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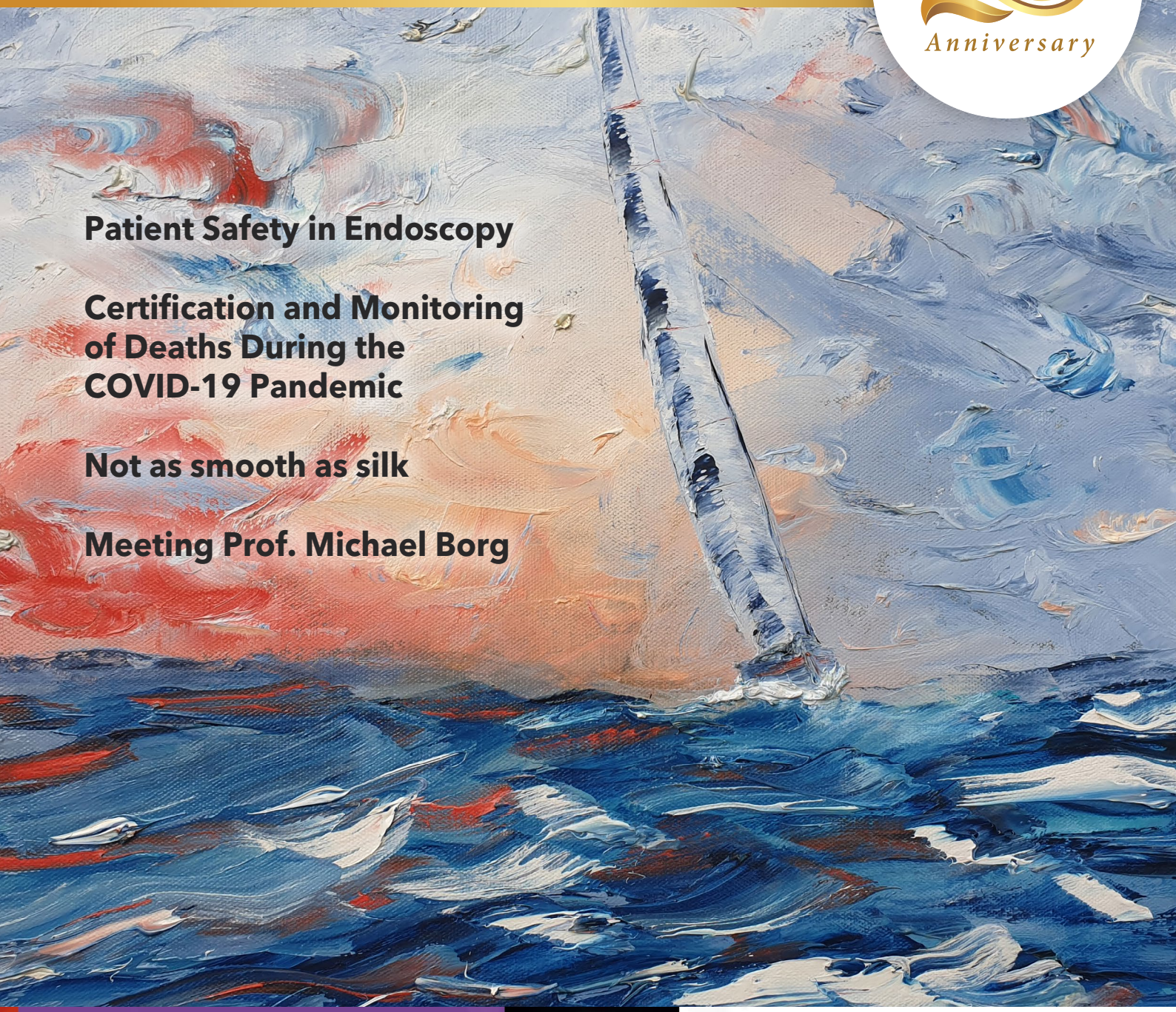
thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

The Synapse Magazine is celebrating its 20th *Anniversary*



Patient Safety in Endoscopy

Certification and Monitoring of Deaths During the COVID-19 Pandemic

Not as smooth as silk

Meeting Prof. Michael Borg

Authors

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Issue Guide

TheSynapse

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MPSA

MADS Malta Association of Dental Students

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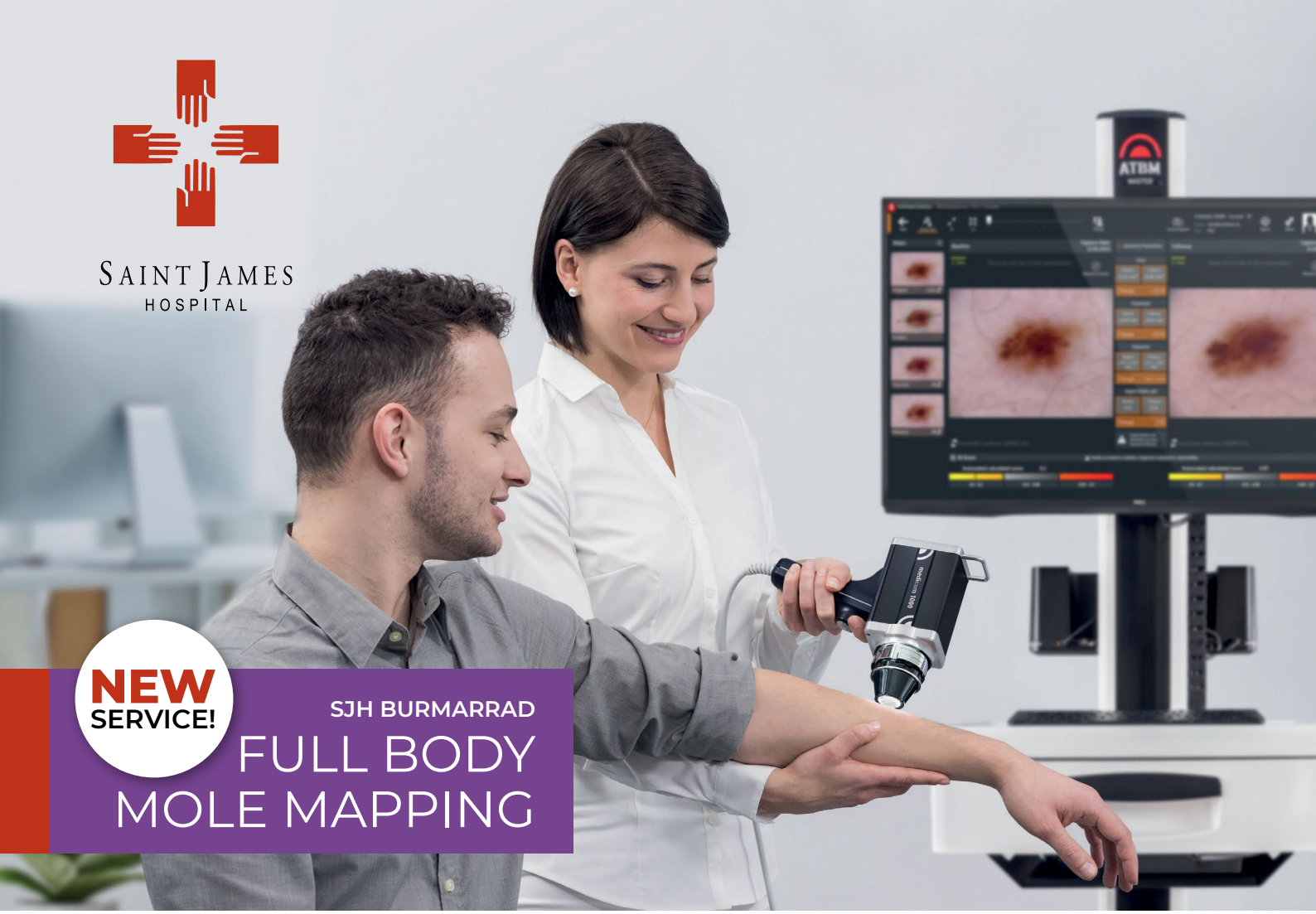

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Targeted Therapy in Cancer

The purpose of the session is to discuss the molecular pathology of tumourogenesis and define the targeted treatment of tumours.

Prof. Christian Scerri
Consultant Geneticist at Mater Dei Hospital

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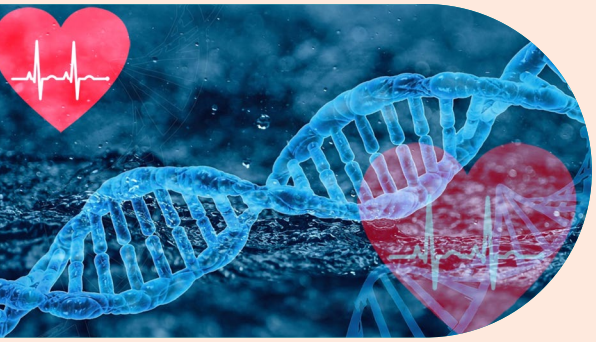

Inherited Cardiomyopathies

The purpose of this session is to know when to refer to tertiary care, review the diagnosis and patterns of inheritance, and also, how to manage these conditions.

Dr Tiziana Felice
Consultant Cardiologist and
Clinical Lead of the Inherited Cardiomyopathy
Clinic at Mater Dei Hospital.

Management of the Most Common Orthopedic Conditions Affecting the Upper Limb

The purpose of this session is to discuss the diagnosis and management of the most commonly encountered hand, elbow and shoulder conditions met in medical practice.

Mr Alastair Pace
Consultant Orthopedic Surgeon

Supported by the MENARINI group

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DR ALISON ANASTASI, HEAD OF OPERATIONS (PROCUREMENT), CPSU
ING KARL FARRUGIA, MANAGING DIRECTOR (SOURCING AND SUPPLIES), CPSU

Public Procurement as Linchpin

The Central Procurement Supplies Unit (CPSU) within the Ministry for Health encompasses sourcing of medicines, medical devices, materials, services, and works, amongst other varied processes. For procurement processes to be managed successfully, planning and forecasting are the mainstay. Most of the users request a specific product with a general lack of accurate data. This leads to delays in the process and further repercussions once the procurement cycle is issued. Thereby, the importance of epidemiological data has been highlighted for health conditions and ensuing treatments. The cycle is initiated by decisions and actions of the user/requisitioner. This would determine the functional and technical specifications, specific product quantity needs, estimated costs, and the transfer of approval of funding. All these practices are the backbone of an efficient procurement system.

Medicines, nutritional products, medical devices and Personal Protective Equipments (PPEs) entail specific conditions due to the specialized processes required in line with the different EU directives and regulations adopted by the Competent Authorities. For these last years, CPSU has been facing further hurdles and challenges due to the COVID-19 pandemic and the longstanding Brexit issue directly hitting the department and the access of medicines.

The department has been zealously attempting to reduce the dependency on the UK market for the last three years. This exercise has been taking up a lot of time, attention, dedication and resources. This has proved to be an arduous task, due to language barriers and the fact that most of the products sourced from the UK are not marketed in other EU member states. Economical operators were requested to start registering using the Mutual Recognition Procedure, however, there were Marketing Authorisation Holders who objected or encountered resistance due to the small size of the Maltese market.

In 2019, together with the Medicines Authority, CPSU worked on an exercise to liaise with all available Qualified Persons for Pharmacovigilance (QPPV) of economic operators, both local and foreign, to start bidding in the local procurement cycles. Economic operators are evaluated on product standards and quality, service reliability and financial viability when approved as potential suppliers before and after tendering, to avoid counterfeit and substandard medicines on the market.

CPSU managed to raise the interest of 88 different companies from different countries within the EU to quote in emergency procedures. Unfortunately, the same companies rarely make use of the normal processes, that lead to long-term deals, such as tenders. Unlike for the long-term procurement cycles, in emergency procurement CPSU registers the medicinal product or requests an exemption of registrations from the licensing authority. The local and the UK companies used to participate more eagerly in long-term processes but since there were regulatory changes due to Brexit they are simply refraining from bidding.

CPSU actively considered and tried to draw up agreements with Italy as an alternative source, but once again it was faced with language barriers as all the supplies are in Italian thus requiring translation, re-labelling and serialization – another difficult, costly and complex feat that is still not completely exhausted.

CPSU continuously organizes training and familiarization sessions to different manufacturers and suppliers to increase interest and facilitate the process. Initially, the international suppliers would be enthusiastic and eager to start business, including registering on the electronic procurement portal system (EPPS) but in the end they fail to quote.

Purchasing from a well-designed formulary involves the selection of safe and cost-effective medicines that have the greatest benefit for the patient and the lowest financial cost. To try and move away from accessing products from the UK, CPSU regularly tries to reach out to the policy unit to alter technical specifications as different formulations, active ingredients, doses, and medicines exist in other EU countries' formularies. However, it is faced with another barrier being that the clinicians are mostly trained within the UK system, so there has been rarely such a change.

Until the beginning of 2020, CPSU managed to reduce the UK market dependency from 85% to 65% but challenges such as Brexit, local companies not being able to register their products and COVID-19 did not help. The companies are finding resistance from the international industry to register through the Decentralized Procedure/Mutual Recognition Procedure. In 2019, the department started holding a stockpile of six months of the 766 UK originating products and this assisted treatment access during the pandemic. Since 2020, all the 2880 medicinal products are being kept up to a safety level of six months. However, the availability of the stockpiles is being continuously severed. This mainly stems from the fact that the supply in the warehouse is being impeded from reaching the patients due to recent regulatory changes. As discussed this is primarily pinned to the licences of UK products, now invalid, having to wait for the exemption approvals from the local licensing authority.

Malta has made extensive presentations on these cases in constant liaison with the relevant stakeholders, with the Permanent Representation of Malta and the EU Commission, for further consideration and support on the matter. The country has made various efforts to try and divert sourcing to other markets within the EU, which proved to be a real unsurmountable challenge.

In conclusion, the Ministry for Health is in a tight spot as CPSU is encountering situations where healthcare professionals and patients are unable to access treatment in a timely manner, even though such treatment might be available locally, within the CPSU warehouse.

ENTRESTO®(sacubitril/valsartan)

Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex).

Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy.

Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing medicinal product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended. Use of sacubitril/valsartan may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Hyperkalaemia: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation . If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartan immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate. Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered.

Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2). Should not be coadministered with another ARB. Use with caution when co-administering sacubitril/valsartan with statins or PDE5 inhibitors. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartan is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of sacubitril/valsartan and furosemide reduced C_{max} and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

Fertility, pregnancy and lactation: The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether sacubitril/valsartan is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of sacubitril/valsartan to the mother.

Undesirable effects: *Very common (≥1/10):* Hyperkalaemia, hypotension, renal impairment. *Common (≥1/100 to <1/10):* Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. *Uncommon (≥1/1,000 to <1/100):* Hypersensitivity, postural dizziness, pruritis, rash, angioedema.

Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets.

Legal classification: POM.

Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872.

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Entresto® sacubitril/valsartan

ENT AD1 06/21 MT

Dr Ian Ellul chats with **Prof. Michael Borg** on the nuts and bolts of antibiotic stewardship with all its subtle and not so subtle percolations.

Interpreting Dust Patterns

Antibiotic Matters

Deciphering the science through the noise reminds me of the strife of Murphy Cooper to interpret the dust patterns in the science fiction movie *Interstellar,* directed in 2014 by Christopher Nolan. Contrary to the movie, science has no paranormal activity, yet, similar to the movie plot, passion, resilience as well as serendipity play an important part in attaining achievements.

WHEN DID YOU REALISE THAT YOU WANTED TO BECOME A DOCTOR?

When I started University in 1981, there weren't many choices for someone who was inclined for sciences. It was either teaching, pharmacy or medicine. I chose medicine. Truth be told, I was always inclined towards medicine. I remember at St. Aloysius' College when we did a questionnaire on career options, as part of the subjects' choice at the end of Form 2, my resulting preference was a tie between medicine and laboratory science. All these years later, I find myself precisely in those two paths.

WHY SPECIALIZE IN MICROBIOLOGY?

Microbiology was my preferred subject ever since I started listening to Prof. Paul Cuschieri in the lecture rooms during my 3rd undergraduate year. Thus, after graduating, when a call was issued for a senior registrar post in microbiology, I immediately applied for it. So in 1989 I travelled to London together with Dr Chris Barbara, who was also chosen from the same call. First we went to the London School of Hygiene and Tropical Medicine and then to University College Hospital. It was a period to remember for various reasons. It was the first time I lived abroad for such a long period. Also, it was an enriching experience since I had access to facilities which were unheard of locally at the time, including huge libraries and computers. I also interacted with colleagues undergoing training who came from over fifteen different countries, ranging from Chad to Australia.

I ALWAYS ADMIRE YOUR SELF-CONFIDENCE. ALSO, THE MANNER IN WHICH YOU SPEAK SEEMS TO BETRAY A MORE CONVIVIAL DISPOSITION. DESCRIBE YOURSELF IN ONE SENTENCE.

A plainspoken person, hopefully with a bit of self-depreciation and sense of humour.

ONE OF YOUR FIRST ARTICLES ON ANTIMICROBIAL RESISTANCE WAS *OVER-THE-COUNTER ACQUISITION OF ANTIBIOTICS IN THE MALTESE GENERAL POPULATION* PUBLISHED 20 YEARS AGO. WHERE DO WE STAND NOW?

This was one of my first research projects. I remember we participated in the Health Promotion stand at the Malta Trade Fair, choosing attendees randomly and asking them to compile a questionnaire on their antibiotic consumption. At the time there was little or no awareness about antibiotic resistance amongst the public and also, healthcare professionals. Even during my medical undergraduate course and microbiology specialisation abroad, this area was just given a fleeting mention. Today we are facing superbugs on a regular basis in tertiary care … MRSA, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE), extended spectrum β-lactamases (ESBL), etc. The establishment of the ECDC proved to be a watershed moment since it was the first

time a pan-European entity relating to antimicrobial resistance (AMR) and appropriate use of antibiotics was established. Returning to your question, the use of OTC antibiotics has decreased drastically in Malta due to the awareness which has percolated through all societal strata, especially pharmacists.

IN 2015 I CONDUCTED A PROSPECTIVE PHARMACO-EPIDEMIOLOGICAL REVIEW OF MEDICINES PRESCRIBED TO APPROX. 1000 CHILDREN BY COMMUNITY PAEDIATRICIANS AND GENERAL PRACTITIONERS IN MALTA. I FOUND THAT 23% OF PRESCRIPTIONS RELATED TO ANTI-INFECTIVES FOR SYSTEMIC USE. HOW DO WE COMPARE WITH OTHER COUNTRIES? ACCORDING TO A REPORT DRAWN IN 2019 BY THE OECD IN COLLABORATION WITH THE ECDC, IF AMR FOLLOW THE PROJECTED TRENDS, BY 2050, MALTA WILL POSSIBLY HAVE THE SECOND HIGHEST YEARLY EXPENDITURE IN EUROPE, I.E. €4.7 PER CAPITA. ITALY TOPS THE CHART AT APPROXIMATELY €4.8 PER CAPITA.

AMR may be compared to climate change; it has a multifactorial nature. Nonetheless the one factor which stands out is antibiotic use. If we look at statistics, when compared to the EU average, Malta is not an outlier in terms of total volume of antibiotics prescribed. However, 42% of local residents are prescribed at least one antibiotic a year; this is the second highest in the EU and more than twice that reported by Sweden and The Netherlands. We have two additional challenges. The first relates to the use of antibiotics where there is clinical uncertainty if the infection is bacterial or viral in origin. Use of antibiotics to treat sore throats in Malta is massively higher than Scandinavia. We also see this uncertainty in tertiary care in surgical prophylaxis. Although this practice is essential, there is no need to give such cover for several days, when one or two doses are equally effective. The second challenge relates to the type of antibiotics which are prescribed. We tend to steer towards broad spectrum antibiotics which are often unnecessary, especially in the community, and which disrupt our microbiome leading to resistance.

IN 2016 IN ONE OF MY EDITORIALS I DISCUSSED TEIXOBACTIN AS A POSSIBLE GAME-CHANGER FOR AMR. WHAT ARE YOUR VIEWS ON THIS DRUG AND SIMILAR ONES WHICH MAY BE IN THE PIPELINE.

Each conference which I have attended along the years invariably contained posters or oral presentations heralding a drug claimed to be a game changer in the fight against AMR; we are yet to see it. I remember one seminar which I attended at Cambridge University in the mid-nineties where carbapenems were trumpeted as the solution to the treatment of hospital infections. Fast forward by twenty years and we are seeing alarming levels of carbapenem-resistant and pan-resistant *Klebsiella pneumoniae* throughout the world. Obviously, such resistance is delayed by the judicious and focused use of antimicrobials.

We also have the conundrum of antibiotic development. Developing a novel antimicrobial has been estimated to cost up to 1.5 billion dollars. And after that, what happens? People like me telling clinicians to use it sparingly to avoid resistance! You can understand why pharma would look towards investing research and development in other areas e.g rheumatology which would translate in on-demand use of the drug at higher volumes to make the investment worthwhile.

Interestingly we are seeing a resurgence of old antibiotics. Tetracyclines, discovered in the 1940s, had fallen out of popularity by the end of the last century. Precisely because of this, they have been less affected by development of resistance and are now our flagship treatment against MRSA. They have got a very good activity spectrum against Maltese strains, meaning we can avoid using last resort agents such as vancomycin and teicoplanin in mild and moderate infections.

DOES MALTA HAVE ACCESS TO NOVEL ANTIBIOTICS?

We have some pockets of resistance in the community setting, especially for quinolones (most notably ciprofloxacin) as well as for macrolides and cephalosporins. But there are still good alternatives, even for the most serious infections such as those relating to *Streptococcus pneumoniae*. It is in tertiary care where access to novel antibiotics can be vital in specific cases. Thankfully our colleagues at the Central Procurement and Supplies Unit (CPSU) are great in crisis management and, more often than not, can source locally unavailable novel antibiotics in a timely manner on a named patient basis, if the need arises.

LAST DECEMBER YOU PUBLISHED AN ARTICLE ON THE PREVALENCE OF MRSA IN EUROPE, TOGETHER WITH PROF. LIBERATO CAMILLERI, AN OUTSTANDING STATISTICIAN WHOM I HAD THE PLEASURE TO COLLABORATE WITH. WHERE DOES MALTA STAND?

MRSA control is one of our greatest success stories. During the past 20 years, cases have dropped significantly. In 2002, MRSA constituted more than 60% of *Staphylococcus aureus* infections at Mater Dei; this is now less than 25%. There are various reasons for this but the main one is the screening programme which has been implemented since 2014 on all patients admitted to Mater Dei hospital. This means that any asymptomatic carriers are identified and decolonised immediately on admission. Otherwise, they would be a source of infection for other hospital patients. By severing this cycle, we have also improved antibiotic sensitivities of *Staphylococcus aureus* infections in ambulatory care, offsetting the increase in MRSA resistance within the community that we had experienced before the screening initiative.

DOES MALTA CARRY OUT GENOMIC SURVEILLANCE FOR HYPERVIRULENCE AND/OR MULTI-DRUG RESISTANCE?

Unfortunately, we do not have a local infrastructure to do this as routinely as we would like. Indeed, ECDC has recommended that we do regular molecular genetics for resistant strains. This is of particular value in outbreaks in order to identify transmission patterns. Although the antibiogram of different isolates of the same bacterial species may be identical, they could be different clones with no epidemiological linkage. You can only determine this through genomic typing.

We do try to send isolates to laboratories abroad to carry out genomic surveillance as often as we can. This has shown, for example, that we have two main local strains of MRSA. These are the eMRSA-16, the classical UK strain, and a Malta clone which we first reported in 2010. This Maltese clone is a *Staphylococcus aureus* which is resistant only to methicillin and fusidic acid. It almost certainly originated from the abuse of fusidic acid topical creams and ointments which was locally widespread a decade or so ago.

ANTIBIOTIC STEWARDSHIP. YOUNG CLINICIANS ON ONE SIDE OF THE PITCH AND SEASONED CLINICIANS ON THE OTHER SIDE. WHO HAS THE BEST SCOREBOARD?

One cannot generalise but my anecdotal experience suggests that the younger cohort tend to have the best ethos relating to antibiotic stewardship. This probably stems from the fact, that contrary to my undergraduate years, today there is a much stronger focus on AMR in local medical curricula. Such focus is also mirrored in post-graduate specialisation training, including those relating to family medicine.

A STANFORD UNIVERSITY STUDY PUBLISHED IN 2020 ANALYSED DATA ARISING FROM SCIENTIFIC DISCIPLINES BETWEEN 1965 TO 2019 AND COVERING APPROXIMATELY 7 MILLION SCIENTISTS. THE RESEARCH ANALYSED THE NUMBER OF CITATIONS INCLUDING H -INDEX, AMONGST OTHER THINGS. THE RESEARCHERS HAVE ANALYSED THE CITATION IMPACT DURING THE SINGLE CALENDAR YEAR 2019 AND HAVE PLACED YOU AT NUMBER 92,783, MEANING THAT YOU FALL IN THE TOP 1.4% SCIENTISTS. HOW DID YOU HEAR OF THIS AND WHAT WERE YOUR INITIAL FEELINGS?

The news was communicated to me by the University of Malta's Think magazine, which ran a feature on it. Needless to say, I was very pleased considering our limitations. Malta equates to a small European city in terms of research facilities and funding; so to rank on par with scientists from world-renowned centres of excellence was obviously extremely satisfying.

IN KEEPING WITH THE ABOVE, ACCORDING TO RESEARCHGATE YOU HAVE CLOCKED OVER 8,000 CITATIONS FOR YOUR 126 ARTICLES WHICH YOU PUBLISHED OVER A PERIOD OF 25 YEARS. I KNOW OTHER DOCTORS MAY HAVE PUBLISHED MUCH MORE THAN THAT, POSSIBLY OVER A SHORTER PERIOD, BUT WITH LESS CITATIONS. DO THESE 8,000 CITATIONS STEM FROM THE FACT THAT YOUR AREA HAS CLINICAL BUT ALSO ECONOMIC AND POLITICAL PERCOLATIONS?

You are right. In recent years, AMR has been discussed at the G7, G12, European Parliament and even the United Nations General Assembly. This effectively shows the significant impact that AMR has in areas other than medicine. Nonetheless, I believe that my citation track record may be pinned down to the fact that I always sought to avoid parochial publications and try to bridge knowledge gaps in my areas of interest.

In 2003, my department was the first Maltese team to coordinate a multinational EU funded medical research project. ARMed involved 13 Euro-Mediterranean countries over 4 years and proved to be a pioneer in surveillance of antibiotic resistance and consumption in the south-eastern Mediterranean. It yielded 15 papers which are still being regularly cited today.

Over the past decade, my research has focused on a previously unchartered aspect of antibiotic use and AMR … behavioural science and cultural anthropology. My publications have shown that you can explain a large degree of the heterogeneity of AMR (e.g. MRSA) within Europe simply from the country's national culture. In particular, the cultural dimension of uncertainty avoidance explains most of the misuse of antibiotics in the Mediterranean, including prescribing antibiotics for predominantly viral conditions (such as colds, flu and sore throat) and the preference for broad spectrum formulations. This research appears to have been ground-breaking – at least judging from the invitations I have received to speak about it in international conferences.

IN NOVEMBER 2020, THE NEW COMMISSION IMPLEMENTING DECISION (EU) 2020/1729 ON THE MONITORING AND REPORTING OF ANTIMICROBIAL RESISTANCE IN ZOONOTIC AND COMMENSAL BACTERIA WAS PUBLISHED. HOW WILL THIS AFFECT MALTA?

The European Commission's AMR Strategy focuses on a One Health European Joint Programme which also includes veterinary medicine relating to companion-animals as well as husbandry. Thus, when we speak about AMR we even need to factor in antibiotic resistance in plants, residues in sewage, etc which are all important drivers. Although we may not have the intensive farming of bigger countries like The Netherlands, zoonotic infections are also relevant for Malta. To give an example … if there is antibiotic resistance in poultry pathogens, any lack of hygiene during the

cooking process could lead to the transfer of the resistance genes to bacteria in our intestines. Nonetheless our focus should mainly be on human medicine since it is antibiotic use in human, rather than veterinary medicine, that is likely driving resistance in our country.

YOU HAVE OBVIOUSLY BEEN AN ACTOR ON THE COVID-19 STAGE. DO YOU THINK THAT POLITICS AND PUBLIC HEALTH TALLY WITH EACH OTHER?

Politics and public health can be strange bed fellows. We have seen how the US politicized the use of face masks. Or the stand of the UK to achieve herd immunity, at the expense of widespread testing, during the initial stages of the pandemic. Obviously, these may stem from the fact that lockdowns have such major repercussions, including on the economy. It is clear however that the countries that tackled COVID-19 most effectively were those which achieved harmony between these two vital areas.

MIXED MESSAGES HAVE BEEN AN ACHILLES HEEL OF PUBLIC HEALTH DURING THIS PANDEMIC. RECOMMENDATIONS PROPOSED BY INTERNATIONAL PUBLIC HEALTH INSTITUTIONS, AND THEN RELAYED TO US, HAVE BEEN RIDDLED WITH INCONGRUENCIES. I GIVE SOME EXAMPLES ... NO FACE MASKS ARE NEEDED FOR USE BY THE GENERAL PUBLIC ... VISORS ARE AS EFFECTIVE AS MASKS ... CLOTH MASKS ARE FIT FOR PURPOSE [WITHOUT SPECIFYING THAT THEY SHOULD BE THREE-LAYERED] ... WHAT IS YOUR OPINION ON THIS EVOLUTION?

Evidence-based medicine has often been the casualty of this pandemic. Tackling a pandemic, especially in the initial stages, was challenging since there were too many unknowns. I agree with you that there may have been mixed messages. Even today, we still have wide variations between countries relating to wearing of masks in outdoor spaces. The initial reluctance to advocate widespread use of masks by the public stemmed from the Chinese lockdown which severed the supply of PPEs to the rest of the world. There were even anecdotes of aeroplanes full of PPEs being "hijacked" by another country which offered more money, even as the plane was on the airport tarmac awaiting clearance to fly to the original buyer. In this background, WHO could not deliver a message saying that the public should use masks widely since the limited stock had to be prioritised for where it definitely made a difference i.e. for healthcare professionals providing patient care. Amidst this backdrop with rising cases and deaths, I guess it was easy to make knee jerk reactions in lieu of evidence-based decisions.

HOW WILL MALTA EXPERIENCE COVID-22?

Coronaviruses exhibit one of the greatest mutation rates among viruses. Yet we know that, to date, all vaccines available in Malta are extremely effective at reducing the morbidity and mortality caused by all currently identified variants. To a slightly lesser extent, vaccines are also effective at reducing the transmissibility. I suspect that SARS-CoV-2 will remain as part of our microbial background for years to come, similar to what happened with the swine flu. We have had a sterling vaccination campaign banking on our strengths i.e. small country, close team of decision makers, and the resilience shown time and time again by our nation in the face of a crises. We may well need booster doses on a yearly basis. This, together with more effective antivirals, should hopefully ensure that COVID-19 remains under control and allow us to return to some degree of normality.

HOW DO YOU ENVISAGE YOURSELF IN TEN YEARS' TIME ON THE DOORSILL OF RETIREMENT?

I would love to continue teaching since contact with students is so fulfilling. However, I wish to spend a large part of my time travelling the world. I am an avid traveller, even relishing the hours which I spend in mid-air. My academic work has taken me to more than 50 countries in 4 continents but my bucket list is nowhere complete. I especially wish to go to China and Australia as well as do more safaris in sub-Saharan Africa.

WHAT DO YOU THINK OF CME.30, OUR ONLINE CONTINUING MEDICAL EDUCATION PORTAL?

CME30.eu is the future. Since 2020 we have used CME30.eu as an effective portal to convey our messages, ranging from the European Antibiotic Awareness Day to COVID-19 training. We managed to reach out to significantly more doctors and pharmacists than previous years when we used to hold seminars at Mater Dei Hospital. Organising these seminars used to entail massive headaches related to sourcing funding, organising the logistics, etc… and then attendance was often underwhelming. On the other hand, our CME30.eu sessions managed to attract hundreds of healthcare professionals, who are not our usual crowd. I guess it is easier for someone to arrive home after a clinic and simply log in to your portal, rather than to have to drive to Mater Dei, or to a hotel, and then return so late back home. Our message can be delivered more efficiently online, with reduced costs and less administrative hassle. This is probably one of the most useful legacies of COVID-19.

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DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. ♦*Missed doses:* If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. ♦*Treatment transition from monoclonal antibody PCSK9 inhibitors:* Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. ♦*Elderly, hepatic impairment, renal impairment:* no dose adjustment is necessary. Inclisiran should be used with caution in patients with hepatic and renal impairment.♦*Paediatric population:* The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. ♦*Method of administration*: Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: ♦*Haemodialysis*: The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. ♦*Sodium content:* This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

PREGNANCY, LACTATION AND FERTILITY: ♦There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. ♦It is unknown whether inclisiran is excreted in human milk. A risk to newborns/ infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. ♦ No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: *Common*: Adverse reactions at the injection site.

LEGAL CATEGORY: POM

PACK SIZE: One pre-filled syringe.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

2021-MT-LEQ-9-DEC-2020

References: 1. Novartis Europharm Ltd. Leqvio Summary of Product Characteristics.

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A Holistic View on Patient Safety in Endoscopy

Patient safety in endoscopy must be approached from a holistic perspective, through solutions which increase detection rates of abnormalities, increase confidence in the safety of the reprocessing outcome, and control the risk of infection and cross-contamination.

With these important benefits in mind, PENTAX Medical is continuously working to innovate products to establish solutions that directly tackle patient safety in endoscopy – like the DISCOVERY™ , the PlasmaTYPHOON and PlasmaBAG system, and the DEC™ Video Duodenoscope ED34-i10T2 with disposable elements.

INCREASED DETECTION RATES OF LESIONS WITH ARTIFICIAL INTELLIGENCE

In the fight against colorectal cancer, great strides have been taken to protect patients from undetected abnormalities. However, up to 26% of lesions are still missed in examinations.[1] Endoscopists' tiredness or distraction can play a role in complicating the detection. This can lead to fewer lesions detected, with studies showing early-morning cases yielding 27% more polyps per patient, than cases later in the day.[2] The human factor is responsible for complications leading to missed lesions, thus having negative impact on the medical outcomes of examinations, ultimately compromising patient safety.

By incorporating artificial intelligence (AI) technology in colonoscopies the procedures become more objective and operator independent. No matter how subtle or unremarkable the lesion, the DISCOVERY™ is always a focused observer.

The database of the DISCOVERY™ is what truly sets it apart from any other solution in the market. During a procedure, the DISCOVERY™ highlights suspicious areas according to insights learned from the database. This database contains thousands of dedicated images of each kind of polyp, annotated by five renowned CRC centers worldwide. By learning from this database, the DISCOVERY™ is able to raise the attention to lesions otherwise difficult to detect.

With patient safety as the greatest priority, this solution could have a positive impact on the 26% of lesions still missed in examinations.[1] Peter Siersema, Professor of Endoscopic Gastrointestinal Oncology at the Radboud University Medical Center Nijmegen explains, "Computer-aided detection has been shown to increase the detection of pre-cancerous colorectal lesions. The introduction of the DISCOVERY™ artificial intelligence system opens the door to a new era where endoscopists

and DISCOVERY™ jointly reduce healthcare costs by decreasing the prevalence of colorectal cancer." The DISCOVERY™ not only presents the opportunity to improve the patient's lives, it can also be implemented in hospitals cost-effectively.

IMPROVED CONFIDENCE IN REPROCESSING OUTCOMES THROUGH OPTIMIZED DRYING

As patient safety requires a holistic approach, other concerns such as improper reprocessing must be addressed. Meticulous cleaning and high-level disinfection is needed to guarantee a clean and safe use on subsequent patients. When flexible endoscopes are not dried properly after reprocessing, microorganisms can proliferate due to residual moisture and represent a source of infection for subsequent examined patients.[3,4]

As effective drying and storage procedures are crucial to prevent post-endoscopic infection, this is an important aspect of patient safety.[4] The PlasmaTYPHOON is the first solution to guarantee a dry endoscope in one to five minutes (the drying time depends on the endoscope type), and storage up to 31 days in a fully controlled environment (storage times are subject to local regulations).[5] After the completion of the drying process, the single use PlasmaBAG comes into play: Plasma, containing ozone molecules, is insufflated into the bag ensuring the dry and disinfected state of the endoscope is maintained due to biocidal effect of the ozone.

MINIMIZED RISK OF CONTAMINATION WITH DISPOSABLE ELEMENTS

Innovative solutions for proper cleaning of endoscope channels are critical to minimizing the risk of contamination, and safeguarding patient safety. Concerns of cross-contamination arose after increasing incidences of Carbapenem-resistant Enterobacteriaceae (CRE) and other infections. These infections may be linked to improper cleaning and/or disinfection of the duodenoscope's elevator mechanism. Prof. Marco Bruno, Director of Endoscopy in the Department of Gastroenterology and Hepatology at the Erasmus Medical Center in Rotterdam explains, "a solution to the risk of infection, is to modify current endoscopes so that they have disposable parts. Especially the parts that are most susceptible to contamination. Another solution would be to have fully disposable endoscopes. This of course introduces questions about pricing and the environmental impact, which need to be solved by manufacturers and medical facilities before this solution can be used in daily practice."

PENTAX Medical has developed an innovative product which aims to address one of the main areas of concern in terms of potential infection … the elevator. The DEC™ Video Duodenoscope ED34-i10T2 seeks to respond to the need for enhanced patient safety in endoscopy; it is a unique and innovative advancement in cleaning capabilities for infection prevention and control, with the single-patient use, sterile, disposable elevator cap (DEC™). The DEC™ allows simplified reprocessing and increased cleaning capability, thus helping to reduce the risk for cross-contamination. With this solution there is greater reprocessing efficiency, 35% reduction in distal end reprocessing steps due to better access for cleaning and disinfection, as well as disposability of the elevator (In comparison to the standard duodenoscopes of the major manufacturers. Source: PENTAX Medical internal benchmarking). In line with Prof. Marco Bruno's recommendation to introduce disposable elements, as part of their hygiene commitment, PENTAX Medical has also introduced single use valves and single use cleaning brushes, allowing for simplified reprocessing and increased cleaning capability. Additionally, PENTAX Medical will soon offer the DEC™ in a hygiene procedure pack combined with core consumables in order to further minimize the risk of infection in complex endoscope areas.

With patient safety as the greatest priority, manufactures should offer innovative solutions that protect patients and provide clear benefits to clinicians.

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What is Melanoma?

SAINT JAMES HOSPITAL

Malignant melanoma (MM) is a malignant tumour arising from melanocytes, which are mainly found in the skin. Its incidence is increasing worldwide including in Malta. In 2017 the incidence was reported as 11 per 100,000 population per year.[1]

Cutaneous MM can arise from otherwise normal appearing skin (~70% of cases) or from an existing naevus (~30%). Melanoma can grow on any part of the body, however the most frequent site in males is the back, whilst in females the lower limbs. Rarely it can also arise on the nails, mucous membranes as well as the eye and brain.

The main risk factors for developing MM are:

1. Previous history of MM
2. Multiple atypical melanocytic naevi – these moles are often numerous, highly variable in terms of size, shape, colour and often larger than ordinary naevi
3. Multiple melanocytic naevi
4. Family history of MM in a first-degree relative
5. Organ transplant recipients
6. Those with giant congenital naevi
7. Previous history of other skin cancers (basal cell carcinoma and squamous cell carcinoma).

CLINICAL FEATURES OF MELANOMA

In some patients MM can present as a changing lesion. In this scenario, MM has characteristics described by the Glasgow 7-point checklist.[2] A score of 3 or more should prompt referral to a specialist.

Major features (2 points each):

1. Change in size
2. Irregular shape
3. Irregular colour

Minor features (1 point each):

4. Diameter greater than 7mm
5. Inflammation
6. Oozing
7. Altered sensation

An alternative rule that can be used by health professionals and patients to check for the major warning signs of melanoma is the ABCD rule:[3]

A. Asymmetry – two halves of the mole look different in terms of shape or colour
B. Border – irregular, jagged or blurred borders
C. Colour – two or more different colours or shades, or a single colour that is different to other naevi
D. Dimensions – any change in size, either in diameter or degree of protrusion

Nodular MM, the most dangerous type of melanoma due to the speed at which it grows into deeper tissue, can lack the above characteristics so it is also important to always consider the EFG rule[4] and urgently excise a lesion that manifests such features:

E. Elevation, and
F. Firmness, and
G. Growth that is persistent for a month or more.

MANAGEMENT OF MELANOMA

The initial treatment for suspicious lesions should be prompt complete excision with narrow (typically 2mm) margins. Once an initial diagnosis of MM is determined on histology, further wide local excision is required, the extent of which depends on the staging.[5]

The staging of MM is mainly linked to the Breslow thickness (BT) of the tumour at presentation. This is a histological measurement determined by the pathologist and is measured in millimetres. It reflects how deep the tumour invades and is a strong predictor of prognosis. The thicker the melanoma the more likely it is to metastasise.

The following table guides the multidisciplinary team as to the extent of wide local excision. Anatomical location can mean such margins are not always achievable.

Melanoma *in situ*	5mm
Melanoma <1mm BT	10mm
Melanoma 1-2mm BT	10-20mm
Melanoma >2mm BT	20mm

Further staging may involve sentinel lymph node biopsy. This procedure involves lymphatic mapping in order to identify the first downstream node from the MM. This is generally reserved for MM over 0.8mm BT. If the sentinel node is positive, removal of the entire lymph node basin is usually offered as well as further imaging to determine the extent of metastasis. In recent years targeted molecular therapy and immunotherapy have revolutionised the treatment of metastatic MM. These treatment details are outside the scope of this article.

LONG-TERM MANAGEMENT OF MELANOMA

A vital aspect of melanoma management is patient education. Reducing their future risk through avoidance of excess ultraviolet radiation can be challenging particularly whilst living in a country like Malta. Below are key messages for your patients:

1. *Wear long sleeves, trousers, hat and sunglasses when outdoors. Ideally the clothing is tight-weaved or has an ultraviolet light protection rating.*
2. *Seek shade during peak hours of the day e.g. 11am – 3pm; consider directing patients to the UVLens App*[6]
3. *In addition to the above use sunscreen habitually. It should be at least SPF 30 with UVA cover too. Sunscreen needs to be reapplied every 2 hours as well as after swimming.*

Regular ongoing follow-up is also very important particularly during the first five years after diagnosis. This allows for the earliest possible detection of locoregional recurrence but also the diagnosis of a second primary melanoma. The literature suggests a subsequent melanoma develops in up to 20% of patients.[7] The aim is to detect MM as early as possible when the degree of invasion is at its thinnest. However, a major clinical challenge is finding an acceptable balance between identifying early-stage melanoma whilst avoiding too many biopsies/ excisions which are associated with a number of morbidities. Such decision-making is particularly difficult in patients with multiple atypical naevi.

Total body photography (TBP) facilitates the identification of new or changing lesions particularly in those with atypical naevi and has been shown to reduce the number of biopsies.[7] Taking such images in an automated fashion enables the creation of a standardised image collection for each individual patient. This is useful for future clinic visits and also as a reference for the patients themselves to facilitate and encourage regular self-skin examinations.

In a 5-year cohort study of 977 patients with a history of melanoma, 48% of second melanomas were identified by TBP.[7] Furthermore, a study of high-risk patients saw a 3.8 fold reduction in biopsies after the incorporation of TBP in their follow-up.[8] This is important to avoid the potential complications associated with such procedures including infection with consequent antibiotic use, scarring and psychological trauma as well as economic costs. The use of TBP has also been shown to reduce cancer worry and as a result improve quality of life and adherence to screening.[9]

Dermoscopy, otherwise known as epiluminescent microscopy, is now considered standard practice in the examination of pigmented lesions. It is also increasingly used to aid diagnostic accuracy for non-melanocytic lesions and inflammatory dermatoses. It relies on a high-quality magnifying lens and a powerful lighting system in the form of a dermatoscope.

Dermoscopy use by trained clinicians improves diagnostic accuracy for melanoma compared with visual inspection alone.[10] Furthermore, sequential digital dermoscopic imaging permits longitudinal dermoscopic monitoring. It is particularly useful for suspicious lesions, which do not have sufficient criteria to warrant excision biopsy. Three-month dermoscopic follow-up offers a safe alternative as it allows for close short term-monitoring of changes indicative of early stage melanoma.[11] Studies have shown improved specificity for melanoma diagnosis and a 3.3 fold reduction in unnecessary biopsies with the use of sequential digital dermoscopic imaging.[12] Furthermore most melanomas diagnosed using digital photography and dermoscopy are either *in situ* or minimally invasive (<1mm).[7]

The new FotoFinder® technology (FotoFinder Systems GmbH, Bad Birnbach, Germany), now available locally at **Saint James Burmarrad**, combines TBP and dermoscopy. It creates high resolution total body photographs in a standardised manner, thus capturing all the patients' moles for baseline referencing. This will be used as an adjunct to total body skin examination, by a dermatologist, at subsequent visits. The patient will also receive these images as a reference to aid self-skin examination. Furthermore FotoFinder® records digital dermoscopic images of concerning moles thus allowing for serial close follow-ups with the aim of identifying melanomas as early as possible.

The following patients should be considered for referral to a dermatologist for consideration of FotoFinder®:

1. Personal history of malignant melanoma
2. Patients with multiple (atypical) naevi
3. Patients with a first-degree relative who has had melanoma
4. Patients with a significant history of sun exposure (in particular occupational sun exposure)
5. Patients with fair skin types (unable to tan).

References are available online.

DR KATHLEEN ENGLAND, PROF. NEVILLE CALLEJA

Certification and Monitoring of Deaths

During the COVID-19 Pandemic

1. INTRODUCTION

The SARS CoV-2 pandemic which began late in 2019 has caused and continues to cause much morbidity and mortality worldwide. It was declared a pandemic by WHO on 11 March 2020.[1] Up to 26 May 2021 there has been 167,848,565 reported cases of COVID-19 worldwide and 3,485,787 reported deaths.[2] Malta reported its first case locally on 7 March 2020 and its first death a month later, on 8 April 2020. Though geographical disparities in incidence of COVID-19 are evident across the globe, the geographical distribution of COVID-19 deaths shows even wider disparities between some continents and also between countries.[3,4] However the situation is still evolving all the time, with unprecedented cases and deaths being currently observed in India. At an EU level (+ the United Kingdom) cumulative crude mortality rate due to COVID-19 per million population in Malta compares well with the other member states as per figure 1.

Different measures and indicators are being used to monitor the COVID-19 situation in different countries. These aim to guide policy and decision-making based on trends within the country as well as comparison with other countries. International Organisations such as WHO and the European Centre for Disease Control have issued

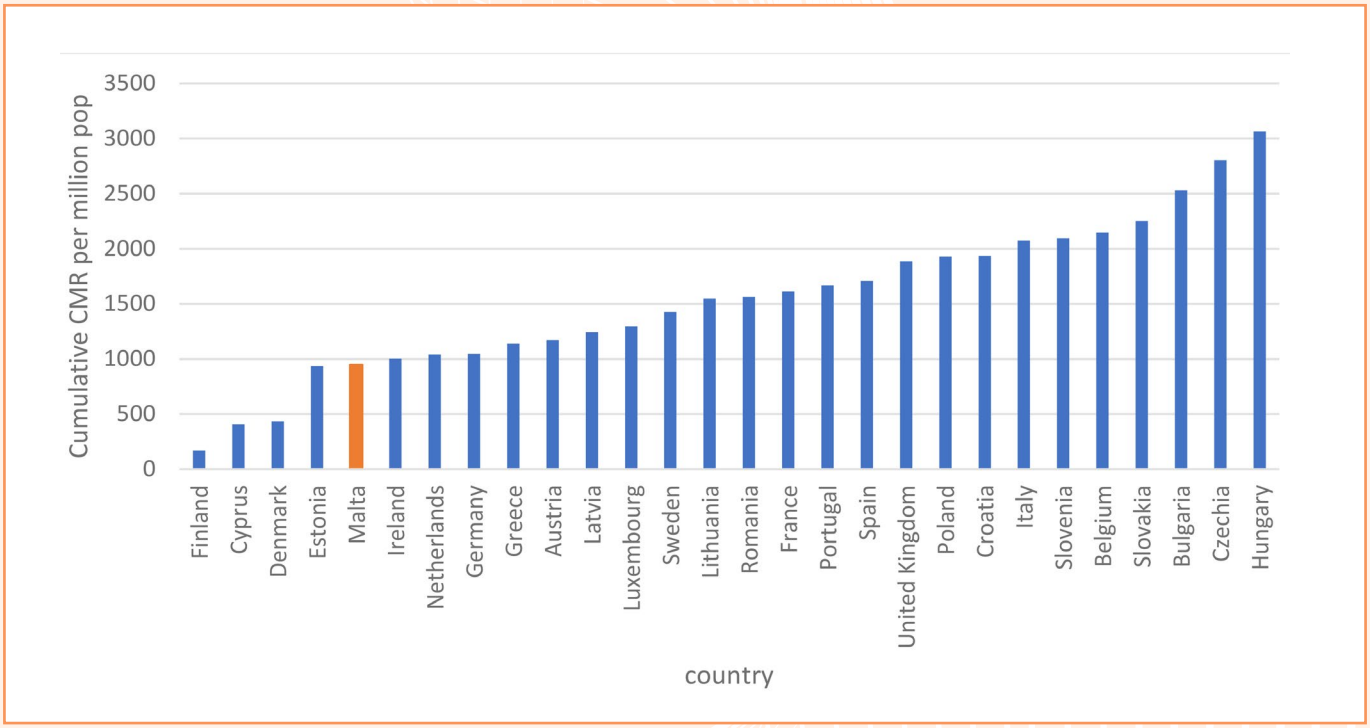

Figure 1. Cumulative crude mortality rate per million population in EU 27 + UK countries.[3]

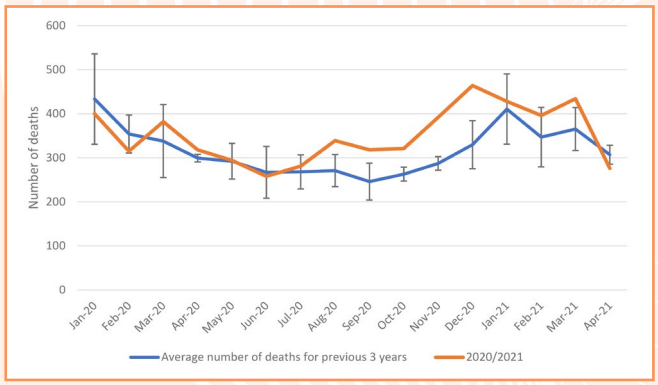

Figure 2. Trends in monthly all-cause mortality during 2020/21 compared to previous 3-year average.

guidelines and standard definitions aimed at standardising as much as possible data reported by different countries world-wide.

This paper aims to review the common mortality indicators in place with a special emphasis on the situation in the Maltese Islands.

2. OVERALL MORTALITY

If one looks at monthly trends from all deaths locally from January 2020 till April 2021 compared to the previous 3-year average (figure 2), significant increased mortality is mainly observed from August 2020 reaching a peak in November and December 2020. Mortality figures returned to expected levels of previous years in April 2021. COVID-19 mortality as seen further down in the article follows this pattern with the peak in COVID-19 deaths also observed in a similar period.

However monthly mortality data only gives an overall indication of trends in mortality and often information and data which is needed during the pandemic needs to be available in a more timely - often daily - frequency.

3. COVID-19 DEATHS

The collection of mortality data on COVID-19 deaths is one of the important epidemiological indicators used to assess the disease situation in a country as well as to monitor public health interventions and gauge how well the health care system is coping.[1]

Early in June 2020, WHO issued guidelines on how the medical cause of death section should be completed for COVID-19 related deaths. According to the WHO guidelines, COVID-19 should be reported on all death certificates where the 'disease caused or contributed to the death'. However, this should be reported specifying the causal sequence of events and with as much detail as possible. The use of official terminology i.e. COVID-19 should be used for all certification of this cause of death. The use of 'coronavirus' in place of COVID-19 is not recommended as there are many types of coronavirus.[5] The aim of these guidelines is to assist countries to report COVID-19 deaths correctly, allowing standardisation of mortality data collection as much as possible.

Despite WHO guidelines, different countries count COVID-19 deaths differently. This also depends on resources available to count COVID deaths and reliability of certification which depends not only on the compilation of the death certificate but also on testing and diagnostic resources available.

According to a briefing by the European Parliament published in July 2020, although all EU member states report COVID-19 deaths, the definition of what constitutes a 'COVID-19 death' may vary from country to country.[6] Further to this, at a death certification level, differences in reporting may relate to the time frame that a COVID-19 death may be accepted as such, distinguishing between deaths which are primarily or secondary due to COVID-19, distinguishing between confirmed and suspected COVID-19 deaths and other sources of heterogeneity which makes effective comparison even at an EU level difficult.[6] Reporting of COVID-19 deaths also depends on cases being diagnosed in the first place which may depend on the testing capacity within the country.

In keeping with the above, in another study which compared 6 EU countries,[7] apart from differences in testing capacity between the countries and also differences in the stages of the pandemic the countries were in, differences were also observed in reporting of deaths and death certification which may lead to differences in the observed number of deaths due to COVID-19 reported. In some countries it is at the discretion of the certifying doctor as to whether to order a COVID-19 test posthumous especially for deaths in care homes and in the community, and there is a cost involved which is not covered by insurance. Differences were also observed in how and where COVID-19 was put down on the death certificate, as well as the transfer of this information to the authorities involved, with some countries using electronic death certification while other countries using a number of different sources of information to determine the number of COVID-19 related deaths. Under-reporting of deaths due to COVID-19 especially in care homes and in the community has also been highlighted in some countries especially earlier on in the pandemic.[7]

Since COVID-19 often causes death among the elderly with several co-morbid conditions it may be challenging to decide on the causal chain of events leading to the death of a patient as there may be a number of competing causes of death.

When comparing COVID-19 deaths between countries, it is very important to compare like with like. Apart from the issues highlighted, choosing the best mortality indicator to allow comparability is also very important but this depends also on data availability. Whilst the number of deaths may be a useful measure for one country, this has very limited scope for comparing different countries. Other measures which are used include the crude mortality rate which describes the number of deaths per population; however, this does not take into account the age structure of the

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population. Great variations in age structure between countries will not allow valuable comparisons and were possible, standardised rates should be used. Other issues which also must be taken into consideration include the 'stage' of the pandemic the country is in and also the often imbalance found between different regions of the same country affected by COVID-19.[8]

Locally from the start of the pandemic high testing rates were deemed to be of utmost importance as a measure to control the disease.[9] Testing took place in hospitals, residential homes and community and was free of charge. Persons who died suddenly, and cases were there was any suspicion of COVID-19, underwent a PCR test after death. All confirmed deaths where COVID-19 was either a primary or secondary cause of death were coded in a timely manner; when queries arose as to whether COVID-19 was considered a primary or secondary cause of death, these were discussed with the certifying physician. Locally a confirmed death due to COVID-19 is one in which the patient had a positive laboratory test for and died due to COVID-19 or its complications. COVID-19 related deaths are reported on a daily basis.

From the beginning of the pandemic to date (26/05/2021), Malta reported 419 COVID-19 related deaths. COVID-19 was considered as the underlying cause of death in 85% of cases while in the remaining 15% COVID-19 was considered as a contributory cause. Malta reported few COVID deaths in the first wave of the pandemic and from week 15 up to week 22 there were only 9 reported COVID-19 deaths. This was followed by a lull, however increasing deaths were then observed from week 34 (figure 3) with a peak in deaths observed in November and December 2020.

4. EXCESS DEATHS FROM ALL CAUSES

Another important mortality indicator often used to monitor deaths during the pandemic is what is known as 'excess deaths'. In simple terms one compares the mortality experienced during a specific time period in the country or region against the average of example the last 5 years or some other baseline. The advantage of this indicator is that it does not depend on testing availability in the country or cause of death certification which may be either under or over-reported, as all deaths are included. Excess deaths also serve to monitor trends and is often available more rapidly in some countries than deaths by cause. Another advantage of monitoring excess mortality is that since mortality in a specific country is compared with itself in previous years, it is not affected by differences in age structure and other factors in different countries.[10]

A study carried out in Portugal during the first few months of the pandemic found that there were 14% excess deaths of which 49% were directly related to COVID-19 and 51% were due to other causes. The study supports the idea that some COVID-19 deaths may not have been reported or were missed, however it also reports that patients who were suffering from other acute medical conditions may have been afraid to access hospital care due to the pandemic. The study also states that the reduction of traffic deaths during this period due to COVID-19 restrictions could have led to some compensation of excess deaths from the other causes.[11]

Because of these advantages, excess mortality monitoring is sometimes viewed as 'the gold standard' when comparing deaths. However, as with other indicators it too has its drawbacks. Measuring excess mortality is not possible in all countries. In order to be effective, real time or close to real time data must be available, as well as comparative data for previous years. Also, excess mortality does not give information on the cause of the excess' e.g. during the COVID-19 pandemic health care facilities may have not been able to cope and treat effectively patients needing hospitalization due to other causes because of the excessive influx of patients with COVID-19, resulting in possibly excess deaths from other causes. On the other hand, measures implemented during the COVID-19 pandemic may have resulted in a decrease in deaths which are usually observed e.g. decrease in influenza deaths which compensated for the increased deaths from COVID-19, so the true excess deaths due to COVID-19 is masked.[8]

Malta has been monitoring excess deaths on a weekly basis through its membership with the European Mortality Monitoring system called EuroMOMO[12] since 2009. EuroMOMO has the overall objective to monitor in real time excess deaths due to influenza and other public health threats across 27 European countries who are currently members of this network. Other countries are also encouraged to join the network. The advantage of being a member of EUROMOMO is that comparable, standardised monitoring of excess mortality is available on a weekly basis. Trends in mortality across these 27 European countries by number of deaths, age group and z-scores are available for all countries in an aggregated manner, while at individual country level z-scores allow comparative analyses to be done between countries and are updated on a weekly basis and available on the EuroMOMO website. The z-score relates to the standard deviation from

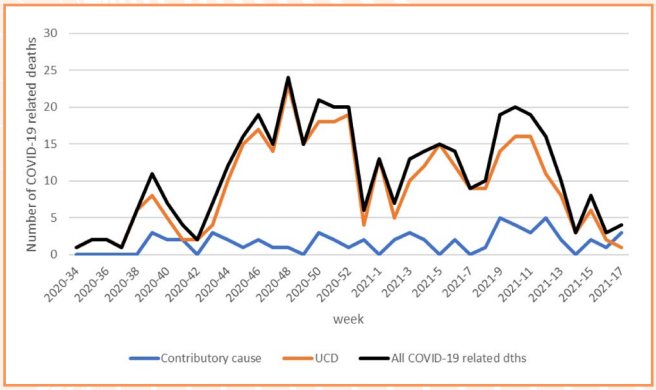

Figure 3. COVID-19 related deaths from week 34 in 2020 to week 17 in 2021. (UCD: Underlying cause of death).

the norm (mortality expected) during that period of the year. A standard deviation > 2 represents excess mortality, with values > 2 and ≤ 4 representing low excess in mortality and scores > 4 and ≤ 7 representing moderate excess in mortality, etc.

Figure 4 shows the weekly number of excess deaths for all ages and all causes of death from week 34 in 2020 to week 18 in 2021 in Malta, compared to similar periods in the previous two years. Excess mortality exceeding 20 deaths or more per week is considered significant. Significant excess deaths were consistently observed from week 44 to week 52 in 2020, quite comparable to the peaks in COVID-19 deaths observed in figure 3. In the first weeks of 2021 a peak in excess mortality is observed similar to that in the previous two years. In previous years (2018-19, 2019-20) this was due to the influenza season as well as cold weather. January 2021 observed few, if any, influenza deaths locally, but we were still observing a number of COVID-19 deaths. The 75-84 year age group accounted for 38% of all excess mortality, followed by the 85+ age group which accounted for 32% of all excess deaths and the 65-74 year age group which accounted for 23% of all excess deaths.

As seen in figure 4 quite a sharp decrease in excess mortality is observed from week 12 onwards and can be attributed to the high COVID-19 vaccine uptake among the elderly and vulnerable populations who were prioritised and started being vaccinated first, late in December 2020.

5. CASE FATALITY RATIO

Another indicator which is often quoted is the case fatality ratio (CFR), sometimes referred to as the case fatality rate. WHO defines this as the 'proportion of deaths (due to COVID-19) among identified confirmed cases (of COVID-19)'.[13] CFR is an important indicator as it reflects the severity of the disease under investigation.[14]

Another indicator which is sometimes used is the infection fatality ratio. This represents the true measure of the severity of the disease and is the total number of deaths from COVID-19 divided by the number of infected individuals. However, this often can only be estimated using serological testing on a representative random sample of the population, due to the substantial proportion of persons in which infection can be subclinical or asymptomatic; this may be costly and time consuming.[13]

However, there are a number of limitations when using the CFR. Apart from issues related to the variations in counting of COVID-19 deaths as outlined previously, another issue which will affect it is that severe cases of COVID-19 who are still alive but will die later will be counted as cases but not as deaths leading to underestimation of the CFR.[3] The denominator can also vary substantially between countries according to what criteria are used to test individuals for COVID-19. In countries which mainly allow testing for hospitalised or very symptomatic patients will overestimate the CFR as those who are tested are often more severely sick and could possibly die compared to the mildly symptomatic or asymptomatic cases who are less likely to be tested and therefore not included in the denominator.[15] Also, especially in the beginning of the pandemic or when countries were overwhelmed, the limited testing capacity of some countries may have resulted in missed cases and deaths.[14] Further to this, in some countries, underprivileged sectors of society may have limited access to healthcare and testing, and testing outside hospital facilities may be against payment.

CFR varies between countries and regions and it also varies according to the stage of the pandemic; it can also

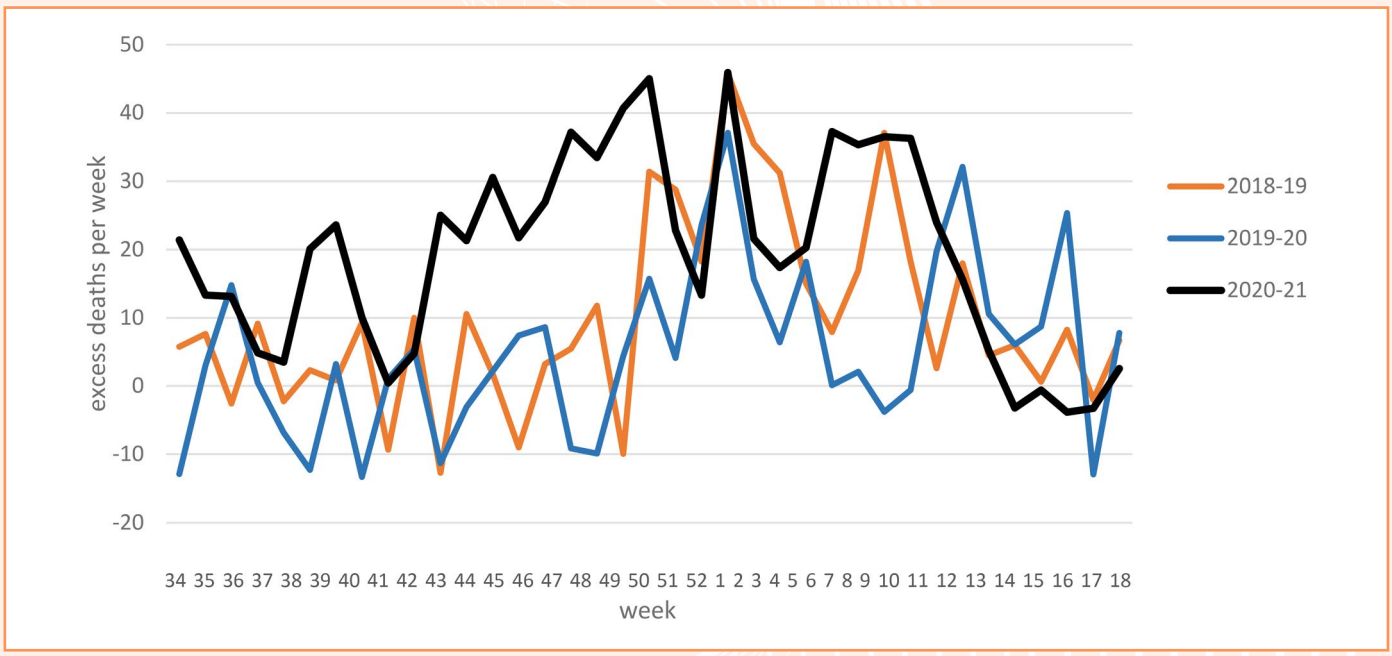

Figure 4. Excess number of deaths per week in the years 2018-19, 2019-20, 2020-21.[12]

be calculated by different age groups and according to pre-existing medical conditions.[3] However, because of the limitations and variations outlined above one needs to be very careful how this measure is used especially when comparing different countries. The highest CFR documented in Malta was on 28 December 2020 (1.73%). This was also the time where the mortality rate from COVID-19 was highest locally. Currently it has stabilized at 1.37% (24/05/2021) compared to the EU average which is currently 2.25%.[3]

Two other measures proposed to overcome the limitations of CFR are 1) individuals' survival probability which depends on the availability of individual data and, 2) number of deaths due to COVID-19 as a proportion of number of deaths + number of recovered persons from COVID-19; however some bias still remains on the utilisation of these two measures. [13,15]

6. POLICY IMPLICATIONS

While the importance of gathering timely data and information has been highlighted during this pandemic, the correct interpretation of data presented is essential in order for it to serve health policy.[10] Also it is very important that an indicator is interpreted in light of the bigger picture in terms of both all other indicators available to monitor the pandemic, and also in respect to the local and international situation, public health measures and strain on the healthcare system. Consideration of the impact of the pandemic on the wider aspects of society is also needed to make the best decisions possible for the good of the population.

The death certification process as well as the monitoring of deaths during the pandemic needs to be viewed as part of a larger health monitoring system as well as part of the public health response available. This pandemic also serves to highlight the challenges relating to accessing real-time data, as well as the need for the implementation of measures to collect data which is of better quality. Malta has one National Mortality Register which captures all deaths occurring on the Maltese Islands and also has good communication channels with certifiers and public health policy makers which allowed the timely verification of all COVID-19 related deaths. However, there is always room for improvement and currently an important project that is being developed locally by the Public Registry Unit of Identity Malta is the 'electronic death certificate' which will allow the instant transfer of death certificates and allow even more timely monitoring of deaths.

Data on various COVID-19 indicators are available from a number of international sources[10] which are updated very frequently; however, understanding the limitations of the different data sources should always be considered when interpreting and understanding the data. The Institute for Health Metrics and Evaluation[16] has very recently updated its method of calculating total mortality due to COVID-19 based on excess deaths but taking into account 'drivers of change in mortality…. since the onset of the pandemic'. These drivers which need to be taken into account include possible increases in other causes of death due to, example, delay in accessing health care, as well as decrease in other causes of death e.g. influenza. As highlighted by the Institute there is great heterogeneity between countries in deaths due to COVID-19 and also gross underestimation in some countries between what is reported and the estimated mortality due to COVID-19[16] More work is needed locally to dissect excess mortality experienced during the pandemic into the different causes of death, however trends in COVID-19 related deaths and excess mortality followed a similar pattern to date.

Monitoring of the impact of the COVID-19 pandemic goes beyond the time we are living in now when the virus is still rampant and causing havoc across the world. Its impact on the health, social and economic sphere is still developing and needs close surveillance to be able to implement needed policies in hard hit areas.

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DR KATYA MUSCAT, DR DONIA GAMOUDI,
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Not as smooth as silk

ABSTRACT

Genital ulceration is a common presentation to general practitioners, dermatologists, gynaecologists and genitourinary physicians alike. Differential diagnosis is broad and includes sexually transmitted infections (STIs) and other non-infectious conditions such as malignancies, skin diseases and drug allergies.

This case report describes a case of genital herpes virus infection triggering Behçet's disease (BD). As current treatment options for BD remain limited and often unsatisfactory, more research into the pathogenesis will hopefully lead to the development of successful therapeutic strategies in the near future.

Keywords: FGM, genital, HSV, ulcer, Behçet's

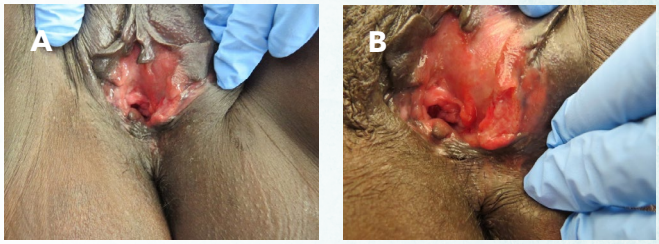

Figure 1. A, B show solitary ulcer with irregular borders on the left labia majora. It was tender on palpation and infiltrated. Loss of the clitoris and labia minora can also be appreciated and this is consistent with FGM type 2.

CASE REPORT

A 37-year-old Ethiopian refugee, married to a conational and mother of two children, was referred to the Genito-urinary clinic (GUC) in view of a 5-year history of painful intermittent oral and genital ulceration. The rest of her medical and sexual history was unremarkable. She had tested negative for blood-borne viruses (HIV, Hepatitis B and C) and syphilis before referral. Examination revealed multiple oral ulcers and a solitary, tender, infiltrated ulcer with irregular borders on the left labia majora and loss of the clitoris and labia minora, the latter consistent with female genital mutilation (FGM) type 2. Skin scarring was also present (Figure 1). A polymerase chain reaction (PCR) swab from the genital ulcer was requested for herpes simplex virus (HSV) and *Treponema pallidum,* resulting in the detection of HSV-1. A swab taken from the oral ulcer was negative for HSV. A course of aciclovir 400mg three times a day for 7 days was initiated but no improvement was seen at follow-up. Haematological and biochemical blood investigations were normal except for slightly raised inflammatory markers. HLA-B*51 was negative. A biopsy from the edge of the genital ulcer was performed and histopathological features are described in Figure 2A and B, which excluded HSV [HSV was however detected in the PCR, discussed earlier]. No signs of uveitis or hypopyon were detected on slit lamp examination. This was done to investigate Behcet's disease. The patient was started on a course of prednisolone 40mg daily which was then tailed down gradually over 8 weeks. At follow-up, the oral and genital ulcers had resolved. On cessation of the steroids, the patient experienced a recurrence of oral and genital ulceration and once again HSV-1 was detected from the genital lesion.

The diagnosis of Behçet's disease (BD) was formulated on clinical criteria, response to immunosuppressive treatment and exclusion of other conditions. The trigger factor in this case was thought to be HSV-1. The patient was started on prednisolone, and colchicine 0.5mg twice a day thereafter as a steroid-sparing agent. One year later, the patient remains well and free from symptoms.

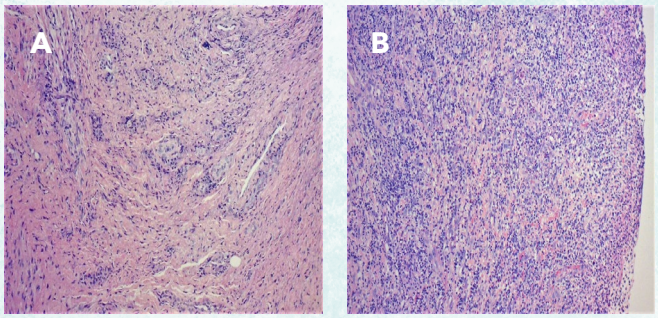

Figure 2. A The histology specimen from the genital ulcer shows an intact squamous mucosa which is irregularly acanthotic with an underlying chronic inflammatory infiltrate. No sclerosis was identified. **B** shows complete loss of the mucosa with extensive ulceration, and an infiltrate of a few large lymphoid cells associated with prominent vascular endothelial cells. No evidence of HSV or malignancy was identified.

DISCUSSION

BD, also known as 'Silk Road disease' as this condition is considered more prevalent in the areas surrounding the old silk trading routes in the Middle East and Central Asia, is a rare immune-mediated systemic vasculitis.[1] Whereas epidemiological studies have been carried out in Asia and Europe, data from African regions are scanty and only few cases have been reported in the literature.[2] The disease's aetiology is unknown but the most widely held hypothesis is that of a profound inflammatory response triggered by an infectious agent in a genetically susceptible host.[3] HSV, hepatitis, mycobacteria and *Helicobacter pylori* have all been implicated.[4] The genetic susceptibility has been linked to HLA-B*51. However, expression of this antigen is neither sensitive nor specific as a diagnostic test.[5]

Although BD is relatively a new disease (described in 1937), it has already 16 sets of classification criteria.[6] Recurrent oral and genital ulcerations are highly discriminatory diagnostic criteria. Morphologically, genital ulcers are deeper, larger and can take longer to heal. Genital scarring is usually a strong evidence of the presence of BD. Reactivation of HSV infection could have triggered BD,[4] but unlikely to be the sole agent responsible for the ulceration. The lack of response to antiviral treatment with nucleoside analogues is uncommon in immunocompetent hosts with antiviral resistance reported as low as 0.3%.[7] The diagnosis of HSV-induced necrotising granuloma was also considered. In the literature, there are several reports of granulomatous reactions at sites of previous varicella zoster virus infection,[8] but only 2 case reports of HSV-induced granuloma.[9] However, the absence of a granulomatous infiltrate on histology excluded this diagnosis as well as malignancy.

The scarring which persisted after the vulval biopsy and after healing of the genital ulceration, led to a lot of anxiety and psychological distress. Our patient was therefore referred to the plastic surgical team for consideration of surgery. FGM is recognized in international law as a human rights violation, but it remains deeply entrenched in the cultures in which it is practised.[10] In some African countries, FGM is performed for cosmetic reasons and regarded as a procedure that improves women's desirability.

To conclude, diagnosing BD in non-endemic regions is often delayed and has to be decided on clinical grounds, with due diligence in excluding other conditions. Although BD's prognosis is good, flare ups can have a negative impact on the psychosexual health and wellbeing of the affected person. In migrants, cultural aspects must also be considered and a more comprehensive approach to diagnosis and treatment adopted.

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DR PIERRE VASSALLO

Imaging Ovarian Tumours
Part III

INTRODUCTION

In the first article of this three-part series, we outlined the large spectrum of ovarian tumours which are grossly divided into four groups: epithelial surface cell tumours, germ cell tumours, sex cord/stromal tumours and metastases.[1]

A general introduction of the subtypes of each tumour group was presented and the most common tumour group, the serous epithelial tumours, was discussed in more detail.

The second article discussed mucinous epithelial tumours, other less common epithelial tumours (endometrial and clear cell carcinomas) and epithelial-stromal tumours (Brenner tumours, adenofibroma and cystadenofibromas).

This third and final article in the series will deal with germ cell tumours and sex chordstromal tumours and metastases to the ovary.

GERM CELL TUMOURS

Ovarian Germ Cell Tumours (OGCTs) are true primary ovarian neoplasms since they arise in embryonic germ cells that originate within the ovary. Since germ cells are the precursor cells to all embryonic tissues including the placenta, OGCTs constitute many different tumour types. They include teratomas (mature, immature and monodermal types), dysgerminomas, yolk sac tumours (previously called endodermal sinus tumours), embryonal carcinomas, polyembryomas and choriocarcinomas.

OGCTs are the second most common type of ovarian tumor after epithelial neoplasms. They are usually benign (95%) and tend to affect the younger age group. Some tumour types may be distinguished clinically by the presence of specific tumour markers.

The ***mature teratoma*** (also known as dermoid) is the most common OGCT. It occurs at a mean age of 32yrs and is usually asymptomatic. Large tumours may cause pain and may undergo torsion. These tumours are benign with malignant transformation occurring rarely (2% of cases) and in an older age group (>40yrs).[2] Other rare complications include tumour rupture, infection, autoimmune haemolytic anaemia and paraneoplastic encephalitis.[3]

Mature teratomas characteristically contain sebaceous material, fat, hair, teeth, bone or cartilage. Fat components are hyperechoic on US (Fig. 1a) and hypodense on CT (Fig. 1b). Teeth, bones and calcified cartilage are best seen on CT (Fig. 1c). On MR imaging, fat components show high signal

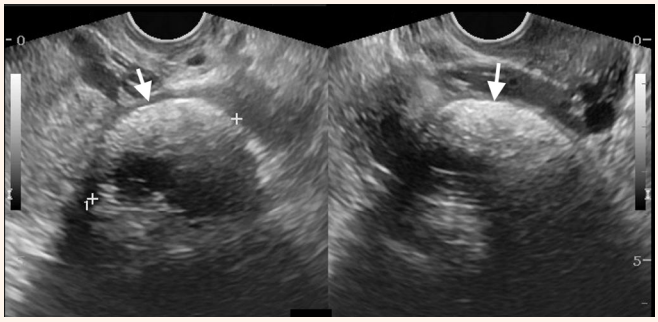

Figure 1a. US scan showing a mature teratoma (arrows) with characteristic hyperechoic texture, a well-defined anterior margin and ill-defined posterior margin, the latter occurring due to beam attenuation. Dorsal shadowing may also be present as a result of the latter phenomenon.

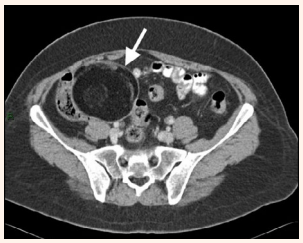

Figure 1b. CT scan shows a mature right ovarian teratoma (arrow) with central low density and a thin well-defined capsule.

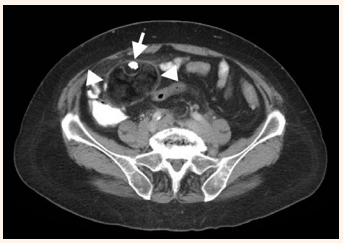

Figure 1c. CT scan shows a mature right ovarian teratoma (arrowheads) containing a tooth (arrow).

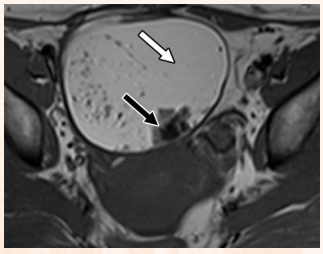

Figure 1d. T1-weighted MR scan demonstrates a mature teratoma containing central high signal contents (white arrow) and a peripheral intermediate signal mural nodule containing an area of low signal (black arrow).

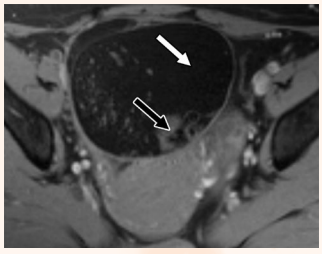

Figure 1e. Contrast-enhanced fat-suppressed T1-weighted MR scan shows suppression of signal within the lesion (white arrow) compared to Fig. 1d, which confirms the presence of mature fat. The mural nodule shows mild enhancement while the low signal area within it (black arrow) shows no enhancement; this represented a tooth.

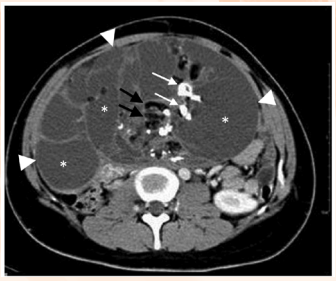

Figure 2a. Contrast-enhanced CT scan showing a large immature teratoma (arrowheads) filling most of the abdomen, containing irregular calcifications (white arrows), fluid filled loculi (*) and very small fat-containing areas (black arrows).

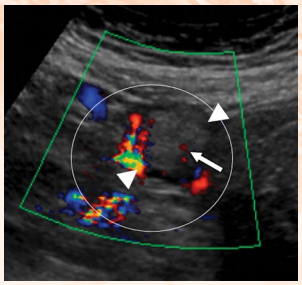

Figure 2b. Left adnexal monodermal teratoma (arrowheads) with small internal foci of blood flow (white arrow) seen on colour Doppler US.

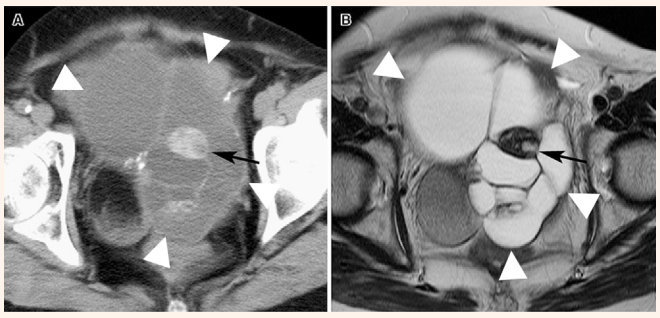

Figure 2c. Non-enhanced CT (A) and T2-weighted MR (B) scans through the pelvis show a large cystic teratoma (arrowheads) containing a central solid nodule. The nodule is dense on the CT image indicating the present of iodine and hence struma ovarii within lesion that might otherwise mimic a mature teratoma. However, the abundant fluid components and irregular calcifications are indicative of an immature or monodermal teratoma.

on T1-weighted images and low signal on T2-weighted images with low signal on fat-suppressed images (Fig. 1d and e). A fat/fluid level may occasional be noted within a mature teratoma and is usually detected on all three imaging modalities. Fat suppressed T1-weighted images are crucial for distinguishing fat signal from haemorrhage; the latter remains hyperintense on fat-saturated T1-weighted images.

By definition, mature teratomas should contain at least two of the three germ cell layers (ectoderm, mesoderm and endoderm).

Immature teratomas comprise the malignant counterpart to mature teratomas. They are the most common malignant germ cell tumour[4] and are seen in younger women. They are often large and therefore palpable at the time of presentation.

Immature teratomas are larger that mature teratomas at the time of imaging. They appear more heterogeneous, with more solid contrast-enhancing components, containing irregular calcifications rather than coarse and tooth-like structures, and containing fluid rather than fat (Fig. 2a).

Foci of haemorrhage are common within immature teratomas. The tumour grade is based on the presence and amount of neuroepithelium. The amount of yolk sac tumour that may be present within immature teratomas is the source of α-fetoprotein (AFP) and is useful for monitoring response to treatment and for detecting tumour recurrence.[5]

Monodermal teratomas are rare and consist predominantly of a histologically mature cell type, most commonly thyroid tissue (in the case of struma ovarii). However, they can also contain carcinoid and neural tumours. Struma ovarii may lead to hyperthyroidism and rarely, malignant transformation may occur (mostly to papillary carcinoma).[6]

On imaging, monodermal teratomas usually appear similar to mature teratomas but with solid components that either display blood flow detectible on colour Doppler US (Fig. 2b) or show avid contrast enhancement on CT and MR imaging. Thus, if flow is detected on colour doppler imaging or solid contrast avid components are noted on CT or MR within an otherwise classic appearing mature teratoma, the possibility of struma ovarii must be considered.

In addition, high iodine content that is common in thyroid tissue and hence within struma ovarii leads to high density on CT (Fig. 2c).

Dysgerminomas are the ovarian counterparts of testicular seminomas. They are the second most common OGCT and manifest in adolescents or young adults. They show rapid growth leading to abdominal distension and pain. Non-specific elevation of lactate dehydrogenase (LDH) and alkaline phosphatase may occur. Elevation of β-human chorionic gonadotrophin (β-hCG) may be caused by syncytiotrophoblasts (placental precursor cells) present within the tumour.[7]

At imaging, dysgerminomas are large (>10cm), predominantly solid, unilateral, with intervening fibrovascular septa, solid enhancing components and increased vascularity on colour Doppler imaging (Fig. 3). Speckled calcifications may also be present. In comparison with other predominantly solid tumours, such as Brenner tumours and fibromas, dysgerminomas contain less fibrous tissue and hence show higher T2 signal on MR imaging.

Yolk sac tumours are rare and aggressive tumours that present in young females (mean age 19yrs) and have poor prognosis. They grow rapidly and are associated with increased AFP levels like dysgerminomas. They are usually large at the time of diagnosis and contain cystic and solid components, the latter showing high vascularity on colour

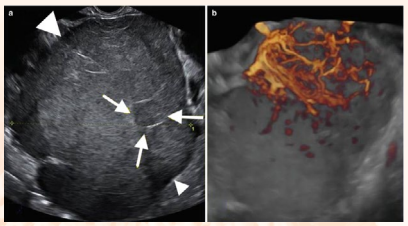

Figure 3. US image (a) of a 14cm dysgerminoma (arrowheads) showing internal septations (white arrows). 3D Power Doppler image (b) shows numerous branching vessels and some marked vessel calibre change.

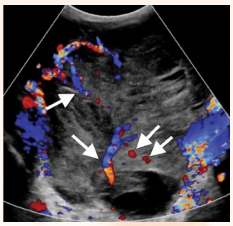

Figure 4. Colour doppler ultrasound of a yolk sac tumour showing abundant vessels (arrows).

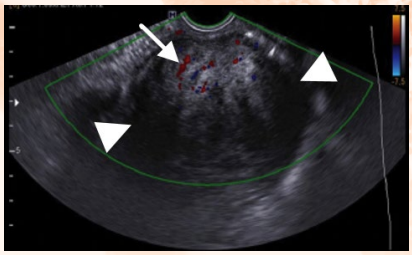

Figure 5a. Ovarian fibroma seen on ultrasound as a solid hypoechoic mass (arrowheads) with minimal vascularity on colour Doppler imaging (arrow).

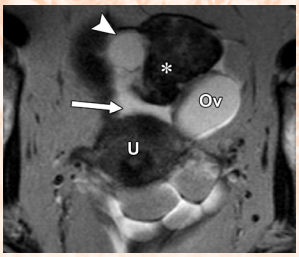

Figure 5b. Ovarian fibroma (*) seen on axial T2-weighted MR image showing low T2 signal and a small cyst (arrowhead) separated from the uterus (U) by a small amount of ascites (arrow).

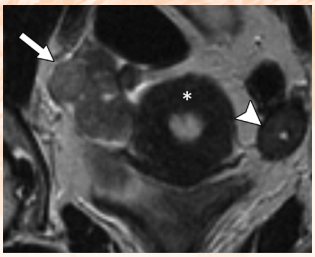

Figure 6. Right ovarian Sertoli-Leydig cell tumour (arrow) on an axial T2-weighted MR image showing higher T2 signal than myometrium (*) and than, an incidentally noted left ovarian fibroma (arrowhead).

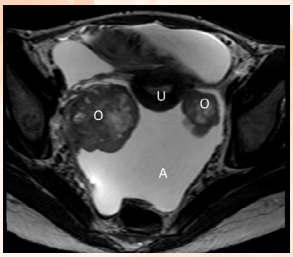

Figure 7. Axial T2-weighted image shows bilateral gastric cancer metastases (Krukenberg tumours) to the ovaries (O), which show mixed internal T2 signal. Ascites is present (A). (U) uterus.

MATURE TERATOMAS CHARACTERISTICALLY CONTAIN SEBACEOUS MATERIAL, FAT, HAIR, TEETH, BONE OR CARTILAGE

Doppler US (Fig. 4) and enhancement on CT and MR imaging. Haemorrhage is common within this tumour.

Other malignant OGCTs including choriocarcinoma, embryonal carcinoma, polyembryoma and mixed germ cell tumours are all rare and very aggressive tumours. Choriocarcinoma may be gestational and non-gestational; the latter are seen in children and young women who present with precocious puberty and exhibit high β-hCG levels. These tumours are large, predominantly solid and highly vascular which may contain areas of haemorrhage similar to yolk sac tumours.[7] Embryonal carcinomas, polyembryomas and mixed germ cell tumours may also cause increasing levels of β-hCG, but in these tumours we also see elevations in AFP and LDH.

SEX CORD-STROMAL TUMOURS

Primitive sex cord cells (granulosa and Sertoli cells) and stromal cells (fibroblasts, thecal cells and Leydig cells) surround the oocytes in the ovary and are involved in hormone production (such as oestrogens, androgens and corticoids). Thus, tumours originating from this cell group are likely to be associated with excess oestrogen or androgen production.

Ovarian sex cord-stroma tumours are uncommon and are more often benign than malignant. They manifest early mainly due to increased hormone production, are usually small and confined to the ovary at the time of detection. Some rare subtypes may be aggressive.[8]

On imaging, these tumours are mostly solid with the exception of granulosa cell tumours.

Granulosa cell tumours have a variable appearance on imaging and may mimic malignant tumours presenting as large solid or mixed solid/cystic lesions with areas of haemorrhage. Due to oestrogen effect, endometrial thickening may be evident on US and MR imaging.

Extraovarian spread is rare but may occur and may present as late recurrence with peritoneal seeding and retroperitoneal deposits.[9]

Fibromas, thecomas and fibrotechomas occur mainly in middle-aged women. Meigs syndrome (pleural effusion and ascites associated with an ovarian mass) may occur with these tumours, particularly fibromas. On US, these present as hypoechoic masses with no flow on colour Doppler imaging (Fig. 5). They may resemble a pediculated fibroid. On MR imaging, these tumours tend to have low T1 and T2 signal due to their fibrous component. However cystic degeneration and oedema may be present in larger tumours (>6cm) and in those undergoing torsion. Contrast enhancement in these lesions is usually evident on delayed imaging.

Sertoli/Leydig cell tumours are rare, mixed sex cord-stromal tumours that manifest mainly in young women with virilisation or amenorrhoea, vaginal bleeding from the oestrogenic effects and abdominal pain.[10] These tumours appear mostly as solid masses with some cystic components and some internal colour Doppler flow and marked contrast enhancement on CT and MR imaging (Fig. 6).

Collision Tumours are neoplasms that contain more than one histologic subtype, such as a mucinous neoplasm with a germ cell tumour. This further complicates imaging diagnosis since image features of both components co-exist.

METASTASES

Metastases to the ovary occur mainly from gastrointestinal (GI) malignancies including those in the colon, appendix, stomach and pancreas. Malignancies other than GI that may spread to the ovary include breast, lung and contralateral ovarian neoplasms. Ovarian metastases may be the first signs of the presence of a distant primary tumour. In comparison with primary ovarian neoplasms, metastases are often bilateral, smaller at the time of detection, and often associated with peritoneal carcinomatosis (Fig. 7). Pseudomyxoma peritonei may be present particularly with appendiceal tumours. Ovarian metastases vary in texture on US, CT and MR imaging based on the nature of the

primary tumour; gastric and breast cancer metastases tend to be solid, while appendiceal, colorectal and pancreatic metastases tend to be more cystic.[11] Carcino-embryonic antigen (CEA) may be elevated in GI malignancies and increased CA-125 levels may be seen in primary serous tumours; these tumour markers may help in both diagnosis and for monitoring effectiveness of treatment.

Lymphomas of the ovary are usually secondary as part of disseminated systemic disease. This occurs within lymphocytes in the ovarian hilum. The most common lymphoma type to affect the ovary is diffuse large B-cell lymphoma.

CONCLUSION

Given the complexity and variety of ovarian cancers, one needs to maintain a clear diagnostic algorithm to ensure that detection, accurate initial staging and subsequent follow-up of patients is performed to have the best treatment outcome. Endovaginal ultrasound is the first imaging modality to evaluate a suspected ovarian mass. In case of equivocal findings or with large masses that cannot be visually encompassed by ultrasound, MR imaging should be the second imaging modality since it provides the best tissue contrast resolution and allows tumours to be clearly distinguished from adjacent organs and helps with tissue characterisation. CT is recommended for preoperative staging and follow-up of surgical or systemic treatment.

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Gut Health Yoghurt Recipe

by Dr Antonella Grima

Numerous studies, especially in recent years, are demonstrating the crucial role that the gut microbiome plays in our health.[1] A healthy gut microbiome facilitates digestive processes and strengthens our immune responses, while also supporting many other aspects of our health. When the population of organisms that inhabit our large intestine are imbalanced or depleted, this may contribute to weight gain, hyperglycaemia, hypercholesterolaemia and other disorders.[2] The list of conditions that can be traced back to the microbiome, and that respond to an improvement in the gut microflora is ever growing, so it is worth considering improving the microbiome together with other treatment modalities for conditions where the association is known.

Here is a gut health yoghurt that is rich in probiotics, fibre and antioxidants to keep a balanced microbiome and the bowel movements regular. It can be made in under 5 minutes and eaten as a quick breakfast or as a snack.

INGREDIENTS

One cup (240ml) of 0% fat plain yoghurt
Five pitted prunes
15g Walnuts
5g Pumpkin seeds
5g Coconut flakes

NUTRITION FACTS

Calories	298Kcals
Total Fat	16g
Saturated Fat	5g
Total Carbohydrates	24g
Dietary Fibre	2g
Total Sugars	20g
Proteins	18g

The population of healthy microbes in our microbiome can be increased by including food containing probiotics such as natural yoghurt or fermented foods in our diet on a regular basis. This is especially important after events like antibiotic treatment, acute illness and stress as these deplete our microbiome populations, making us more prone to infections and disease.[3]

We can also nourish our microbiome by feeding it prebiotics found in foods like apples and bananas. Prebiotics are a type of dietary fibre that, once digested by the gut bacteria, produces nutrients that are absorbed by the large intestine, leading to a healthier digestive system. These nutrients include the short-chain fatty acids butyrate, acetate, and propionate.[4]

Roughage found in fruit such as prunes, nuts and seeds provides a pediment upon which our microbiome can grow and flourish.[5]

Prunes are a source of vitamin K, vitamin A and some B vitamins, and they help bowel movements, mainly due to the insoluble fibre they contain.

Nuts and seeds are also rich in monounsaturated and polyunsaturated fatty acids and vitamin E. These are antioxidant and anti-inflammatory.

References are available online.

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