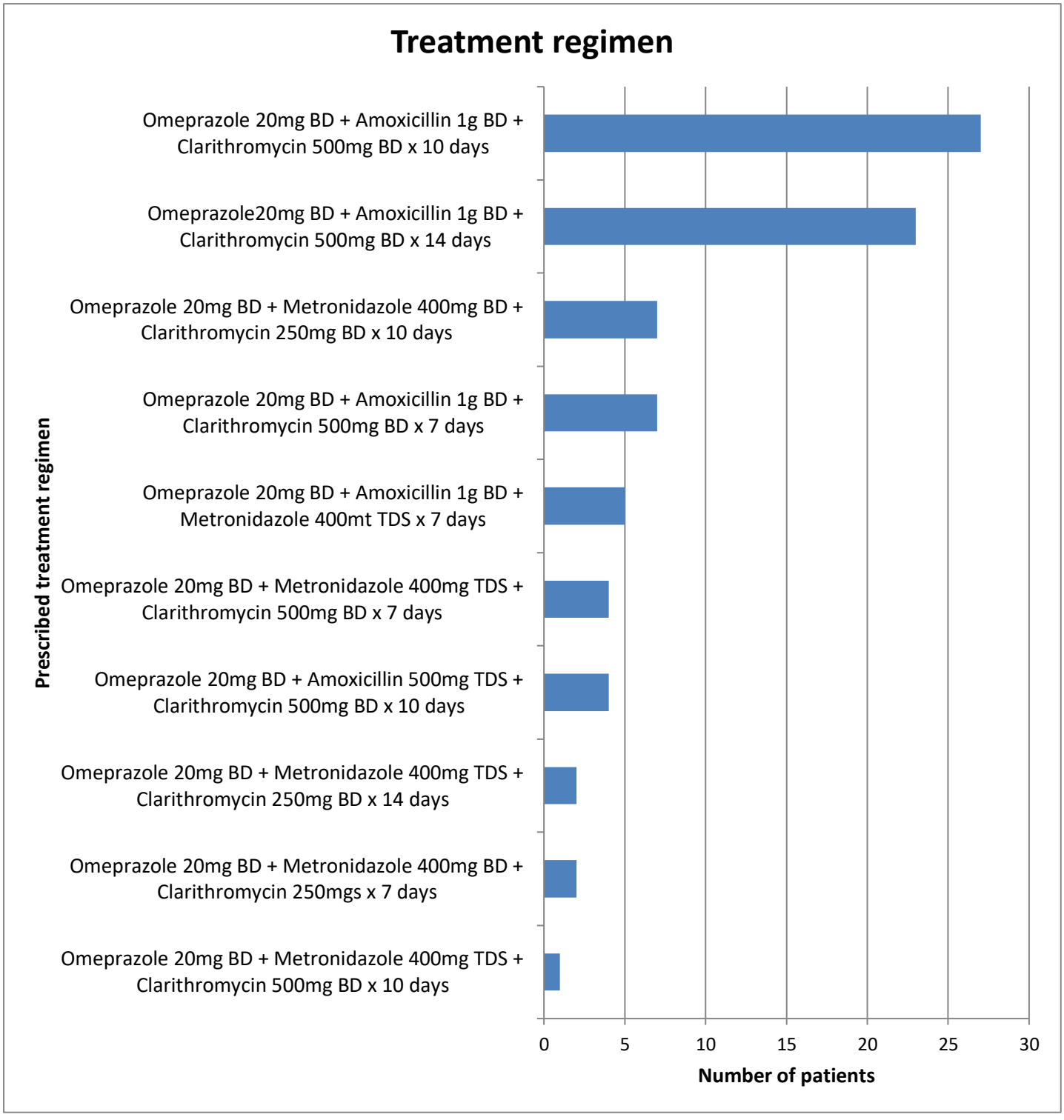


***Figure 3**: Treatment regimen prescribed to patients with a positive RUT*
The most commonly prescribed regimens were omeprazole 20mg BD + Amoxicillin 1g BD + Clarithromycin 500mg BD for 10 days (33%) and 14 days (28%). In the rest (39%), 10 different regimens were prescribed



From the patients with a negative RUT test, 25.4% were smokers. Similarly, from those with a positive result, 28.4% were smokers. There was no statistical significance between the H.pylori results and smoking (p=0.6).

The most commonly prescribed regimens were omeprazole 20mg BD + Amoxicillin 1g BD + Clarithromycin 500mg BD for 10 days (33%) and 14 days (28%). In the rest (39%), 10 different regimens were prescribed, as can be demonstrated in Figure 3.

Discussion

H. pylori infection is a cause of peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. RUTs are used widely throughout the world in endoscopy units to determine if patients are infected with H. pylori. The accuracy of these tests is important because a missed diagnosis of H. pylori infection can thus result in various pathologies.[15]

In the RUT, the gastric biopsy is put into a gel medium containing urea and a pH indicator. If present, the urease enzyme of H. pylori splits urea into ammonia and carbon dioxide. Ammonia alters the pH of the medium which then causes the colour change of the pH indicator. This process can take a variable amount of time and potentially there are various variables such as previous exposure to PPI`s, antibiotics and amount of urease that is produced by the bacterium.[16] The expectation from a clinical perspective and also administrative is to provide a quick and reliable result before the patient leaves the endoscopy unit in view of patient satisfaction and as to decrease the need for phone calls on the next day and other related paperwork.

The overall prevalence of 15% does not support the empirical treatment for H. Pylori amongst symptomatic patients within our population. There was a statistically significant difference in prevalence between patients below and above the age of 60 years (p=0.013). Furthermore, in patients under the age of 20 years, none of the patients had H. Pylori. One possible bias within the study group could have been that although patients were told to stop proton pump inhibitors 2 weeks prior to the OGD, they might not have done so and they might have consumed antibiotics in the preceding 4 weeks. This would have led to an under representation of H.pylori. Similarly, we only tested for H. pylori with one modality (the RUT) and did not compare the result with histology and/or culture as a reference standard. This could also have led to a lower incidence. However, previous studies have demonstrated that the RUT is 97% specific and 98% sensitive when compared to histology which was 100% specific and 91% sensitive[16] Furthermore, previous data from studies has demonstrated that overall positivity is 75% within 20 minutes, 85% are detected at 1 hour, 90% by 3 hours and 95% by 24 hours.[17] Data from our study contrasts significantly with this data as 42% of the RUT turned positive after 4 hours.

In view of this previous data and the costs involved, we did not check for H.pylori with other modalities. However, we assessed what really happens in the day-to-day clinical practice. It is important to note that there is limited recent analysis about the timing of the colour change for this RUT and most data is coming from the late 1980s. Thus, in view of increasing or changing antibiotic resistance patterns it might be prime time to review this, as analysis of the RUT at an early stage and not reviewing at 24 hours might lead to missing out on the diagnosis of H.pylori and thus not treating it.

Previous studies have demonstrated both positive and negative associations of smoking with H.pylori.[14] In this study there was no correlation between the presence of H.pylori and smoking. No H.pylori related malignancies were noted within this cohort.

Inconsistencies regarding the eradication regimes prescribed in the endoscopy unit are evident and depend on consultant preference and the junior doctors who prescribe the treatment after checking RUT. As culture with antibiotic sensitivities is not routinely performed when H.pylori infection is diagnosed, it is generally recommended that different antibiotics be given at higher doses for 14 days. [18] Our study concluded that only 28% of the positive RUT patients were prescribed such a regime.

Increased antibiotic resistance is a recognised problem affecting the overall success rate of eradication of H.pylori. To minimise the clinical impact of antimicrobial resistance and eradication failure, several studies recommend antimicrobial susceptibility testing prior to initiating treatment.[19-20] Ideally antibiotic choice should be based on culture and sensitivity of each H.pylori strain

cultured in the biopsy however this is not practiced at Mater Dei Hospital and the eradication therapy is chosen empirically.

The difficulties associated with performing culture and antibiotic sensitivity studies for H.pylori include both expense and the fastidiousness of the organism. Studies have shown that the use of a single antral biopsy for assessing efficacy of a particular treatment regimen may fail to detect resistant strains.[21] Thus resistance variability of H.pylori organisms at different gastric mucosal sites is a contributing factor to higher eradication rates and such antibiotic resistance would require multiple gastric biopsies from different sites.

Limitations to this study which may have affected the positivity rate of the RUT and thus the outcome of the study is that there is no recorded data of how many biopsies and from where they were taken and used for each RUT, although it is standard practice to take at least one sample from the antrum of the stomach.

Another possible limitation to the study is that there is no available follow up on successful eradication of H. Pylori though this was not one of the intended aims of the study as this is not routine practice at Mater Dei Hospital but the choice of the respective endoscopist.

Conclusion

This study demonstrates that various regimens are used in clinical practice. However, we have to note the increasing antibiotic resistance. Various eradications rates have been ascribed to different regimens. In view of the relatively low prevalence of H.pylori, especially amongst young patients, antimicrobial resistance studies of H.pylori should be actively considered as to have better guidance with regards to antibiotic prescription. Furthermore, the significant increase in positivity post- 4 hours necessitate that if the test is still negative at 4 hours, it has to be re-analysed at 24 hours.

References

1. Manuel A, Peek, Richard MP Jr. "Pathobiology of Helicobacter pylori–Induced Gastric Cancer". *Gastroenterology*. 2016**;150 (1):** 64–78.
2. Infection with Helicobacter pylori. *IARC MonogrEvalCarcinog Risks Hum.* 1994**;61:**177–240.
3. Bytzer P, Dahlerup JF, Eriksen JR, Jarbøl DE, Rosenstock S, Wildt S, *et al.*"Diagnosis and treatment of Helicobacter pylori infection". *Dan Med Bull*. 2011**;58 (4):** C4271
4. Malfertheiner P, Megraud F, O'Morain C. "Guidelines for the management of Helicobacter pylori infection". *Business Briefing: European Gastroenterology Review.* 2005**.** Accessed October 2016 on: http://www.helicobacter.org/download/summary_guidelines_hp_infection%20_business_briefing.pdf
5. Stenström B, Mendis A, Marshall B. "*Helicobacter pylori*—The latest in diagnosis and treatment". *AustFam Physician*. 2008**;37 (8):** 608–12.
6. NICE (2014) Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Clinical guideline 184. Published September 2014, Last updated November 2014. Accessed October 2016 on: https://www.nice.org.uk/guidance/cg184/chapter/1-recommendations?unlid=7844170620162313724
7. Graham DY, Shiotani A. New concepts of resistance in the treatment of Helicobacter pylori infections. *Nat ClinPractGastroenterolHepatol*. 2008**;5:**321–331.
8. Bao-Zhu L, Diane Erin T, Ji-Yao W, Jian-Ming X, Jin-Qiu Y, Chao Z *et al.* Comparative effectiveness and tolerance of treatments for Helicobacter pylori : systematic review and network meta-analysis. *BMJ.* 2015**;**101hh21**.**
9. Ogihara A, Kikuchi S, Hasegawa A, Kurosawa M, Miki K, Kaneko E *et al.* Relationship between Hellicobacter pylori infection and smoking and drinking habits. *J GastroenterolHepatol.* 2000**;15(3):** 271-6.
10. Parasher G and Eastwood GL. Smoking and peptic ulcer in the Helicobacter pylori era. *Eur J GastroenterolHepatol.* 2000**;12(8):** 843-53.
11. Camargo MC, Piazuelo MB, Mera RM, Fontham ETH, Delgado AG, Yepez MC *et al.* Effect of smoking on failure of H.pylori therapy and gastric histology in a high gastric cancer risk area of Colombia. *ActaGastroenterolLatinoam***.** 2007**; 37(4):** 238-45.
12. Takeshi S, Keitaro M, Hidemi I,Sawaki A, Hirose K, Wakai K *et al.* Smoking Increases the Treatment Failure for *Helicobacter pylori* Eradication. *The American Journal of Medicine.* 2006; **119(3):** 217-224.
13. Borody T. Quadruple should be the first-line therapy for Helicobacter pylori infection. *Helicobacter pylori.* 2000; **26–29**: 623–9.
14. Mohie A AA K, Shabaan E K, Amal A A. Cigarette smoking status and Helicobacter pylori infection in non-ulcer dyspepsia patients. *Egyptian Journal of Chest Diseases and Tuberculosis.* 2014; **63(3):** 695-699.
15. Gisbert JP, Khorrami S, Carballo F,Calvet X, Gené E, Dominquez-Muñoz JE. H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. *Cochrane Database Syst Rev.* 2004: CD004062.
16. Dye KD, Marshall MJ, Frierson HF, Barrett LJ, Guerrant RL, McCallum RW. Is CLO test* alone adequate to diagnose Campylobacter pyloridis. *Am J Gastroenterol.* 1988**; 83:**1032.
17. Marshall BJ, Warren JR, Francis GJ, Langton SR, Goodwin CS, Blincow ED. Rapid Urease test in the management of Campylobacter pyloridis- associated gastritis. *Am J Gastroenterol.* 1987; **82(3):** 200-10.

18. Sonnenberg, A. "Time trends of ulcer mortality in Europe". *Gastroenterology.* 2007*;* **132 (7):** 2320–7.
19. Toracchio S, Cellini L, Di Campli ED *et al.* Role of antimicrobial susceptibility testing on efficacy of triple therapy in Helicobacter pylori infection. *Aliment Pharmacol Ther*. 2000; **14**:1639–43.
20. Romana M, Ioyene MR, Montella F *et al.* Pre-treatment antimicrobial susceptibility testing in eradication of *H. pylori* infection. *Am J Gastroenterol*. 2000; **95**: 2317–18.
21. Jorgensen M, Daskalopoulos G, Warburton V, Mitchell H, Hazell S. Multiple strain colonisation and metronidazole resistance in Helicobacter pylori-infected patients: Identification from sequential and multiple biopsy specimens. *J Infect Dis*. 1996; **174**: 631–5.

Original Article

Risk factors for adolescents developing substance use disorders; what should our prevention programs be targeting?

Nigel Camilleri, Andrea Saliba

Abstract

This review identifies the main risk factors and high-risk groups of adolescents with substance use disorders (SUD). Furthermore, it presents the epidemiological data on SUDs in Malta and discusses possible ways of tackling prevention, whilst offering suggestions based seminal studies from published literature to service developers.

Adolescence is a developmental period of high risk, more than half individuals with SUDs identify that the problem began before the age of 20. 18% of adolescents in Europe have reported a lifetime use of illicit drugs, the prevalence rates in Malta are similar.

Risk factors for SUDs include; heritable factors; familial patterns and psychiatric disorders. Environmental factors include; family functioning, parenting practices, child maltreatment, peer influences, substance availability and consumption opportunities. One predictive phenotype for SUDs is psychological dysregulation characterised by cognitive, behavioural and emotional difficulties with daily challenges in childhood. The regular use of substances is associated with depression, anxiety, PTSD, behaviour problems. Highest risk groups as those having two parents with a SUD, living with single parents, sexual orientation differences, early use of substances, psychological dysregulation and an attitude of ambivalence towards the use of substances. Over 70% of adolescents receiving treatment for SUD had a history of trauma.

Parental practices such as knowledge, communication and awareness are an important protective factor which may help reduce the influential negative influence from peers on substance use.

Preventive programs should not focus on abstinence alone in treatment, since this is insufficient as adolescents present with; lower problem recognition, higher rates of binge use and co-morbid psychiatric problems compared to adults. Preventative measures should be targeted towards high risk adolescents, with the aim of correcting misperceptions as a primary focus. Honesty from professionals may reduce the general ambivalence with regards to drug use, thereby reducing the serious influence friends have on each other. Secondly, correcting misconceptions may lead to adolescents changing the assumption that one's friends are all positively predisposed to substance use. It's estimated that for every Euro invested in addiction treatment, 3 to 5Euros are saved in drug related crime, theft and criminal justice costs.

Nigel Camilleri MD (Melit), MD (Newcastle), MRCPsych (UK), CCT (CAP), RCP (IRE)*
Consultant Child and Adolescent Psychiatrist.
Mental Health Malta
Mount Carmel Hospital
Attard, Malta
Newcastle University
Newcastle upon Tyne
Tyne and Wear, UK
nigel.camilleri@newcastle.ac.uk

Andrea Saliba MD (Melit), MRCPsych (UK)
Higher Psychiatric Trainee
Northumberland
Tyne and Wear NHS Foundation Trust
St. Nicholas Hospital
Newcastle
Mental Health Malta
Mount Carmel Hospital
Attard, Malta

**Corresponding author*

Keywords

Adolescents, Substance Use Disorders, Risk factors, High Risk groups, Prevention

Background

Epidemiology of Substance use disorders

The majority (58%) of individuals who develop substance use disorders (SUD) report their drug use began before age 20.[1] Adolescence is the developmental period of highest risk for onset of alcohol and substance use problems.[2] Some experimentation with alcohol may be considered normal within adolescences. However, substance experimentation in adolescence increases the risk of persistent substance use and dependence.[3] Adolescence has been described as "the critical period of addiction vulnerability" because during this period the brain pathways that enable people to experience motivation and rewarding experiences are still developing. During this period adolescents are more prone to risk taking and less prone to impulse control.[4]

In Europe, 18% of school aged children age 15-16 years reported lifetime use of illicit drugs.[5] Amongst young adults age 15 to 34 years, the life time prevalence use of cannabis is 32%, cocaine 6%, amphetamines 5%, ecstasy 6%.[4] The National Institute of Drug Abuse 2011 USA survey reported that the trend in daily marijuana use among adolescents has increased to its highest in 30 years with at least 25% of high school seniors using at least once per month.[6] Daily marijuana use has surpassed daily tobacco use, the latter trend is in decline. This raises a public health concern in the light of regular marijuana usage in adolescents showing to be associated with a reduction in 6 to 8 points in adult IQ.[7] Also, of note is that there has been a slight decline in the consumption of alcohol use in adolescents. Of public health significance is that early initiation of substance use is correlated with an increased risk of a constellation of behaviours, such as selling drugs, violence, driving under the influence, physical, sexual and emotional abuse, in addition to the increased risk of developing a substance use disorder (SUD).

The ESPAD 2015[8] reported data on prevalence rates and trends of alcohol and substance misuse in adolescents who were about to turn 16 years, in 25 EU countries. In this survey, data were collected on the whole population of Malta, for children aged 16 years (*n*=3,326), there was a response rate of 93% and the mean age was 15.7 years. ESPAD 2015 reported that the lifetime risk for alcohol use amongst Maltese adolescence over the past 30 days was 6.6% for males and 7.4% for females, placing the Maltese adolescents amongst the top 5 EU countries for alcohol consumption. The lifetime prevalence in 2015 was 86% however, it was reported that there was an overall slight decrease in trend of alcohol use from 1995. For the Maltese population surveyed, there was a decrease in the trend of cigarette smoking in adolescence with a lifetime prevalence of 29% and for any illicit substance (14%). The only reported drug in Malta with an increased trend was cannabis (13%), placing Malta mid table compared to other EU countries. The use of inhalants (8%) and pills (3%) in Malta was reported to have decreased over the past 20 years. The lifetime prevalence of cocaine was 3% and heroine 1% for adolescents aged 15.7 years in Malta. Lastly the prevalence of internet use was 6.1 days out of 7 days in Malta with most time being spent on social media; this places Malta amongst the top of the EU countries.

It is estimated that 1.5 million adolescents meet criteria for SUD but of these only 111,000 (7%) receive treatment for the disorder[3] possibly due to; poor health care coverage, low motivation from YP or parents, lack of specialised adolescent programs and inconsistent quality in adolescent services. Similar figures are not available for the Maltese population however, the authors are aware that services for adolescents are few and understaffed and under resourced in Malta. Another factor contributing to the unique challenge centred around adolescent drug use pertains to biological factors of the developing brain. The prefrontal cortex is still immature whilst the nucleus accumbens is also still developing. The latter is the centre for thrill seeking and acting impulsively. Therefore this could in part explain the disregard for negative consequences of alcohol and drug use, whilst reinforce the importance of individual tailored therapeutic approaches.[9] It is imperative to take hold in mind the higher rates of impulsivity of adolescents compared to adults when considering tailored made service development.

In this narrative review paper, the authors aim to highlight the identified risk factors and high-risk groups of adolescents for developing SUDs, from the published evidence in seminal papers within the literature. Furthermore, they seek to provide service

developers with an understanding of the more effective preventative models when providing care for this cohort for young people.

***Table 1**: Early onset of substance use: prevalence of students experiencing substance use at the age of 13 or younger (percentage)*

	Malta	Average	Range
Cigarettes	13	23	9-47
Daily smoking	3	4	1-10
Alcohol	54	47	14-72
Intoxication	8	8	2-22
Cannabis	3	3	1-13
Ecstasy	1	1	0-2
Amphetamine/methamphetamine	0	1	0-3
Cocaine/crack	0	1	0-2

***Table 2:** Illicit drug use: lifetime prevalence of the use (percentage)*

	Malta	Average	Range
Any drug	14	18	6-37
Cannabis	13	16	4-37
Ecstasy	2	2	0-5
Amphetamine	2	2	0-10
Methamphetamine	1	1	0-5
Cocaine	3	2	0-5
Crack	1	1	0-3
LSD/other hallucinogens	1	2	0-5
Heroin	1	1	0-3
GHB (gammahydroxybutyrate)	0	1	0-3

Adolescents at risk for substance use disorder

Early childhood characteristics can increase the risk of adolescent SUD, thus identifying the characteristics can be important for prevention of alcohol and substance use. Risk factors for developing a SUD are divided into heritable such as; familial patterns and psychiatric disorders. Environmental factors may include; family functioning, parenting practices, child maltreatment, peer influences, substance availability and consumption opportunities and phenotypic factors.[10] The presence of SUD in a parent has consistently been shown to be a strong risk factor (genetic and environmental) for adolescent alcohol and SUD.[11]

One predictive phenotype is psychological dysregulation for SUDs. Psychological dysfunction is characterised by a deficiency in cognitive, behavioural and emotional difficulties when it comes to addressing daily challenges in childhood. Furthermore, Clark 2004,[12] reported a link between parents with psychological dysregulation and their children as being at increased risk for SUDs. Psychological dysfunction in its more severe form presents itself as conduct disorder, oppositional defiant disorder (ODD), attention deficit hyperactivity disorder (ADHD), depression and later in life; antisocial and borderline personality disorders and is seen as a predictor for higher levels of alcohol use.

Several environmental factors have been identified as having an influence on increasing the risk of onset of SUDs (the timing), whilst genetic factors seem to accelerate the progression from initiation to heavier use. Some of these risk factors include; children maltreatment, traumatic experiences, parental practices and peer influence and these can in turn lead to manifestations of psychological dysregulation such as conduct disorder, ADHD and depression.[13]

Traumatic events in childhood and development of SUDs.

Childhood traumatic events mimic environments with psychological dysregulation which in turn meditate the body's response to stress through the hypothalamic-pituitary-adrenal (HPA)-axis. Sartor 2007[14] reported in a study involving more than 3,500 female twins, that those who suffered childhood sexual abuse were associated with higher rates of alcohol use and dependence. Kaufman 2007[15] reported in a longitudinal study of 76 maltreated children compared to matched controls that the former were seven times more likely to use alcohol at age 12 (two years earlier

than controls). More than 70% of adolescents receiving treatment for SUD had a history of trauma exposure.[16] Increased shyness, anxiety, depressions, anger were found to be risk factors for initiating use of nicotine, alcohol, marijuana amongst adolescents aged 9-15 years.[17] Childhood trauma was reported to be a risk factor for transition from experimental to regular use. Lastly childhood trauma may increase the risk of relapse however, results were not consistent across studies and seem to be mostly limited to nicotine and alcohol.[18]

The association between mental disorders and substance use disorders

The association between mental disorders and SUDs has been well established. Adolescence is a risk period for substance use disorders.[2] The regular use of alcohol and substances is associated with depression, anxiety, PTSD, behaviour problems such as conduct disorder and further substance use.[19]

In early to mid-adolescence, the trends for female substance use is similar and sometimes extends the use by males however, by 17 years of age males outpace their female counterparts with respect to heroine, steroids, hallucinogens, marijuana and alcohol use, amphetamine use remains similar.[17]

Substance use in adolescents with mental disorders and gender influences:

Schwinn 2010[20] in a clinical trial of 400 adolescents, mean age 17.5 years (range 15-20 years) reported that although indices of mental disorders differed by gender, anxiety and depression was more common in females, whilst hostility symptoms of conduct disorder were more common in males. However, there was no evidence of gender being a risk factor on the relationship between mental disorders and past month drinking, binge drinking, cigarette smoking, marijuana use and substance use.[18]

Racial and ethnic differences and SUD

African-Americans are less influenced by their peers who drank alcohol but more influenced by parental support than Caucasians, which in part explains their different alcohol use patterns. African-American adolescents reported less SUDs than Caucasians while Hispanic adolescents reported more use.[21] Given the sudden increase in population in Malta, one can no longer consider the population to be homogenous and with increase in heterogeneity within the island, public service commissioners should aim to target their preventive measures towards the higher risk ethnic groups.

Sexual orientation and adolescent substance use

Several decades of research have shown that there are high rates of SUDs in lesbian, gay and bisexual (LGB) adolescents.[22] However, large gaps still exist in the literature in understanding who is the most vulnerable within the LGB community. Published studies seem to be consistent in the findings that bisexual adolescents are at greater risk for substance misuse. In a meta-analysis of 18 published studies Marshsal 2008[23] reported higher rates of SUDs compared to heterosexual adolescents (Odds Ratio=2.89, Cohen's d=0.59). The effect size was large to very large with the average Cohen's d for relationship between sexual orientation and lifetime cigarette use and injection drug were >0.80. The odds for SUD in the LGB group was found to be on average 190% higher than for heterosexual adolescents and higher within some sub populations; highest females 400% and bisexual adolescents 340%. Furthermore, the gender of the participant was also a significant risk factor (Q16.6, d.f=1, p<0.0001), females were more at risk for SUDs than their male counterparts.

The most prominent theoretical and explanatory frameworks of the LGB health risk is the 'minority stress' model,[24] which proposes that LBG adolescents suffer from more harassment, maltreatment, discrimination and violence compared to their peers. For most LGB adolescents in addition to developing a healthy gay identity they may be faced with stress from social stigma and fear of discrimination, therefore they have greater challenges to use coping skills to protect themselves. When considering psychoeducation sessions aimed schools, one needs to be aware of the considerable higher risk of developing SUD adolescents with different sexual orientation face.

Parenting practices

A longitudinal study[25] reported that low levels of parents monitoring are a significant risk factor for adolescents to develop SUDs. Barnes 2000[26] reported the relationships between parenting practices and SUDs are due to environmental influences such as inadequate parental involvement,

inadequate emotional support behaviours, cognitive dysfunction in parents, psychological disorders and direct modelling of drinking and substance misuse.

Effective parenting is inversely associated with adolescent SUD. Parental knowledge is an important construct that reflects reasonable parent-child communication and relations leading to parental awareness of their adolescents, friends' activities and whereabouts. Studies have reported that parental knowledge is a protective factor against adolescent use of cigarettes, alcohol and marijuana. Girls and younger adolescents experience a higher level of parental knowledge which may in turn protect them from SUD and delinquency overall.[27] Infrequent communication and less time spent together between parent and child has shown to be associated with higher rates of alcohol and tobacco use.[28] Overall the demographics, parenting variables and their interactions explained 12% of variance in smoking scores, 8% of alcohol consumption scores, 10% of aggression scores and 17% of the delinquency scores.[27]

In a survey of school aged children from 11 to 16 years in the USA on data obtained from n=8,795 Wang 2009[21] reported that peer influence had a direct influence on adolescent substance use. Peer influence has consistently shown that it is amongst the strongest predictor of adolescent SUD. Adolescents who associate with substance using peers are more likely to use illicit substances.[29] Therefore, when focusing on developing preventative measures for SUD, one needs not only to address the adolescent but also provide parenting training, since minor changes such as more communication, time spent together and knowledge of who their friends are may drastically diminish the negative influence adolescents suffer in peer pressure.

Attitude ambivalence and friend norms to SUD

Of the potential risk factors mentioned on attitude to substance use behaviour, ambivalence is the one which has most evidence. Ambivalence is characterised as a person holding a positive and negative attitude towards an object simultaneously. Priester 2002[30] reported that adolescents who were ambivalent about alcohol consumption and safe sex practices had less attitude-behaviour congruence than participants of low ambivalence. Hohman 2014[31] reported that the higher perceived behavioural control to resist marijuana use was negatively related to intentions to use marijuana (p<0.001). Furthermore, the more friends approved the use of marijuana the stronger was the intention to use substances (p<0.001). The more adolescents felt they could refuse marijuana the less likely they were to intend to use the drug in the future. The younger the adolescent the higher was the prevalence who hold negative attitudes to marijuana use, as time passes this change.[32]

Findings from published research suggests two potentially preventable possibilities. The first prevention model suggests that professionals should make use of hard scientific knowledge to facilitate adolescents adopting correct attitudes to SUDs and consequently inform their behaviours. This model reduces ambivalence in adolescents and provides a strong knowledge base for anti-drug attitudes and behaviours. Information that is truthful, credible and not exaggerated or falsified would be more persuasive.[33] The second suggestion is that prevention messages should be designed to attenuate ambivalence, thereby reducing the susceptibility to their peers' influence.[34] Given that published studies report that one of the strongest risk factors to developing SUDs is peer influence, psychoeducation from professionals sharing the honest truth about the pros and cons of substance use, could help reduce the ambivalence adolescents have and reduce the false belief which they may hold that is 'all my peers hold a positive regard to substance use'.

Effectiveness of treatments for adolescents with SUDs

Adolescents are more susceptible to peer influence and focused more on immediate concerns. The effectiveness of available treatments for adolescents with SUDs is currently a reason for concern due to the high rates of treatment drop-out and post treatment relapse. Behavioural interventions are considered 'first line' treatment however, medications are often used adjectively to reduce drug cravings, symptoms of withdrawal and to treat co-occurring psychiatric conditions. Lipsey et al conducted a meta-analysis on a variety of treatment modalities that were tested against a control or alternative treatment sample and a consistent pattern emerged that showed an overall positive effect for all treatment modules when compared to controls however, family therapy, CBT

and motivational enhancement therapy/CBT tended to show the best outcomes.[35] Overall CBT and family interventions have been consistently shown to have moderate effects sizes. Moreover, CBT in adolescents (d=0.45)[36] have consistently shown greater sustained or post-treatment effect size compared to family-based interventions.

For every Euro invested in addiction treatment it is estimated that it yields cost savings of between 3 to 5 euros in reductions in drug related crime, theft and criminal justice costs. These costs are greater when health and societal savings are considered.[37]

Recovery

Nearly all adolescent treatment approaches are based on the abstinence model, unfortunately a return to drug use occurs in one third to one half within 12 months following treatment.[38] Preventive measures should focus on specific treatment variables include; the adolescents treatment experience, counsellor rapport and aftercare attendance.[39] Individual variables include psychiatric comorbidity, lack of family involvement, continuing influence with drug using peers and poor coping skills.[40] All these variables are known to have strong evidence to support one's decision on whether the adolescence would choose to continue or not to continue attending and engaging therapy.

Conclusion

The results from a cluster analysis report[41] highlight that the highest risk groups include; those having two parents with a SUD, early use of one or more substances and the highest level of psychological dysregulation. This group is associated with significantly earlier use of tobacco, alcohol, marijuana and cocaine. The first steps of interventions are treatment programs but focusing on abstinence alone is insufficient. Rather, multimodal programs addressing various aspects as psychological dysregulation such as in the case of multi systemic therapy, a process which includes the young person, their family and their environment are optimal.[42]

The suggested core elements for adolescent treatment programs in Malta should include; screening and comprehensive assessments to ensure understanding of the full range of issues of the adolescent and family, comprehensive services to address the substance use problem. Given the limited funds available for prevention programs in Malta, research has demonstrated that there are three main groups to target. These include: children with ADHD, ODD and conduct disorders should be provided with a primary care provider for parental education and a child psychiatrist. Briones 2006 reported that frequent screening in schools for problematic alcohol and substance use during late childhood and early adolescence, to identify, then offer education should, whilst treatment to be offered to parents with SUDs is an effective preventative method to reduce the onset go SUDs. Encouraging adolescents in Malta to engage in positive social activities such as organised sport, voluntary activities and regions activities as these are less likely to develop SUDs ablate other negative behaviours.[43]

References

1. von Sydow K, Lieb R, Pfister H, Höfler M, Sonntag H, Wittchen H. The natural course of cannabis use, abuse and dependence over four years: a longitudinal community study of adolescents and young adults. 2001;64(3):347-61.
2. Camilleri N, Newbury-Birch D, McArdle P, Stocken DD, Thick T, Le Couteur A. Innovations in Practice: A case control and follow-up study of 'hard to reach'young people who suffered from multiple complex mental disorders. 2017;22(1):49-57.
3. Winters KC, Botzet AM, Fahnhorst T. Advances in adolescent substance abuse treatment. Curr Psychiatry Rep 2011;13(5):416-21.
4. European Monitoring Centre for Drugs and Drug Addiction. Multidimensional family therapy for adolescent drug users: a systematic review. EMCDDA Papers, Publications Office of the European Union 2014.
5. Hibell B, Guttormsson U, Ahlström S, Balakireva O, Bjarnason T, Kokkevi A, et al. The 2011 ESPAD report: substance use among students in 36 European countries.: ESPAD; 2012.
6. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future national survey results on drug use, 1975–2012. 2013;1: Secondary school students.
7. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. 2012;109(40):E2657-E2664.
8. Kraus L, Guttormsson U, Leifman H, Arpa S, Molinaro S. ESPAD Report 2015: Results from the European School Survey Project on Alcohol and Other Drugs.: Publications Office of the European Union; 2016.
9. Winters KC. Adolescent brain development and drug use. 2004.
10. Knudsen HK. Adolescent-only substance abuse treatment: Availability and adoption of components of quality. 2009;36(2):195-204.

11. Sartor CE, Lynskey MT, Heath AC. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. 2007;102:216–25.
12. Clark DB, Thatcher DL, Maisto SA. Adolescent neglect and alcohol use disorders in two-parent families. 2004;9(4):357-70.
13. Thatcher DL, Clark DB. Adolescents at risk for substance use disorders: role of psychological dysregulation, endophenotypes, and environmental influences. Alcohol Res Health 2008;31(2):168-76.
14. Sartor CE, Lynskey MT, Bucholz KK, McCutcheon VV, Nelson EC, Waldron M, et al. Childhood sexual abuse and the course of alcohol dependence development: Findings from a female twin sample. 2007;89(2):139-44.
15. Kaufman J, Yang B, Douglas-Palumberi H, Crouse-Artus M, Lipschitz D, Krystal JH, et al. Genetic and environmental predictors of early alcohol use. 2007;61(11):1228-34.
16. Funk RR, Mcdermeit M, Godley SH, Adams L. Maltreatment issues by level of adolescent substance abuse treatment: The extent of the problem at intake and relationship to early outcomes. 2003;8(1):36-45.
17. Tschann JM, Adler NE, Irwin CE, Millstein SG, Turner RA, Kegeles SM. Initiation of substance use in early adolescence: the roles of pubertal timing and emotional distress. 1994;13(4):326.
18. Back SE, Hartwell K, DeSantis SM, Saladin M, McRae-Clark AL, Price KL, et al. Reactivity to laboratory stress provocation predicts relapse to cocaine. 2010;106(1):21-7.
19. Harris KM, Edlund MJ. Self-medication of mental health problems: New evidence from a national survey. 2005;40(1):117-34.
20. Schwinn TM, Schinke SP, Trent DN. Substance use among late adolescent urban youths: mental health and gender influences. 2010;35(1):30-4.
21. Wang J, Simons-Morton BG, Farhart T, Luk JW. Socio-demographic variability in adolescent substance use: mediation by parents and peers. Prevention science 2009;10(4):387-96.
22. Cochran SD, Ackerman D, Mays VM, Ross MW. Prevalence of non-medical drug use and dependence among homosexually active men and women in the US population. 2004;99(8):989-98.
23. Marshal MP, Friedman MS, Stall R, King KM, Miles J, Gold MA, et al. Sexual orientation and adolescent substance use: a meta-analysis and methodological review. Addiction 2008;103(4):546-56.
24. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. 2003;129(5):674.
25. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings, 2003. 2004(04–5506).
26. Barnes GM, Reifman AS, Farrell MP, Dintcheff BA. The effects of parenting on the development of adolescent alcohol misuse: a Six-Wave latent growth model. 2000;62(1):175-186.
27. Griffin KW, Botvin GJ, Scheier LM, Diaz T, Miller NL. Parenting practices as predictors of substance use, delinquency, and aggression among urban minority youth: Moderating effects of family structure and gender. 2000;14(2):174.
28. Cohen DA, Richardson J, LaBree L. Parenting behaviors and the onset of smoking and alcohol use: a longitudinal study. 1994;94(3):368-75.
29. Stanton B, Li X, Pack R, Cottrell L, Harris C, Burns JM. Longitudinal influence of perceptions of peer and parental factors on African American adolescent risk involvement. 2002;79(4):536-48.
30. Priester JR. Sex, drugs, and attitudinal ambivalence: How feelings of evaluative tension influence alcohol use and safe sex behaviors. 2002:145-62.
31. Hohman ZP, Crano WD, Siegel JT, Alvaro EM. Attitude ambivalence, friend norms, and adolescent drug use. Prevention science 2014;15(1):65-74.
32. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the future national results on adolescent drug use: Overview of key findings, 2009. 2010(10–7583).
33. Crano WD. Experiments as reforms: Persuasion in the nation's service. 2010:231-48.
34. Crano WD, Siegel JT, Alvaro EM, Lac A, Hemovich V. The at-risk adolescent marijuana nonuser: Expanding the standard distinction. 2008;9(2):129.
35. Lipsey M, Tanner-Smith E, Wilson S. Comparative effectiveness of adolescent substance abuse treatment: Three meta-analyses with implications for practice. 2010.
36. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. 2010;33(3):511-25.
37. Abuse NIoD. Principles of Drug Addiction Treatment: A Research Base Guide. 2012.
38. Grella CE, Joshi V, Hser Y. Effects of comorbidity on treatment processes and outcomes among adolescents in drug treatment programs. 2004;13(4):13-31.
39. Whitney SD, Kelly JF, Myers MG, Brown SA. Parental substance use, family support and outcome following treatment for adolescent psychoactive substance use disorders. 2002;11(4):67-81.
40. Anderson KG, Ramo DE, Schulte MT, Cummins K, Brown SA. Substance use treatment outcomes for youth: integrating personal and environmental predictors. 2007;88(1):42-8.
41. Clark DB, Cornelius JR, Kirisci L, Tarter RE. Childhood risk categories for adolescent substance involvement: a general liability typology. 2005;77(1):13-21.
42. Henggeler SW, Pickrel SG, Brondino MJ. Multisystemic treatment of substance-abusing and-dependent delinquents: Outcomes, treatment fidelity, and transportability. 1999;1(3):171-84.
43. Briones DF, Wilcox JA, Mateus B, Boudjenah D. Risk factors and prevention in adolescent substance abuse: a biopsychosocial approach. 2006;17(2):335-52.

Original Article

Incidence of Acoustic Neuroma in Malta

Ryan Grech, Kenneth Muscat, Joseph Attard

Introduction

Vestibular schwannoma, also known as acoustic neuroma, is an uncommon entity, with incidence estimated at 1 in 100,000 individuals.[1-2] They make up 8% of all intracranial tumours, but around 80% of all cerebello-pontine angle growths.[3]

These lesions usually present with a mix of asymmetrical hearing loss, occasionally acute, tinnitus, vertigo and unsteadiness, which occur due to compression of the vestibulocochlear nerve directly or pressure on its blood supply.

The main concern with these benign tumours is the pressure on surrounding structures.

This study was performed to have a picture of the incidence of vestibular schwannomas in Malta.

Method

Review of the reports of MRIs of the Internal Auditory Meatus (MRIAM) performed between 2009 and 2016 in Mater Dei Hospital (MDH), the main hospital in Malta was done and findings of acoustic neuroma recorded.

Ryan Grech MD (Melit.), MSc(Edin.), MRCS (Edin.), DOHNS (Edin.)*
Department of Otorhinolaryngology
Mater Dei Hospital
Msida Malta
ryangrech88@gmail.com; ryan.grech@gov.mt

Kenneth Muscat M.D. (Melit), M.R.C.S. (Edin), Dip. O-HNS (Edin), F.E.B. ORL-HNS (Vienna), MSc Voice Pathology (UCL), FRCS (ORL) (Edin)
Department of Otorhinolaryngology
Mater Dei Hospital
Msida Malta

Joseph Attard MD (Melit.), MSc (Edin.), MRCS(Edin.)
Surgical Clinical Research Fellow,
Queen Elizabeth Hospital,
Birmingham

**Corresponding author*

For the years 2000 until 2008, no reliable electronic records of MRIs performed are available. The records of patients referred for treatment to specialist centres in the UK were accessed and the patients referred for management of acoustic neuroma included.

These records were also used to find any patients discovered by MRI brain which were not investigated by MRIAMs.

Results

In all, 76 new cases of acoustic neuroma were found over 17 years.

4.5 new cases per year were discovered on average, which results in an incidence of 1.1 per 100,000.

The age range of the cases was from 20 to 81 years, with a median age of 57 and mean age of 54.6 years.

37 were males and 39 females.

Discussion

The incidence of 1.1 per 100,000 is similar to that found in other studies. [4-5]

A slight female preponderance was found, which is similar to the findings of similar studies which found a greater percentage of females affected by vestibular schwannoma.[6,7] The average ages affected were similar to those reported in other studies. [6,7]

The number of acoustic neuromas discovered have gradually increased over the years, 43 of the cases were discovered in the years 2012 - 2016, while only 33 were discovered in the previous 12 years. This might be due to the increasing availability and use of MRI.

Limitations of this study include the relatively small number of cases when compared to other similar studies. Due to the small population of Malta, this can only be mitigated by increasing the number of years included in the study.

Another limitation of this study is that cases of acoustic neuroma which were not investigated by MRIAM in Mater Dei Hospital and/or referred for treatment abroad were not included in this study.

This might have resulted in missing a small number of cases of acoustic neuroma discovered in private hospitals and acoustic neuromas discovered by MR head which did not have a subsequent MRIAMs and were not referred for management abroad.

Conclusion

This is the first such study investigating the incidence of acoustic neuroma in Malta. An incidence similar to that found in other incidence studies performed in Europe and the US was found. In spite of the limitations of the study, it is a good picture of the epidemiology of acoustic neuroma in Malta.

Figure 1. *Number of Newly Diagnosed Acoustic Neuromas per Year*

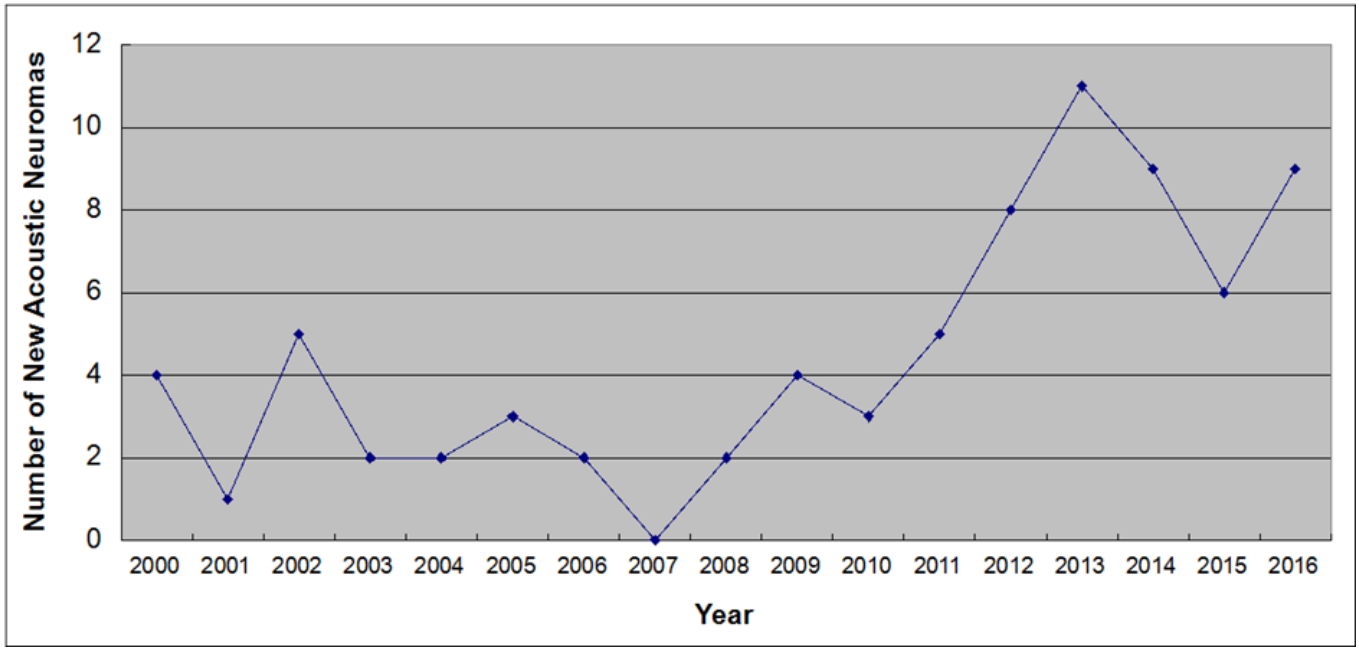


Table 1*. Number of Newly Discovered Acoustic Neuromas from 2000 to 2016*

Year	Number of Cases Discovered
2000	4
2001	1
2002	5
2003	2
2004	2
2005	3
2006	2
2007	0
2008	2
2009	4
2010	3
2011	5
2012	8
2013	11
2014	9
2015	6
2016	9

References

1. Penner M. Linking spontaneous otoacoustic emissions and tinnitus. Br J Audiol. 1992; 26:115–23.
2. Gal T, Shinn J, Huang B.. Current epidemiology and management trends in acoustic neuroma. Otolaryngol Head Neck Surg. 2010; 142(5):677-81.
3. Coles R. Epidemiology, aetiology and classification. In: Reich GE, Vernon JA, editors. Proceedings of the Fifth International Tinnitus Seminar, 1995, Portland, OR, U.S.A. Portland (OR): American Tinnitus Association. 1996; p. 25–30.
4. Stangerup S, Tos M, Thomsen J, Caye-Thomasen P. True incidence of vestibular schwannoma? Neurosurgery. 2010; 67(5):1335-40;
5. Babu R, Sharma R, Bagley J, Hatef J, Friedman A, Adamson C. Vestibular schwannomas in the modern era: epidemiology, treatment trends, and disparities in management. J Neurosurg. 2013.;119(1):121-30.
6. Howitz M, Johansen C, Tos M, Charabi S, Olsen J. Incidence of vestibular schwannoma in Denmark, 1977-1995. Am J Otol. 2000; 21:690–694.
7. Propp J, McCarthy B, Davis F, Preston-Martin S. Descriptive epidemiology of vestibular schwannomas. Neuro Oncol. 2006; 8:1–11.

Original Article

Re-operation Rates in Breast cancer after Breast Conserving Surgery in Malta

Alexia Farrugia, Gordon Caruana Dingli

Abstract

The Agatha Breast Unit at Mater Dei Hospital, Malta performed 340 wide local excisions for cancer in 2013-4. Further surgery for close or involved surgical margins was performed in 45 cases (13%), of these 26 (58%) underwent cavity excision and 19 (42%) underwent mastectomy. Residual tumour was found in 9 (35%) in the cavity excision group and 13 (68%) of the mastectomy group. The authors discuss how their unit follows the recommendations of the "Toolbox to reduce lumpectomy reoperations and improve cosmetic outcome in breast cancer patients of the American Society of Breast Surgeons Consensus Conference" and what can be done to reduce re-operation rates further.

Keywords

Breast neoplasms, Margins of Excision, Reoperation

Alexia Farrugia M.D (Melit.), MRCS (Edin.)*
Agatha Breast Unit
Mater Dei Hospital
Msida, Malta
lexy519@gmail.com

Gordon Caruana Dingli MD (Melit), LRCP(Edin) LRCS (Edin), LRCP&S (Glasg) FRCS (Edin) FRCS RCP&S (Glasg)
Agatha Breast Unit
Mater Dei Hospital
Msida, Malta

**Corresponding author*

Introduction and Aim

Breast cancer is the most prevalent cancer in European women and the incidence is increasing but mortality rates are decreasing. In our unit 70% of patients undergo breast conservation therapy (BCT) aiming to control local disease and achieve cure with the best possible cosmetic result and allowing the patient to have a good quality of life.1 An inadequate surgical margin may lead to local recurrence but re-excision to achieve an optimum margin leads to a worse cosmetic outcome and other problems.

The aim of this study is to assess re-operation rates in breast cancer patients after wide local excision in our unit. This was done by reviewing the histology results of the original surgery and those of the subsequent cavity excision or mastectomy, studying residual tumour rates in the two types of re-operation.

Methods

Data Collection and Sampling.

Data was collected from theatre lists of the two local breast surgeons for all wide local excision operations performed for cancer during 2013 and 2014 at the Agatha Breast Unit at Mater Dei hospital, Malta. Histology reports were accessed from the hospital database and patient records were reviewed as necessary.

Results

A total of 340 wide local excisions were performed in 2013 and 2014. Further surgery was performed in 45 (13%) to achieve clear margins. Of these, cavity excision was performed in 26 patients (58%) and mastectomy in 19 patients (42%). Residual tumour was found at the second operation in 9 patients (35%) in the cavity excision group and in 13 (68%) in the mastectomy group (49% overall). This is outlined in table 1.

The collected data was analysed statistically using IBM SPSS to check if there is a statistically significant difference in the size of original tumour

between patients undergoing cavity excision or mastectomy at subsequent surgery.

***Table 1**: Wide local excisions and re-operations for breast cancer in 2013 and 2014*

2013		2014	
Wide Local Excision 172		Wide Local Excision 168	
Cavity Excisions 7	Mastectomies 12	Cavity Excisions 19	Mastectomies 7
Residual tumour 2 29%	Residual tumour 8 67%	Residual tumour 7 37%	Residual tumour 5 71%

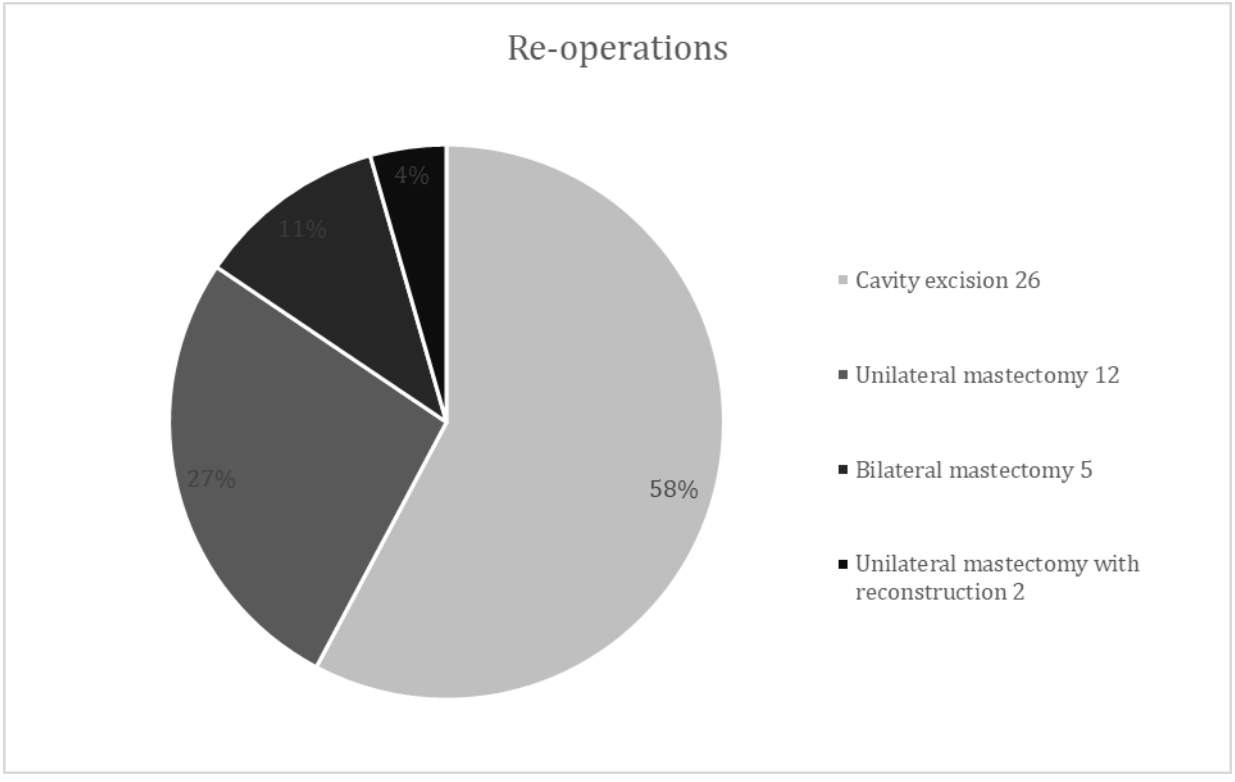
Out of the patients who underwent cavity excisions, 23(88.5%) had invasive carcinoma at original histology while 3(11.5%) had both invasive carcinoma and DCIS. The patients who subsequently had a mastectomy had 12 (63.2%) who had invasive tumour orginally and 7 (36.8%) who had both invasive carcinoma and DCIS. When comparing the two groups, more patients who eventually had mastectomy had both invasive tumour and DCIS in the original histology (P=0.009), while more patient who had a cavity excision had only invasive tumour initially (p=0.02).

The average size of the initial tumour was 23mm (range 8-48) in those who subsequently underwent cavity excision and 33mm (range 6-75) in those who underwent mastectomy. The difference in size was statistically significant, p=0.03 using a T-test.

Out of 26 cavity excisions, 9 (35%) had residual tumour on histological assessment and out of 19 mastectomies 13 (68%) had residual disease. The mastectomy group had a statistically significant higher rate of residual cancer when compared to the cavity excision group (p=0.025, using a Pearson Chi-Square test).

In the mastectomy group 5 patients (26%) had an initial tumour which was larger than 40mm on histology of the original operation, 7 patients (37%) had multifocal disease, 2 (11%) had chemotherapy between the initial and delayed surgery, 4 (21%) had extensive DCIS and one (5%) had previously undergone risk reduction bilateral subcutaneous mastectomy and immediate reconstruction for high-grade DCIS.

***Figure 1**: Re-operations for incomplete excision of breast cancer in 2013 and 2014*



The average length of time in between surgeries was 58.61 days for the mastectomy group (range 27-209 days) and 62.22 days for the cavity excision group, excluding those patients who had chemotherapy in between the surgeries (range 22-205 days). The total average time between surgeries was 60.41 days. This implies that patients undergoing re-operation undergo substantial delays to start adjuvant treatment.

Discussion

Surgery is the mainstay treatment of breast cancer with breast conserving therapy now being the preferred option. Breast conserving therapy (BCT) includes breast conserving surgery (BCS) followed by moderate dose radiation therapy to eradicate residual microscopic disease. An overview of completed trials and 9 prospective randomised clinical trials comparing BCT with mastectomy showed equivalent survival rates between the two approaches.2-11 The main aim of BCT is to provide a more cosmetically acceptable breast associated with a low rate of recurrence in the treated breast. 12 However in breast conserving surgery an adequate negative margin around the tumour is required to achieve full clearance. A positive margin may lead to further surgery which may either involve further local treatment (cavity excision) or mastectomy at a later stage.13 Reoperation may have consequences such as delaying adjuvant treatments, and increased rates of local and distal recurrence.14-16 Other consequences may include poorer cosmetic outcome and emotional distress which may delay recovery, with the resulting socioeconomic impact due to inability or delay in resuming work and also additional financial burden on the healthcare system.17

The latest NCCN guidelines state that for DCIS a margin status of less than 1 mm is considered inadequate, 10mm is considered a good margin but may affect cosmetic outcome. If the margin is between 1-10mm, the wider the margin the lower the local recurrence rate. For margins of less than 1 mm between the fibroglandular boundary (i.e. chest wall or skin) re-excision is not mandatory. However, this may require higher radiotherapy doses postoperatively.18 In infiltrating carcinoma, a negative margin is considered as 'no ink on tumour' as described by the 2014 Society of Surgical Oncology – American Society for Radiation Oncology Consensus Guidelines on Margins.19 Positive margin requires re excision in the form of further breast conserving therapy if appropriate or mastectomy, because there is increased risk of ipsilateral breast tumour local recurrence. There is still controversy regarding the appropriate margin however most surgeons take this to be 2mm. 20

It has been shown that 25% of local recurrences are associated with survival reduction at 20 years.2 Loco-regional recurrence is a product of sufficient tumour volume reduction (a clear margin is a surrogate marker), tumour biology, radiotherapy and systemic treatment. There are no prospective randomized trials that directly address the influence of margin width on local recurrence or define an optimal marginal width. What constitutes an acceptable margin must be individualized within the context of the tumour size, biology, stage and planned treatments.1

Reoperation rates after breast conserving surgery can be high, with rates of 17% to 68% quoted in various studies.21-28 Women having an in situ component were more likely to have at least one reoperation.29 The results from our unit compare well with these figures.

Our unit strives to decrease re-operation rates by following the recommendations of the Consensus Conference Toolbox to reduce lumpectomy reoperations and improve cosmetic outcome in Breast Cancer Patients of the American Society of Breast Surgeons. 30

Pre-operative imaging is done with full-field digital mammography and ultrasound as needed. MRI is used for patients with lobular carcinoma. All patients undergo breast biopsy before surgery and they are discussed at a multi-disciplinary team meeting that includes surgeons, radiologists, pathologists and oncologists. Non-palpable breast lesions are localized, and multiple wires or seeds are used for large lesions, multifocal tumours and extensive DCIS. Oncoplastic surgical techniques allow resection of larger amounts of breast tissue and this may include contralateral breast symmetrization surgery. All operative specimens are oriented by placement of sutures at surgery, a short suture is used to label the superior margin, a medium suture for the medial margin and a long suture for the lateral margin. All specimens are weighed to facilitate reconstruction when necessary. When the lesion is not palpable the specimen is

labelled with metal clips (Ligaclips™) and radiographed. This will document that the lesion has been removed and assessment of the margin. A cavity shave is performed if the margin is "close". We do not perform routine cavity shaves of side walls or intraoperative pathology assessment of lumpectomy margins.

Not all patients who have positive or close margins in the first operation are found to have residual tumour at the second operations. Rates of 18.8% to 33% have been quoted, while we report residual tumour in 49% of re-operated patients.20,22 Residual disease has been associated with multifocality but no other associated factors have been identified.22

Patients treated with repeat BCS had similar outcomes to those who underwent mastectomy. This was shown by a retrospective review and a prospective study which both showed no significant difference in survival rate following both management options i.e. mastectomy versus repeat BCS.31, 32

Our study compared two groups of women who underwent further excision after their initial breast-conserving surgery, for close or involved margins with tumour or in-situ disease. Some underwent a cavity excision while others had a mastectomy as their second surgery. Patients undergoing cavity excision were found to have residual tumour in 35% of cases compared to 68% of patients with residual tumour in the mastectomy group (p=0.025). This implies that mastectomy is more likely to result in a positive result and therefore more likely to result in complete histological excision than breast conserving cavity excision. It may also imply that in repeat cavity excision the surgeon might not manage to excise residual disease as this may be difficult to localize. There was also a significant difference in the initial tumour size, as those patients who underwent a mastectomy as a second procedure had larger average initial tumour size (p=0.03). This implies that a larger initial tumour size may influence the decision to perform a mastectomy as a second surgery if this is required.

Limitations of this study include a small sample size of re-operated patients and the retrospective nature of the study.

Lateral margin cavity shave during the initial breast conserving surgery has been shown to decrease the re-operation rates for margin clearance but the excised volume is increased and this may unnecessarily compromise cosmetic outcome.21,29,33-35 Intra-operative margin assessment using frozen section reduces re-excision rates but this is not widely available.36 A commercially available RF spectroscopy probe (MarginProbe) has been shown to decrease re-operation rates.37 Our unit proposes to study these three techniques in an effort to further improve our re-operation rate.

References

1. MacNeill F, Karakatsanis A. Over surgery in breast cancer. *The Breast* 2017 Feb; 31; 84-289 doi: 10.1016/j.breast.2016.10.023
2. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005 Dec; 366(9503):2087-106 DOI:10.1016/S0140-6736(05)67887-7
3. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995 Nov; 333(22):1456-61
4. Fisher B, Anderson S, Bryant J,Margolese RG, Deutsch M ,Fisher ER et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002 Oct; 347(16):1233-41.
5. Veronesi U, Salvadori B, Luini A, Greco M, Saccozzi R, Del Vecchio M et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients. *Eur J Cancer* 1995 Sep; 31A(10):1574-9
6. Veronesi U, Cascinelli N, Mariani L,Greco M, Saccozzi R, Luini A et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002 Oct; 347)16):1227-32. DOI:10.1056/NEJMoa020989
7. van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000 Jul; 92(14):1143-50.
8. Jacobson JA, Danforth DN, Cowan KH, d'Angelo T, Steinberg SM, Pierce L et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 1995 Apr; 332(14):907-11 DOI:10.1056/NEJM199504063321402

9. Poggi MM, Danforth DN, Sciuto LC, Smith SL, Steinberg SM, Liewhehr DJ et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. *Cancer* 2003 Aug; 98(4):697-702 DOI:10.1002/cncr.11580
10. Institut Gustave-Roussy Breast Cancer Group. Arriagada R, Lê MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data.. *J Clin Oncol* 1996 May; 14(5):1558-64 DOI:10.1200/JCO.1996.14.5.1558
11. Danish Breast Cancer Cooperative Group. Blichert-Toft M, Rose C, Andersen JA, Overgarrd M, Axelsson CK, Andersen KW, Mouridsen HT. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. *J Natl Cancer Inst Monogr* 1992;(11):19-25.
12. Sabel M, Pierce L. Breast Conserving Surgery. www.uptodate.com. Accessed on 17/12/2016
13. Aziz D, Rawlinson E, Narod SA, Sun P, Lickley HL, McDready DR, et al. The role of reexcision for positive margins in optimizing local disease control after breast-conserving surgery for cancer. *Breast J* 2006;12(4):331-7 DOI:10.1111/j.1075-122X.2006.00271.x
14. Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM. Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: current modalities and future directions. *Ann Surg Oncol* 2009;16(10):2717-30 doi: 10.1245/s10434-009-0609-z.
15. Menes TS, Tartter PI, Bleiweiss I, Godbold JH, Estabrook A, Smith SR. The consequence of multiple re-excisions to obtain clear lumpectomy margins in breast cancer patients. *Ann Surg Oncol* 2005;12(11):881-5 DOI:10.1245/ASO.2005.03.021
16. Kouzminova NB, Aggarwal S, Aggarwal A, Allo MD, Lin AY. Impact of initial surgical margins and residual cancer upon re-excision on outcome of patients with localized breast cancer. *Am J Surg* 2009;198(6):771-80 doi: 10.1016/j.amjsurg.2009.05.027.
17. Munshi A, Kakkar S, Bhutani R, Jalali R, Budrukkar A, Dinshaw KA. Factors influencing cosmetic outcome in breast conservation. *Clin Oncol* 2009 May ;21 (4):285-93 oi: 10.1016/j.clon.2009.02.00
18. Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology *J Natl Compr Canc Netw* Mar 1, 2016:324-54
19. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Int J Radiat Oncol Biol Phys Mar 1;88(3):553-64. doi: 10.1016/j.ijrobp.2013.11.012.
20. Unzeitig A, Kobbermann A, Xie XJ,Yan J, Euhus D, Peng Y et al. Influence of Surgical technique on Mastectomy and Reexcision rates in Breast Conserving therapy for cancer. *Int. J. Surg. Oncol*. 2012; 725121 doi: 10.1155/2012/725121
21. Sabel MS, Rogers K, Griffith K, Jagsi R, Kleer CG, Diehl KA et al Residual disease after re-excision lumpectomy for close margins. *J Surg Oncol*, 2009; 99(2):99–103
22. Wiley EL, Diaz LK, Badve S, Morrow M. Effect of time interval on residual disease in breast cancer. *Am J Surg Pathol* 2003; 27(2):194–198
23. Gray RJ, Salud C, Nguyen K, Dauway E, Friedland J, Berman C et al. Randomized prospective evaluation of a novel technique for biopsy or lumpectomy of nonpalpable breast lesions: radioactive seed versus wire localization. *Ann Surg Oncol* 2001; 8(9):711–715
24. Jacobson AF, Asad J, Boolbol S, Osborne MP, Boachie-Adjei K, Feldman SM. Do additional shaved margins at the time of lumpectomy eliminate the need for re-excision? Am J Surg *2008*;*196(4)*:*556*-8.
25. Freedman G, Fowble B, Hanlon A, Nicolaou N, Fein D, Hoffman J, et al. Patients with early stage invasive cancer with close or positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy. Int J Radiat Oncol Biol Phys 1999*;*44(5)*:*1005-*15*
26. Cellini C, Hollenbeck ST, Christos P, Martins D, Carson J, Kemper S, et al. Factors associated with residual breast cancer after re-excision for close or positive margins. Ann Surg Oncol 2004;11(10):915-20 DOI:10.1245/ASO.2004.12.037
27. Talsma AK, Reedijk AM, Damhuis RA, Westenend PJ, Vles WJ. Re-resection rates after breast-conserving surgery as a performance indicator: introduction of a case-mix model to allow comparison between Dutch hospitals. Eur J Surg Oncol 2011;37(4):357-63. doi: 10.1016/j.ejso.2011.01.008
28. Jeevan R, Cromwell AD, Trivella M et al. *Reoperation* rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics BMJ 2012;345:e4505
29. Marudanayagam R, Singhal R, Tanchel B O'Connor B, Balasubramanian B, Paterson I. Effect of Cavity Shaving on Repoeration rate following breast conserving surgery. *Breast Journal* 2008 14(6): 570-3 doi: 10. 1111/j.1524-4741.2008.00649.x
30. The American Society of Breast Surgeons Consensus Conference. Landerscaper J, Attal D, Atisha D, Beitsch P, Bosserman L, Boughey J, et al. Toolbox to reduce lumpectomy reoperations and improve cosmetic outcome in Breast Cancer patients. *Ann Surg Oncol* 2015; 22(10):3174-83 doi: 10.1245/s10434-015-4759-x
31. Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Androla S et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. *Br J Surg* 1999; 86(1):84-7 DOI:10.1046/j.1365-2168.1999.00961.x
32. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG. Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. *Int J Radiat Oncol Biol Phys* 2005; 63(3):845-51 DOI:10.1016/j.ijrobp.2005.02.035

33. Hewes JC, Imkampe A, Haji A, Bates T. Importance of routine cavity sampling in breast conservation surgery. Br J Surg 2009; 96(1):47–53
34. Rizzo M, Iyengar R, Gabram SG, Park J, Birdsong G, Chandler KL, Mosunjac MB. The effects of additional tumor cavity sampling at the time of breast-conserving surgery on final margin status, volume of resection, and pathologist workload *Ann Surg Oncol*. 2010 Jan;17(1):228-34. doi: 10.1245/s10434-009-0643-x.
35. Chagpar AB, Killelea BK, Tsangaris TN, Butler M, Stavris K, Li F. et al. A randomized, controlled trial of cavity shave margins in breast Cancer. *N Engl J Med* 2015 Aug 6; 373(6):503-10
36. Esbona Karla, Li Zhanhai, Wilke Lee. Intraoperative imprint cytology and frozen section pathology for margin assessment in breast conservation surgery: a systematic review. *Ann Surg Oncol* 2012 Oct; 19 (10): 3236-45
37. Schnabel F., Boolbol SK, Gittleman M, Karni T, Tafra L, Feldman S et al. A randomized prospective study of lumpectomy margin assessment with use of MarginProbe in patients with nonpalpable breast malignancies. Ann Surg Oncol, 2014; 21(5):1589-9

Original Article

User Satisfaction of Children and Young People's Service, Malta

Andrea Saliba, Nigel Camilleri

Abstract

Background: Few published studies have evaluated the service users' satisfaction of a Children and Young People Service (CYPS). An association between child and carers' satisfaction and their attendance to CYPS exists. The aims of this study were to evaluate the service users' views of the national CYPS, Malta and disseminate findings to policy makers to inform service development.

Method: Young People (YP) attending CYPS from 1st to 30th November 2014 were invited to fill in an anonymized Charleston psychiatric outpatient satisfaction scale in Maltese or English. The quantitative data was collected from 13 questions using a Likert scale and analysed using statistical correlations. The qualitative data was collected from three open ended questions and analysed using a thematic analysis.

Results: The sample population was 211 (97.7% response rate), average age 9.97 years (SD 3.34, CI ± 0.45). Overall quality of care was significantly (p<0.001) correlated with; 'respect shown for YP's treatment opinions' (r=0.539), 'matching treatment plan to YP's individual needs' (r=0.320), and 'helpfulness of the services received' (r=0.618). Thematic analysis findings included; waiting lists and the interval between reviews were perceived as too long, difficultly establishing a therapeutic relationship, and lack of age appropriate environment which hindered attendance.

Conclusions: This is the first service user satisfaction evaluation for CYPS, Malta. Increasing staff to reduce waiting times and having reviews by the same clinician would ensure continuity of care and improve the therapeutic relationship. Better communication between services is required through school visits and paediatricians. Extending opening times, facilitating the referral process and improving accessibility may decrease barriers to service. Artwork and a well-lit environment could help engagement. Despite the above, YP still felt that overall CYPS provided an individualised treatment plan where staff work collaboratively to scaffold YP and meet their needs.

Andrea Saliba MD (Melit), MRCPsych (UK)*
Northumberland,
Tyne and Wear NHS Foundation Trust,
Mental Health Malta,
University of Malta.
Msida, Malta
andrea.a.saliba@gmail.com

Nigel Camilleri MD (Melit), MD (Newcastle), MRCPsych (UK), CCT (CAP), RCP (IRE)
Mental Health Malta,
University of Malta,
Msida, Malta
Newcastle University

**Corresponding author*

Keywords

Child Psychiatry, User Satisfaction, Parental Satisfaction, Service Evaluation, Quality Improvement, Out Patient Clinics

Background

Professor Sir Ian Kennedy (2010) suggested that the only assessment of the quality of service in child health should be through service user satisfaction questionnaires.[1] To date only a few published studies have assessed the service users' satisfaction of child and adolescent mental health services (CAMHS).[2] Promoting service user satisfaction may be an important aspect with the aim to reduce the dropout rates, which are reported to be between 30 to 60% of young people (YP) in

CAMHS.[3-4] There is an association between YP and parental satisfaction and engagement and treatment completion.[5-6]

Parent satisfaction feedback questionnaires have received criticism for the lack of psychometric evidence including validity and reliability.[7-8] They have also been criticised for not being comprehensive[8] and this is related to content validity. One reliable and validated service user questionnaire is the Charleston psychiatric outpatient satisfaction scale, with a high internal reliability (alpha = 0.87).[9]

The aim of this study was to evaluate the current service users' opinion of the national CYPS in Malta and disseminate them to commissioners and policy makers to be utilised for service development.

Method

Procedure

This study was a one stage survey to which all YP aged 18 years and under who were attending CYPS from the 1st to 30th November 2015 were invited to participate in. Data were collected over a one-month period. This time period was decided upon based on the estimated projected sample size which was considered large enough according to published research[10] for qualitative and quantitative data analysis. The national CYPS covered a population of 75,464 YP in 2015.[11]

The inclusion criteria were all YP attending CYPS with a mental disorder according to ICD-10.[12] YP who had more than one appointment during the data collection period were eligible to participate on one of their visits only. All YP were offered the opportunity to participate or abstain, with the aim of reducing the chance of a selection bias.

Informed consent was obtained from every YP by the three nurses working at CYPS. The YP were then invited to fill in an anonymised questionnaire in either Maltese or English. The researchers (AS and NC) carried out the data collection and analysis had no direct contact with the participants, thus reducing the chance of an observer's bias.

Questionnaire Development

The selected questionnaire was an adapted Charleston psychiatric outpatient satisfaction scale. It is comprised of a 5-point Likert-type response setup which optimises variability and predictive validity while decreasing positive response bias. All questions followed the hospital governance protocol and contained no unethical questions or questions which may negatively affect the mental state of the YP. The English version had a readability score of ages 13-14 years and the questionnaire was translated by a professional translator into Maltese. The questionnaire involved 13 questions with a Likert scale and three open ended questions at the end of the questionnaire.

A pilot study was carried out on 10 YP, to assess the acceptability, readability and reliability of the tool. The YP and carers were then asked to provide written feedback on the three mentioned points above. Both the English and the Maltese version of the questionnaire were found to be acceptable with good readability by all YP and care givers.

Analysis

A mixed method analysis was carried out using both qualitative and quantitative data analysis. The data from the questionnaires were inputted into a password protected Excel 2010 spreadsheet.

All quantitative data were grouped, and correlations were carried out using Statistical Package for the Social Science.[13] The three variants with the highest correlation coefficient to overall quality of care were entered into a logistic regression to test whether the three independent variables were significant in rating the overall quality of care received.

The qualitative data were collected from the three open ended questions which inquired; i. how the service could be improved? ii. what would YP and care givers make sure such a service would include and iii. any other comments that they had. A thematic analysis as written by Braun and Clarke[14] was used to analyse YP's opinions as a combined group. In this thematic analysis four major themes were identified: clinical, administrative, environment and location comments.

Results

The target population was 216, five people refused to participate, either due to literacy difficulties or needing to attend to their child's needs as a priority, thus the sample population was

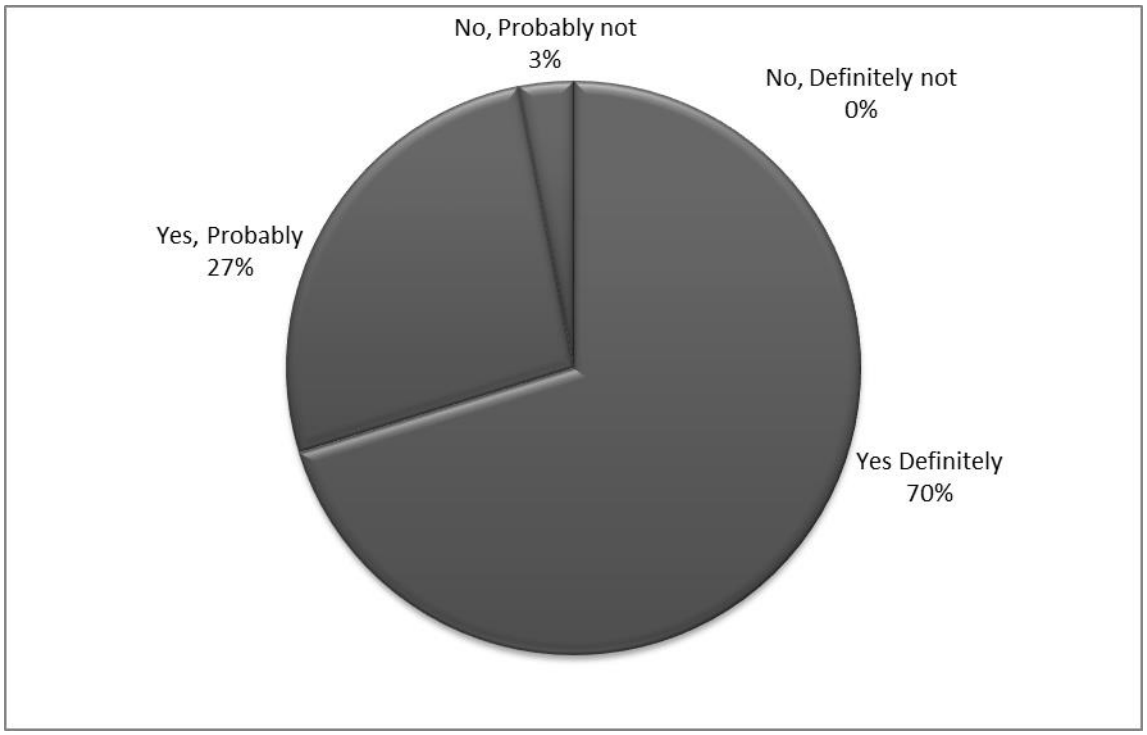
211 (97.7% response rate). The average age of attendance was 9.97 years (SD 3.34, 95% CI ± 0.45) and all the YP were accompanied by a parent or care giver. 112 (53.3%) chose to answer the questionnaire in Maltese.

Results for the qualitative part of the questionnaire are presented in Table 1 and Figure 1. The overall quality of care was significantly correlated with respect shown for YPs' opinions about treatment (r=0.539, $p<0.001$), matching of the treatment plan to the YPs' individual needs (r=0.320, $p<0.001$), and the helpfulness of the services YP received (r=0.618, $p<0.001$).

Table 1. *Describes the frequencies for questions 1 to 12*

		Excellent n (%)	Very Good n (%)	Good n (%)	Fair n (%)	Poor n (%)	N/A n (%)
1	Helpfulness of the reception staff	105 (51.2)	69 (33.7)	29 (14.1)	1 (0.5)	0 (0)	1 (0.5)
2	Amount of time waiting to be seen	18 (8.9)	68 (33.5)	72 (35.5)	37 (18.2)	7 (3.4)	1 (0.5)
3	Amount of information given to you about your problem	64 (31.1)	77 (37.4)	46 (22.3)	18 (8.7)	1 (0.5)	0 (0)
4	Respect shown for your opinions about treatment	62 (29.8)	81 (38.9)	52 (25)	8 (3.8)	0 (0)	5 (2.4)
5	Matching of treatment plan to your individual needs	50 (25.1)	76 (38.2)	51 (25.6)	12 (6)	0 (0)	10 (5.0)
6	Helpfulness of the services you have received	78 (37.9)	73 (35.4)	39 (18.9)	8 (3.9)	3 (1.5)	5 (2.4)
7	Overall quality of care provided	55 (27.8)	82 (41.4)	40 (20.2)	13 (6.6)	0 (0)	8 (4.0)
8	Appearance of the waiting room	25 (12)	68 (32.7)	63 (30.3)	41 (19.7)	11 (5.3)	0 (0)
9	Appearance of the office	20 (9.6)	69 (33.2)	70 (33.7)	41 (19.7)	8 (3.8)	0 (0)
10	Office hours	35 (17.0)	69 (33.5)	68 (33.0)	19 (9.2)	13 (6.3)	2 (1.0)
11	Location of this outpatient service	30 (15.0)	51 (25.5)	76 (38.0)	22 (11.0)	12 (6.0)	9 (4.5)
12	Parking	4 (1.9)	8 (3.9)	19 (9.2)	46 (22.2)	110 (53.1)	20 (9.7)

Figure 1. *Would you recommend this program to a friend or family member?*



Multiple regression analyses were used to test if respect shown for YPs' opinions about treatment, matching of the treatment plan to the YPs' individual needs and the helpfulness of the services YP received significantly predicted overall quality of care. The result indicated that the three predictors significantly account for 48.6% of the variance (R2=0.486, F(3,184)=57.93, p<0.001). Matching of the treatment plan to the YP's individual needs and the perceived helpfulness YP received from the professionals within CYPS significantly influenced the perceived overall quality of care (β 0.325, β 0.361 respectively), p <0.001, that the YP received. However, respect shown for YPs' opinions about treatment was not significantly predictive (beta 0.114) p=0.135.

Thematic Analysis

Service users felt that more guidance, such as parental skills and children's groups were needed to help them understand and deal with their children's behaviours, Figure 2. It was emphasised that better collaborative communication including education was required and as a result, professionals can then prescribe accurate individualised treatment to meet their needs. Having access to a crisis team and helpline were amongst the suggested needs for a more holistic and efficient service.

36 (12.6%) YP said that review appointments were too infrequent and furthermore, having reviews carried out by a different professional on each subsequent review reduced continuity of care and hence the chances of building a meaningful therapeutic relationship with any professional, Figure 3. 20 (7.0%) YP said that the waiting lists for psychologists and doctors were perceived as being too long, some recommended an increase in the number of trained staff to patient ratio. 15 (5.2%) YP stressed the importance of professionals adhering to their respective appointment times. Lastly, it was suggested that clinic hours should be extended so that YP would not have to miss school to attend appointments and care givers not to need to take time off work.

The appearance and facilities in the waiting room were heavily criticised (n=50, 17.5%), YP asked for new and appropriate books to be made available in the waiting room, for there to be age appropriate toys, a larger TV screen, computers, Wi-Fi available, a food and drink machine and an overall warmer and age appropriate environment. 31 respondents (10.8%) reported to finding parking facilities difficult to access.

Figure 2. *Comments pertaining to the clinical aspect of CYPS*

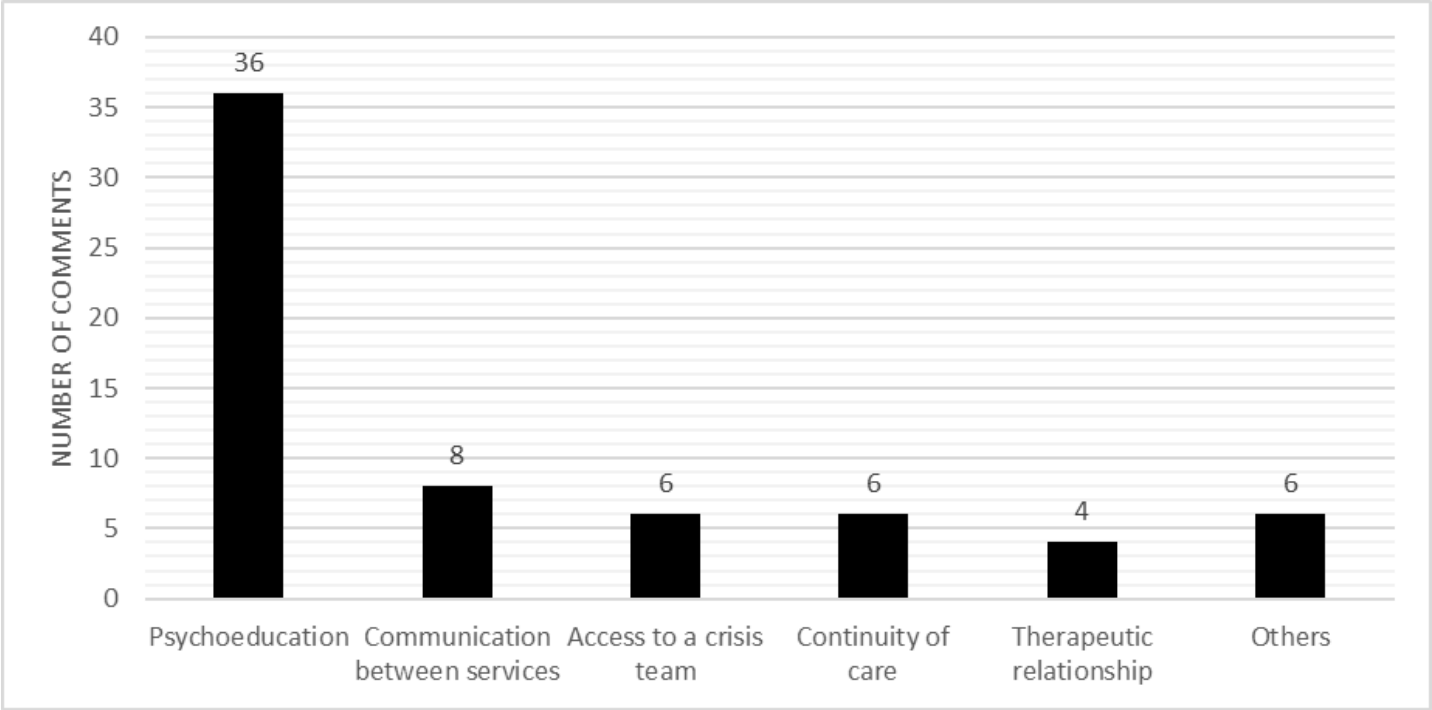
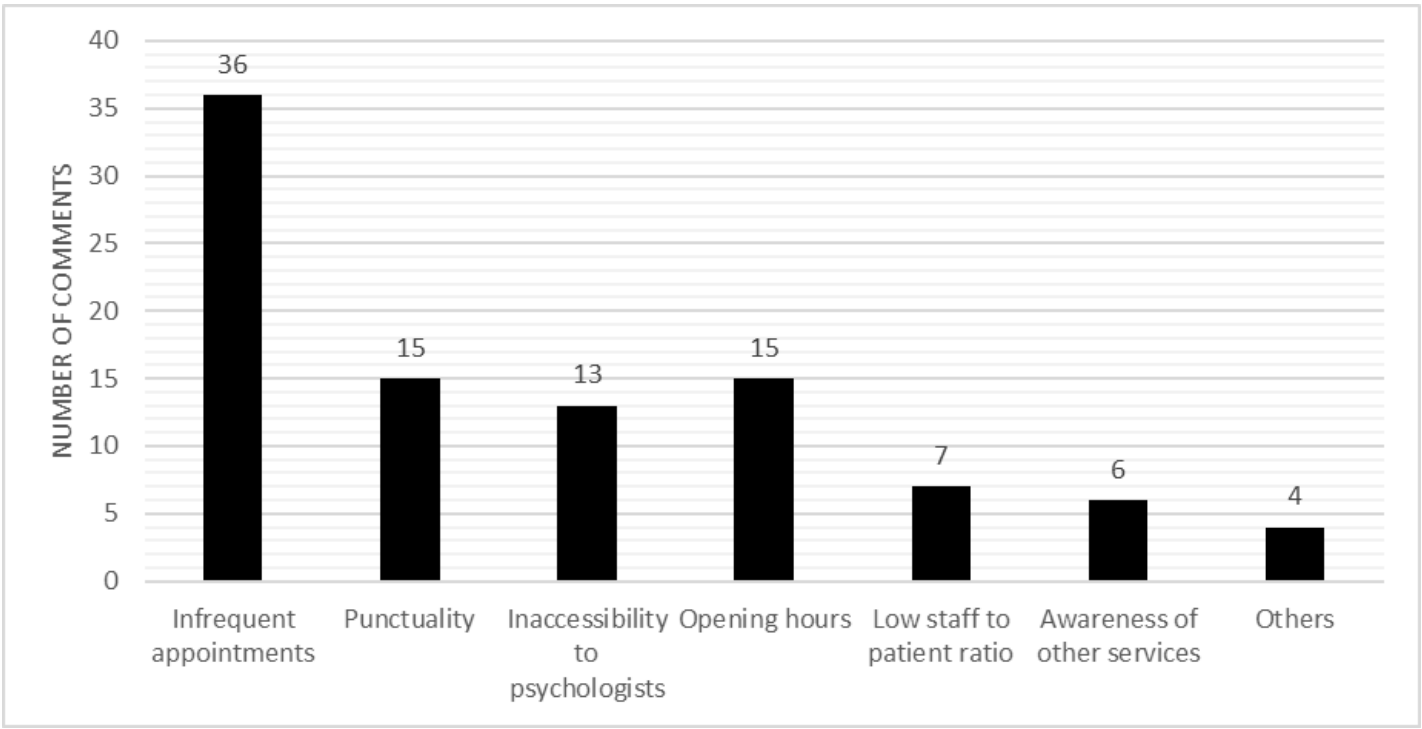


Figure 3. *Comments pertaining to the administration aspect of CYPS*



Conclusions

To our knowledge this was the first service user satisfaction evaluation carried out for the national CYPS, Malta. The overall feedback from the YP and their care givers was positive with regards to the overall quality of the service that they received. 50 (17.5%) YP commented positively and expressed their appreciation towards the service offered at CYPS. The main finding which support this included; YP felt that CYPS provided an individualised treatment plan which was tailored to their needs and that the staff worked collaboratively with the YP to achieve their treatment goals.

However, a substantial number (*n*=36, 12.6%) of YP and their care givers commented that waiting times for appointments were too long. Another recent service evaluation from the same CYPS reported the mean waiting time for the first specialist review was 301 days (CI ± 34.4, range 0-800) in 2014.[15] Therefore, CYPS waiting times did not follow guidelines as recommended by the Local Delivery Plan Standards target in NHS Scotland, which reports that a child should not wait for more than 18 weeks[16] from referral to treatment. This could be achieved by increasing the trained staff to patient ratio and investing in treatment pathways with target waiting times and auditing the service regularly.

The need for better communication between services was emphasized by the responders. To address this limitation CYPS staff have started carrying out more school visits, thereby liaising with the educational system, thus assessing YP in their natural environment to provide a better understanding of the YP's needs resulting in a better outcome of care provided.[17] Furthermore, there has been more emphasis on interdisciplinary communication between paediatricians and clinicians working at CYPS. This has been facilitated by having trained paediatricians working at CYPS and having an exchange training programmes between psychiatry and paediatrics of placements for trainees.

One important theme from this thematic analysis was the absence of continuity of care and therefore the difficultly to establish a therapeutic relationship between the clinician and the YP. This may be the result of the system set up, where by a YP is reviewed by a different doctor at each subsequent visit to CYPS. This limitation in service provision could be managed by each clinician having their own caseload and the YP is followed through from beginning to end, ensuring continuity of care. The study showed that if the YP's individual needs and treatment plans are matched, then YP would feel that the service was helpful, and this significantly predicted overall quality of care.

Although the opening office hours and the location of CYPS were rated as overall good, the authors wonder if a barrier to service use is actually the opening times. Appointments are all given during school hours, this means that YP would need to choose between school and the appointment at CYPS.[18] Furthermore, only referrals made by doctors are accepted to CYPS, meaning other clinical professionals working in mental health, education and care givers themselves cannot directly refer to CYPS. Published research reports that less than half of YP with a mental disorder actually access a mental health service,[1] facilitating the referral process procedure may therefore increase access rates. It was hypothesised from the complaints made by YP about the location of CYPS that there is a possibility that YP would prefer smaller community CAMHS provided in their local area rather than just having one centralised service for the whole island of Malta. However, this would involve a strategic service development plan with costs to cover a substantial increase in staff employment and training.[19]

Parking was rated poorly, and this may be another barrier to attending CYPS. Poor parking facilities may be one of the reasons for parents to choose not to attend CYPS and opt for other independent options available on the island.[18] However, from the logistic regression, no significant correlation between parking and overall quality of care was found. Despite parking being rated most poorly in the quantitative and qualitative responses, this did not significantly contribute to the overall quality of care.

From the information gathered in this study and extrapolated by the authors, it is hypothesised that a substantial number (data still not available in Malta) of YP choose to access independent CAMHS rather than the NHS CYPS. Reasons for the above could possibly be the result of the poor environment and location of CYPS together with unacceptably long waiting lists and the lack of possibility to engage with the same professional. Further contributing to the above hypothesis may be the lack of stigma, shorter waiting lists, age

appropriate environment and the ability to self-refer associated with accessing private services.[19] This hypothesis could be tested in future studies on this service.

Another theme mentioned was the absence of age appropriateness of the environment of CYPS (*n*=50, 17.5%). Moderate associations were found between the subjective experience of the YP attending CAMHS and their evaluation of the physical environment. Relatively small changes, such as adding a piece of artwork can help to improve the general perception of CYPS. The relationship between the physical environment and patient satisfaction suggests a potential for policy makers and commissioners to improve the overall service provided.[20] Whilst appreciating the difficulties in providing an appropriate environment to meet the wide age range of YP reviewed at CYPS, in the published and unpublished literature, YP have pointed out the need for a "happy looking", well-lit, comfortable[21] and age appropriate environment.[22-23] Lastly an innovative concept which may be adopted to help YP attend CYPS is the introduction of static exercise bicycles, which could be placed in the waiting rooms and could be used to charge the electronic device of the YP or their carer. This could keep YP occupied while waiting, whilst help to reduce the ever-increasing problem of obesity in YP in Malta.[24-25]

Strengths and weaknesses

This study was a one stage survey with a large sample population and with a high response rate, which was not limited by a selection or observation bias and data analysed by using mixed method of analyses. However, no demographic data (except for age) was collected, the hypothesis that asking for limited personal identifiable information would increase the acceptability by the YP to participate and reduce the chance of a response bias by a Hawthorne effect. This study was limited by a response bias given that YP who do not attend CYPS were not included in this service evaluation. The authors (AS, NC) were blinded to the responders and recommend that as the next step from this service evaluation, interviews with the YP would be carried out, through independent research assistants, thus increasing the depth and quality of information gathered.

Acknowledgements

Mr Victor Bonanno, Ms Claire Marie Cachia Attard, Ms Anthea Ciantar, Ms Alexandra Falzon, Ms Gertrude Frendo Cumbo, Dr Kristina Vella

References

1. Brown A, Ford T, Deighton J, Wolpert M. Satisfaction in child and adolescent mental health services: Translating users' feedback into measurement. . 2014;41(4):434-46.
2. Garratt AM, Bjertnaes OA, Holmboe O, Hanssen-Bauer K. Parent experiences questionnaire for outpatient child and adolescent mental health services (PEQ-CAMHS Outpatients): reliability and validity following a national survey. 2011;5(1):18.
3. Kazdin AE, Mazurick JL. Dropping out of child psychotherapy: Distinguishing early and late dropouts over the course of treatment.1994;62(5):1069.
4. McNaughton D. Measuring parent satisfaction with early childhood intervention programs.1994;14(1):26-48.
5. Shapiro JP, Welker CJ, Jacobson BJ. The youth client satisfaction questionnaire: Development, construct validation, and factor structure.1997;26(1):87-98.
6. Stallard P. Parental satisfaction with intervention: Differences between respondents and non-respondents to a postal questionnaire.1995;34(3):397-405.
7. Gerkensmeyer JE, Austin JK. Development and testing of a scale measuring parent satisfaction with staff interactions. . 2005;32(1):61-73.
8. Ayton AK, Mooney MP, Sillifant K, Powls J, Rasool H. The development of the child and adolescent versions of the Verona Service Satisfaction Scale (CAMHSSS). . 2007;42(11):892-901.
9. Pellegrin KL, Stuart GW, Maree B, Frueh BC, Ballenger JC. A brief scale for assessing patients' satisfaction with care in outpatient psychiatric services. . 2001;52(6):816-9.
10. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. . 2004;10(2):307-12.
11. Eurostat. Statistical themes - Statistics Explained. 2016;2016.
12. Organization WH. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. World Health Organization; 1993.
13. Hilbe JM. Logistic regression. In: International Encyclopedia of Statistical Science. Springer; 2011. p. 755-8.
14. Stark D, Thomas S, Dawson D, Talbot E, Bennett E, Starza-Smith A. Paediatric neuropsychological assessment: an analysis of parents' perspectives. . 2014;5(1):41-50.
15. Saliba A, Agius D, Sciberras E, Camilleri N. A population service evaluation of the Attention Deficit Hyperactivity Disorder (ADHD) pathway of Children and Young People's Services, Malta. 2018.
16. Hookway G, Lead SQI. HIGHLAND NHS BOARD.

17. Pettitt B. Effective joint working between child and adolescent mental health services (CAMHS) and schools. Citeseer; 2003.
18. Koerting J, Smith E, Knowles M, Latter S, Elsey H, McCann D, et al. Barriers to, and facilitators of, parenting programmes for childhood behaviour problems: a qualitative synthesis of studies of parents' and professionals' perceptions. Eur Child Adolesc Psychiatry. 2013;22(11):653-70.
19. Bell CC. Commentary on the Child-Adolescent Mental Health Services (CAMHS) Conference—Nashville, TN, September 2009. 2010;37(1-2):135-9.
20. Rogers S, Edwards SJ, Hudman P, Perera R. The importance of the physical environment for child and adolescent mental health services. 2016;11(1):33.
21. Mitchell-Lowe M, Eggleston M. Children as consumer participants of child and adolescent mental health services.2009;17(4):287-90.
22. programme,NHS England/Medical Directorate/Parity of Esteem. Model Specification for Child and Adolescent Mental Health Services: Targeted and Specialist levels (Tiers 2/3). 2014.
23. Camilleri N, McArdle P, Newbury-Birch D, Stocken D, LeCouteur A. A case control and follow-up study of "hard to reach" young people who also suffered from multiple complex mental disorders. 2017;41:S82.
24. Grech V, Aquilina S, Camilleri E, Spiteri K, Busuttil ML, Sant'Angelo VF, et al. The Malta Childhood National Body Mass Index Study: A Population Study. J Pediatr Gastroenterol Nutr. 2017 Sep;65(3):327-31.
25. Pandian R. Human power conversion system based on video game play with exercise bicycle. 2005.