THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

Volume 18, 2019 Issue 02 ISSN number 2313-8084

Red Flags in Headache Presentations
An Alphabetical Guide

At the Crossroads of Chemical Pathology and Bariatrics

Is Anti-Ageing Therapy Medical Fiction?

Meeting Dr Deo Debattista

How does your choice of ICS/LABA stand up to a 24-hour world?

Throughout day and night, their **24-hour world** needs an ICS/LABA that lasts. Relvar is the only ICS/LABA providing 24 hours of continuous efficacy from just one daily inhalation,[1] and is superior to ICS/LABAs in helping more patients improve asthma control in everyday clinical practice.*[2]

Relvar 92/22mcg & 184/22mcg are indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists.
- patients already adequately controlled on both inhaled corticosteroid and long-acting $beta_2$-agonist.[3]

Please refer to full SmPC for detailed information.

ZINC Code: MLT_GIB/FFT/0005/18 Date of preparation: April 2018

Relvar Ellipta was developed in collaboration with INNOVIVA

RELVAR ELLIPTA
fluticasone furoate/vilanterol

References: 1. Bernstein DI, Bateman ED, Woodcock A, Toler WT, Forth R, Jacques L, *et al.* Fluticasone furoate (FF)/ vilanterol (100/25mcg or 200/25mcg) or FF (100mcg) in persistent asthma. *J Asthma* 2015;52(10):1073–1083. **2.** Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, *et al.* Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open label, parallel group, randomised controlled trial. *Lancet* 2017; doi.org/10.1016/S0140-6736(17)32397-8. **3.** Relvar SmPC, March 2018.

RELVAR ELLIPTA ABRIDGED PRESCRIBING INFORMATION

Please refer to full Summary of Product Characteristics (SPC) before prescribing

TRADE NAME: Relvar Ellipta. **ACTIVE INGREDIENT:** *92mcg/22mcg dose*: 92mcg fluticasone furoate, 22mcg vilanterol (as trifenatate). *184mcg/22mcg dose*: 184mcg fluticasone furoate / 22mcg vilanterol (as trifenatate). **PHARMACEUTICAL FORM:** Inhalation powder, pre-dispensed. **INDICATIONS:** ***Asthma*** *(92/22mcg dose & 184/22mcg dose):* Regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists and patients already adequately controlled on both inhaled corticosteroid and long-acting $beta_2$-agonist. **COPD** (92/22mcg dose): For symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. **POSOLOGY:** *For Asthma*: One inhalation, once daily. *For COPD*: One inhalation of 92/22mcg dose, once daily. 184/22mcg is not indicated for patients with COPD. Relvar Ellipta should be administered at the same time of day, each day. *Refer to full SPC for full dosage recommendations.* **CONTRAINDICATIONS:** Hypersensitivity to active ingredients / excipients. **PRECAUTIONS:** Should not be used to treat acute asthma symptoms or acute exacerbation in COPD; Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing; Caution for use in severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium; Moderate to severe hepatic impairment: 92/22mcg dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions; Systemic corticosteroid effects may occur, particularly at high doses for long periods. Caution in patients with pulmonary tuberculosis or chronic or untreated infections; Blurred vision or other visual disturbances: referral to ophthalmologist for evaluation should be considered; Caution in diabetic patients; Physicians should remain vigilant for possible development of pneumonia in patients with COPD (clinical features overlap); Incidence of pneumonia in asthma common at higher dose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. **PREGNANCY/FERTILITY/LACTATION:** *Pregnancy:* only if expected benefit to mother outweighs risk to foetus. *Lactation:* consider benefit of breast feeding child and benefit of therapy for woman. *Fertility:* No data. **UNDESIRABLE EFFECTS:** *Very common (≥1/10):* headache, nasopharyngitis. *Common (≥1/100 & <1/10):* pneumonia, upper respiratory tract infetion, bronchitis, influenza, candiasis of mouth and throat. Oropharyngeal pain, Sinusitis, Pharyngitis, Rhinitis, Cough, Dysphonia, Abdominal pain, Arthralgia, Back pain, Fractures, Muscle spasms, pyrexia. *Refer to the SPC for full list of undesirable effects.* **LOCAL PRESENTATION:** Inhaler x 30 doses. **MARKETING AUTHORISATION NUMBER:** EU/1/13/886/001-6. **MARKETING AUTHORISATION HOLDER:** Glaxo Group Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** March 2018.

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

REPORTING ADVERSE EVENTS (AEs):
If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Ltd, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)
Malta: alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal
Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

SUSTAINABLE DEVELOPMENT Goals

We all heard the saying, 'We do not inherit the earth from our ancestors; we borrow it from our children', attributed to the late David Brower, prominent environmentalist. This proverb seems to try to inculcate in us the notion of environmental stewardship, which goes beyond window dressing attitudes. In keeping with this, in 2015 all UN member states including Malta adopted the 2030 Agenda for Sustainable Development which provides a shared blueprint for environmental governance. The underpinnings of the Agenda are 17 Sustainable Development Goals (SDGs), which recognize that ending poverty inherently complements strategies that improve health and education thereby decreasing inequality, spurring economic growth and spearheading environmental governance.

The ambitious SDGs are: **No Poverty; Zero Hunger; Good Health and Well-being; Quality Education; Gender Equality; Clean Water and Sanitation; Affordable and Clean Energy; Decent Work and Economic Growth; Industry, Innovation and Infrastructure; Reduced Inequality; Sustainable Cities and Communities; Responsible Consumption and Production; Climate Action; Life Below Water; Life on Land; Peace and Justice Strong Institutions;** and **Partnerships to achieve the Goal.**

For the first time, we are seeing non-communicable diseases - such as cancer - being enshrined in a global development agenda and recognised to constitute a major health and development challenge, intrinsically impacting sustainable development. The SDGs try to stimulate member states to implement cost-effective interventions across the care continuum. They advocate vaccines, access to healthcare, good air quality, safe disposal of hazardous waste, and ways to tackle pollution, amongst other things.

At this stage I must refer to the article penned last March by Emmanuel Macron, French President, and published in no less than 22 languages and 28 newspapers across Europe. Macron's words stem from an earlier document, *Treaty establishing a Union for Climate and Biodiversity, providing for the establishment of a European Climate and Biodiversity Bank and a European Climate and Biodiversity Fund.*

Mr Macron's underlying message is about preserving 'European civilisation'. I quote ad verbatim, 'Getting back on track with progress also concerns spearheading the ecological cause. Will we be able to look our children in the eye if we do not also clear our climate debt? The European Union needs to set its target – zero carbon by 2050 and pesticides halved by 2025 – and adapt its policies accordingly with such measures as a European Climate Bank to finance the ecological transition, a European food safety force to improve our food controls and, to counter the lobby threat, independent scientific assessment of substances hazardous to the environment and health. This imperative needs to guide all our action: from the Central Bank to the European Commission, from the European budget to the Investment Plan for Europe, all our institutions need to have the climate as their mandate.'

We may well shrug off these words like water off a duck's back. However, several reports highlight that the problem is real and the price which we are paying is already high. Taking air quality as an example, which is often trivialized, the 2018 report published by the European Environment Agency, *Air quality in Europe* states that the Years of life lost (YLL) attributable to PM2.5 exposure in Malta is 629 [YLL/10^5 inhabitants], and the YLL attributable to ozone (O3) pollution is 41 [YLL/10^5 inhabitants] which is above the EU average. Need I add more?

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Publisher:
Medical Portals Ltd
The Professional Services Centre
Guzi Cutajar Street, Dingli
Malta, Europe

Production: Outlook Coop

Printing: Europrint Ltd

OUR COLLABORATORS

The magazine is distributed free of charge to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies.

Annual subscription rates outside Malta: Six issues €90 or equivalent, worldwide

Galvus®
PRESENTATION: Each tablet contains 50 mg of Vildagliptin **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults: i) As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. ii) As dual oral therapy in combination with: metformin in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin; a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. iii) As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of Vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in dual combination with a sulphonylurea, the recommended dose is 50mg once daily in the morning. A lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. Galvus is not recommended for use in children and adolescents (< 18 years) as the safety and efficacy have not been established and no data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. No dose adjustments are necessary in elderly patients (≥ 65 years). **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis and Galvus should be used with caution in these patients. Galvus should be used with caution in patients with renal impairment. Galvus should not be used in patients with hepatic impairment. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class I-III treated with Vildagliptin is still limited. There is no experience with NYHA class IV and therefore use of Vildagliptin is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Exercise caution in patients with a history of acute pancreatitis. Patients with Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding, since no studies on the effect on human fertility have been conducted for Galvus. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with Vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of Vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors ADVERSE REACTIONS: Monotherapy: Common (>1/100 to <1/10): dizziness. Combination with metformin: Common: hypoglycaemia, tremor, headache, dizziness, nausea. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. For a full list of Adverse Reactions please refer to the SmPC. **LEGAL CATEGORY:** POM **PACK SIZES:** 28 tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/0003. **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. 2018-MT-GAL-26-APR-2018

References:

1. Novartis Europharm Ltd. Galvus Summary of Product Characteristics
2. Novartis Europharm Ltd. Eucreas Summary of Product Characteristics
3. Holman RR et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15):1577–1589.
4. Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38(1):140-149.
5. Garber AJ et al. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013; 19(2):327-336.

Eucreas®
PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. DOSAGE: The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma. Severe renal failure (GFR < 30 ml/min). Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. GFR should be assessed before treatment initiation and regularly thereafter. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued at the time of surgery under general, spinal or epidural anaesthesia and resumed no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. The IV administration of iodinated contrast agents can lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. The use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol due to an increased risk of lactic acidosis, iodinated contrast agents, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics and products which can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angiodema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Vildagliptin Monotherapy: Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Metformin monotherapy: Very common (>1/10) Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. Combination vildagliptin with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. Combination with metformin and sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. Combination with insulin: Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence For a full list of Adverse reactions, please refer to the SmPC.**LEGAL CATEGORY:**POM **PACK SIZES:**30, 60 film-coated tablets MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/021, EU/1/07/425/027. **Please refer to Summary of Product Characteristics (SmPC) before prescribing**. Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872 2018-MT-EUC-23-APR-2018

NOVARTIS

Galvus® vildagliptin Eucreas® vildagliptin/metformin

AUTHORS

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Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health (specifically at Paola Health Centre) for these last 27 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-author of the article is Dr Michael Balzan.

Dr Adrian Pace MD MRCP(UK)(Neurology) PhD FRCP(Edin) trained in neurology at the South West Peninsula Deanery in the UK during which he completed a PhD in health outcome measurement and psychometrics. He has presented and published widely on various neurological disorders, and has been Chief UK Investigator or principal local investigator for numerous phase 3 clinical trials in multiple sclerosis and epilepsy. He is now consultant neurologist at Gozo General Hospital and Karen Grech Hospital.

TheSynapse

ISSUE GUIDE

RED FLAGS IN HEADACHE PRESENTATIONS
AN ALPHABETICAL GUIDE

DR ADRIAN PACE

Headache is the prototypical neurological complaint – an intrusive and limiting symptom that is subjective in its severity, intangible in nature and extremely difficult to quantify or measure. It is also by far the most commonly experienced neurological symptom, occurring as either a primary disorder or secondary to another systemic illness. Its high prevalence across populations regardless of race, gender, age and geographical distribution reflects its generally benign nature and outcome, but results in difficulty in identifying the small minority of individuals whose headaches are underpinned by serious or potentially life-threatening conditions. This leads to concern among medical specialists and primary care physicians alike, often exposed to 'headache fatigue' from regularly evaluating patients with this complaint, about missing serious headache cases and on how to judiciously apply finite health resources including imaging across this large population of patients.

There are a number of headache guidelines that indicate specific patient characteristics, accompanying symptoms or signs, and other 'red flags' that may either indicate the need for investigation or point towards an underlying cause. While a comprehensive review of these documents is beyond the scope of this short article, hereunder are summarised alphabetically many of the readily identified markers for secondary causes of headache that may be swiftly assessed for and hopefully discounted in a physician-patient encounter.

AGE

While headaches are a common occurrence throughout life, it is less common to develop recurring or chronic headache for the first time beyond the age of 35. Depending on the character, location and severity of the pain, it may be prudent in these cases to refer for neurological assessment or request imaging. All patients 50 years of age and older should be investigated for giant cell arteritis / temporal arteritis by requesting ESR and CRP.

BEHAVIOUR

Changes in behaviour or personality associated with headache must always be investigated thoroughly for a possible space-occupying lesion, in particular when these are persistent, occur pervasively across different settings, or associated with worsening fatigue or cognitive issues.

COITAL HEADACHE

Pain in the head and neck during sexual intercourse is an under-reported complaint which raises the spectre of subarachnoid haemorrhage. Although reportedly more common in men, clinical practice suggests no difference in incidence between genders. It may occur very suddenly or build up progressively. When patients describe multiple episodes at presentation, it is safe to ascribe this to a form of benign exertional headache and manage accordingly. Conversely, first episodes must be investigated urgently.

DRUGS

All medications may cause side-effects, and headache may sometimes be one of them. It is helpful to take a drug history to exclude headaches resulting from the introduction of medications. Common culprits are vasodilators like nitrates, oral contraceptive medication, cimetidine and asthma medication. If the patient describes taking regular painkillers for chronic headache, their symptoms may be aggravated by MOH (medicationoveruse headache, also called rebound headache). This is estimated to occur in up to 70% of patients with chronic migraine, making them more resistant to treatment. Ask about the number of days per week when painkillers are taken (MOH is likely if taken >2 days/week), frequency of purchase of painkillers ("Do you always get some paracetamol when you're out shopping?") and fluctuating severity of headache related to timing of medication.

EYES

Any patient with headache should have an eye exam, including fundoscopy. Papilloedema, field defects, pupillary asymmetry or diplopia may all be indicative of a space-occupying lesion. Drooping of an eyelid (ptosis) with ipsilateral small pupil (miosis) is indicative of damage to the sympathetic trunk (Horner's syndrome) and requires immediate referral for investigation.

FEVER

Headache and pyrexia most commonly are caused by a unifying underlying systemic illness, such as influenza, glandular fever, the common cold or sinusitis. Patients with accompanying neck stiffness and/or confusion should be investigated immediately for meningitis or encephalitis, as should those known to have a history of cancer, immunosuppression, inflammatory or rheumatic disorders.

GONE TO GROUND

Headaches are rarely associated with loss of consciousness, and a collapsed patient with headache should lead to a careful history from the patient and any witnesses (enquire about prior illnesses, premonitory symptoms, appearance or movements while unconscious, and recovery) and a thorough neurological examination. Causes to consider include severe headache leading to vasovagal syncope, epileptic seizure or subarachnoid haemorrhage.

HIV

Headache in a patient known to have HIV or AIDS may be the result of a cerebral infection or abscess, CNS tumour, HIV-related systemic disease or toxicity caused by highly active antiretroviral medication. New or severe headaches in HIV carriers should always be carefully assessed.

INCREASING...

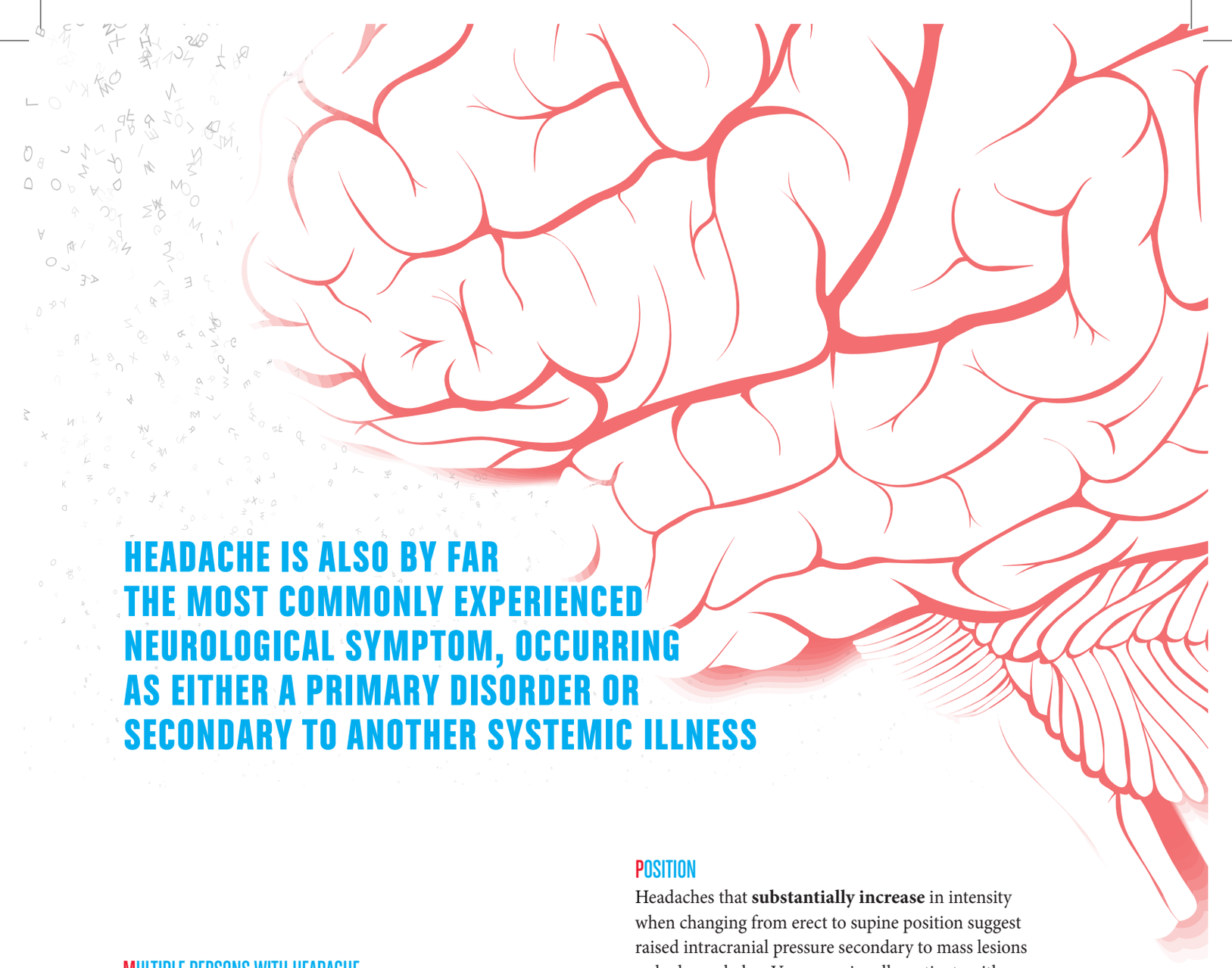
frequency and severity of headache may be due to an enlarging mass lesion or subdural haematoma (especially when eliciting a history of falls). It may also be an indication of medication-overuse headache.

'JUST HERE DOC'

Sometimes patients will describe a well-circumscribed pain within a round, oval, or elliptical-shaped region of the head that they can point to or trace around with a finger. This may raise concern about a directly underlying lesion. However further questioning often reveals that the pain is superficial rather than deep seated, and patients may report allodynia or dysaesthesia over the area. This is a form of scalp neuralgia or 'nummular headache' due to damaged sensory nerve endings that is benign, although sufficiently uncommon (and worrying for the patient) to sometimes necessitate imaging for reassurance.

LOCALISED...

neurologic signs or symptoms of disease are most often features of migraine-related aura, but may fail to be recognised as such if not typical of the patient's headache. In these cases, mass lesions, vascular malformations including aneurysms and stroke must be excluded as possible differential causes.



HEADACHE IS ALSO BY FAR THE MOST COMMONLY EXPERIENCED NEUROLOGICAL SYMPTOM, OCCURRING AS EITHER A PRIMARY DISORDER OR SECONDARY TO ANOTHER SYSTEMIC ILLNESS

MULTIPLE PERSONS WITH HEADACHE

It is helpful to ask quickly if other family members or friends residing at the same address are also suffering from headache, as this may suggest an environmental cause, in particular carbon monoxide poisoning.

NEOPLASM

A history of previous or current malignancy should always lead to evaluation for possible intracranial metastases, especially when associated with signs of raised intracranial pressure (such as vomiting or blurred vision), seizures, neurological signs on examination or cognitive changes. Cancers of the lung, colon, breast and kidney, as well as melanoma, all have a proclivity for spreading to the brain and must be excluded via brain imaging.

OBESITY

Constant or very frequent generalised headache in young overweight women that worsens on bending forward should raise the suspicion of idiopathic intracranial hypertension, especially when patients report episodes of visual obscuration or blurring. While fundoscopy is necessary, papilloedema is not invariably present in early stages and investigations or referral to a neurology service must be considered.

POSITION

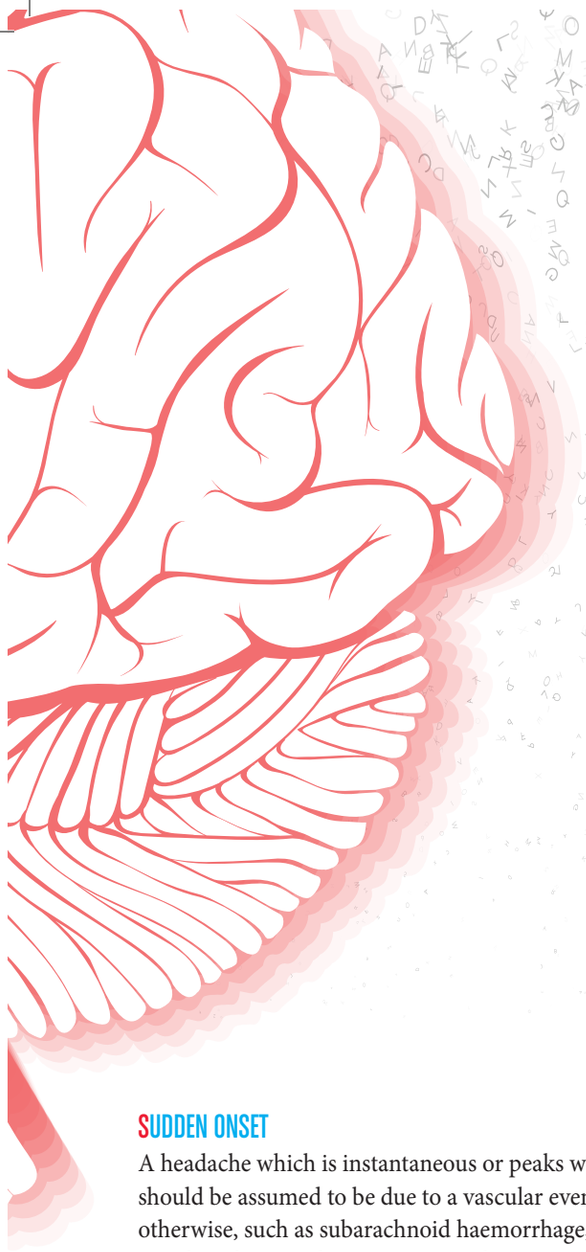
Headaches that **substantially increase** in intensity when changing from erect to supine position suggest raised intracranial pressure secondary to mass lesions or hydrocephalus. Very occasionally, patients with spontaneous intracranial hypotension report headache that resolves on lying down.

PREGNANCY...

may be complicated by headache during any trimester. Prior migraineurs may experience either improvement or aggravation of their usual headache pattern. Lack of sleep and stress later in pregnancy due to discomfort, restless legs or carpal tunnel syndrome are frequent causes of headache. Headaches in the third trimester may also result from pre-eclampsia (so remember to check for hypertension, low platelet count and proteinuria) and uncommonly from cerebral venous sinus thrombosis.

RASHES OR NUCHAL RIGIDITY

Headache, a non-blanching rash and nuchal rigidity form the classical presenting triad for bacterial meningitis, and patients should be immediately started on broad spectrum intravenous antibiotics as per local protocols while awaiting investigations with blood cultures, CSF analysis and imaging. When occurring in the returning traveller, other infections to consider include Dengue fever, Zika virus, enteric fever and acute HIV infection.



SUDDEN ONSET

A headache which is instantaneous or peaks within seconds should be assumed to be due to a vascular event until proved otherwise, such as subarachnoid haemorrhage, pituitary apoplexy, haemorrhage into a mass lesion or vascular malformation. Patients should be referred immediately for brain imaging which if normal should be followed by lumbar puncture for CSF analysis for xanthochromia.

TRAVEL

Many illnesses with headache in returned travelers are caused by mundane, self-limiting infections but unusual infections ought to be considered too, especially contagious diseases of public health interest that may need notification and isolation of the patient. The geographic area of travel helps narrow the list of possible infections based on local prevalence. Ask about vaccinations before travel, details about activities while abroad such as freshwater exposure (which may lead to schistosomiasis in endemic areas), animal bites, sexual activity or tattoos, and accommodations in areas with malaria (enquire about the use of bed nets, window screens and air conditioning) during travel.

UNREMITTING HEADACHE...

that never goes away, is featureless and present even when a patient wakes up at night generally necessitates investigation to exclude structural intracranial causes before attempting treatment.

VALSALVA

Intense head pain (classically in the occipital region but may occur anywhere in the head) that is triggered by straining, coughing, sneezing, laughing or physical exertion (such as when lifting weights at the gym) are usually benign, but may occur due to a Chiari malformation or less commonly subarachnoid haemorrhage. A complete neurological examination should be performed to look for loss of retinal venous pulsations (raised intracranial pressure), loss of pain and temperature sensation of the upper torso and arms, and weakness in the hands and arms (due to an associated syrinx in the spinal cord). Ask about a history of associated symptoms such as neck pain, gait imbalance, loss of fine motor skills in the hands, sensory disturbances in the hands, dizziness, visual disturbances, difficulty in swallowing or changes in speech.

WORST EVER HEADACHE

Despite what is suggested in many medical textbooks, asking a patient the leading question whether they are suffering their "worst ever headache" is not particularly helpful in formulating a differential diagnosis. However, the tenet that a very severe or worst ever headache of dramatic onset should automatically lead to the suspicion of a subarachnoid haemorrhage still generally holds in practice.

X, Y, ZZZZ

There is a strong association between sleep quality and headache. Regular, adequate sleep leads to fewer headaches, while both sleep loss and oversleeping are common headache triggers. Repeatedly waking from sleep with headache is a potential sign of obstructive sleep apnoea, especially if the patient is a habitual snorer. Hypnic headache is a rare, primary headache disorder where headache only develops during sleep and wakes the sufferer 1-4 hours after falling asleep, usually at the same time.

FURTHER READING

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Prepared: June 2018 Job No: MLT_GIB/AES/0001/18b

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QUORUM SENSING

DR ALFRED GRECH AND DR MICHAEL BALZAN

ABSTRACT

Quorum sensing is the intercellular communication used by a bacterial population, once it reaches a certain threshold, to collectively synchronize the expression of pathogenic traits, such as biofilm formation, swarming motility, and the production of virulence factors. This coordinated behaviour is mediated via small molecules called auto-inducers. In quorum sensing research, the aim is to inhibit quorum sensing molecular mechanisms, which could provide an alternative to the conventional antibiotic control of infections. Several natural (such as coumarin, curcumin, and garlic) and synthetic compounds have been suggested as quorum sensing inhibitors.

INTRODUCTION

Less than two decades ago, at the end of the 20th century, humanity started seeing the comeback of several lethal infectious diseases. Since then, it has become apparent that bacteria can adapt to the selective pressure of antibiotics. One of today's global concerns is that we are entering a post-antibiotic era with no knowledge on how to fight microbes.[1] The World Health Organization anticipates that antibiotic resistance will be one of the biggest problems, and if the existing trajectory is sustained, it could kill up to 1.3 million people in Europe by 2050. Humanity is being threatened by antibiotic-resistant bacteria and we need to do something about it fast. Other antimicrobial strategies are required, and quorum sensing might be one road to discover them.

What is Quorum Sensing (QS)?

It would be of little value for just a few bacterial cells to produce a gene product such as an extracellular enzyme or virulence protein, because the concentration of the protein would be too low to be effective. QS is a type of regulatory process that ensures that there is sufficient cell density (the quorum) before a particular gene product is made. Such a process allows bacteria to increase in numbers before starting to produce a specific gene product. Each species that uses QS produces a small signal molecule, called an autoinducer.

Autoinduction was discovered around 50 years ago in the Gram-negative bacterium *Vibrio fischeri*. *V. fischeri* is a bioluminescent symbiont of the Hawaiian bobtail squid, whose rich nutrients allow the bacteria to proliferate. Bioluminescence genes are expressed when the density of the bacteria is significantly high. Interestingly, the light produced serves as an anti-predatory response, stopping the squid from producing a shadow under the moonlight.

There are several molecular mechanisms for intercellular signalling.[2]

A. QS based on AHL (Acyl Homoserine Lactone) or 'autoinducer-1' (AI-1) system

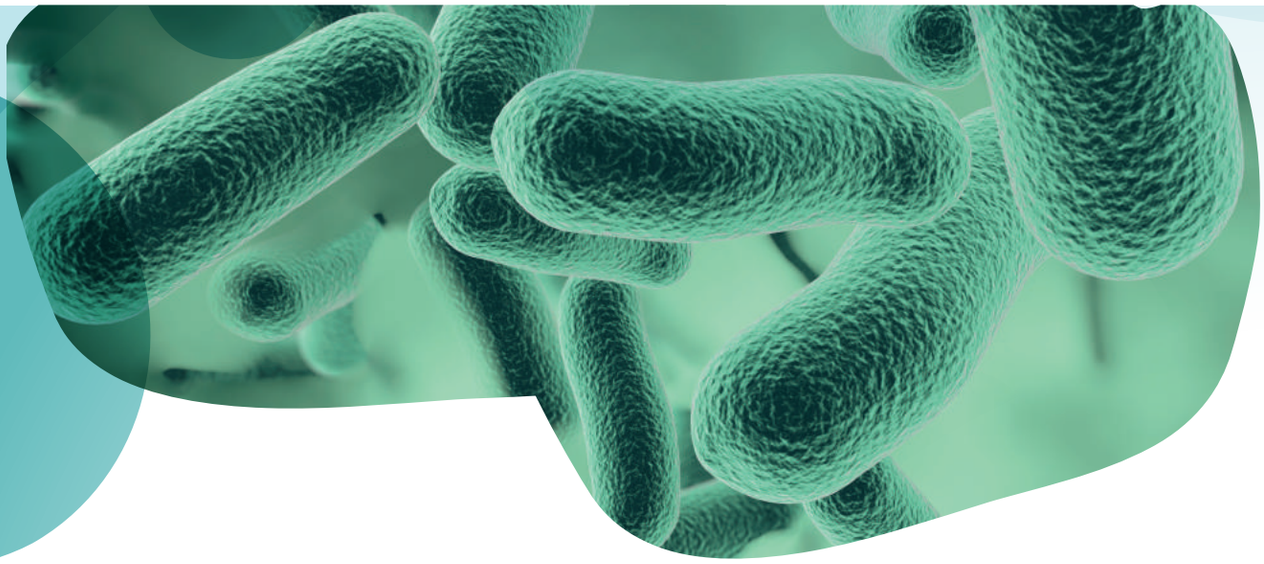
In Gram-negative bacteria, the signal molecule is acyl homoserine lactone, or AHL. When the AHL signal molecule reaches a threshold concentration, it binds to and activates a regulatory protein which then binds to a specific site on the DNA. The binding of this regulatory protein transcription activator results in the production of the specific quorum-dependent protein, as well as more enzymes to make the AHL.

B. QS based on autoinducing peptides (AIPs)

In Gram-positive bacteria, QS involves a different type of signal molecule. First, a precursor oligopeptide is cleaved into functional signal molecules of 10 to 20 amino acids. These molecules are transported out of the cell through a special transporter protein. When the signal oligopeptides reach a threshold concentration on the outside of the cell, they are detected by a sensor protein on the surface of the cell. When the oligopeptides react with the sensor protein, the protein becomes phosphorylated on the inside of the cell membrane. The phosphate is then transferred to a response regulator protein which allows it to bind to a specific site on the DNA. This binding results in alteration in the transcription of target genes. Finally, quorum-dependent proteins such as specific virulence factors are produced.

C. QS based on the 'autoinducer-2' (AI-2) system

Based on the molecule furanosyl borate diester, the AI-2 system is found in both Gram-negative and Gram-positive bacteria. For instance, it is found in pathogenic bacteria such as *Salmonella typhimurium*, *Streptococcus gordonii* and *Vibrio harveyi*.[3]



Depending on the cell density and threshold concentration, the Al-2 molecule changes between the inter- and intra-species signal, and is used to serve bacteria in their surrounding environment, including signal transduction.

D. Other QS systems

Over the last decades, other molecules have been identified; these include 4-quinolones, fatty acids, and the A-factor from *Streptomyces.*[3] Pyrones have also been recognised as QS signals in *Photorhabdus luminescens.*[4] In all probability, this only represents a small percentage of the metabolites involved in QS.

INTERFERING WITH QS SIGNALLING

QS signalling has provided important benefits to bacteria in their adaptation to changing environments, defence against competitors, formation of biofilms, and host colonisation. Several QS-controlled activities are involved in the pathogenic and virulence potential of bacteria. Indeed, understanding and targeting QS molecular mechanisms could provide an alternative to the conventional antibiotic control of infections. However, while bacterial QS inhibitors (QSIs) have been studied for their QS interfering capabilities, none have been applied in the clinical setting so far. In general, this is attributed to the co-existence of multiple AHL QS systems in individual bacterial species.

In principle, QSIs should inhibit the genes that are QS-controlled. Specifically, QSIs should target the QS regulator without detrimental effects on the bacteria. It is important that the essential life processes that aid bacterial growth are not disrupted by QSIs, because then the selective pressure to develop resistance is abated,[5] which is a key problem with many antibiotics.

In QSI research, one of the most commonly studied bacterial species is *Pseudomonas aeruginosa*. *P. aeruginosa* is a Gram-negative bacterium with three QS systems, namely Las, Pqs, and Rhl.[6] It is estimated that ~5% of the total number of genes in *P. aeruginosa* is controlled by QS. Critically, *P. aeruginosa* is responsible for a large number of nosocomial infections, and is particularly damaging for patients with weakened immune systems.[7] Therefore, intensive research efforts are focused on *P. aeruginosa* in particular, on both natural and synthetic QSIs.

QS Inhibitors

Both natural and synthetic compounds have been identified as QSIs.[5] In recent years, however, the focus may have shifted towards medicinal natural plants since they offer a phytochemical repertoire with microbial disease-controlling potential.[8] In part, this is due to the range of secondary metabolites found in extracts, which include alkaloids, flavonoids, phenolics, polyacetylenes, quinones, and terpenoids. Most of these compounds inhibited QS in screens that used AHL-dependent biosensor strains.

The Coumarin family of natural plant-derived compounds, for instance, possesses bioactive molecules that have been investigated for their efficacy as QSIs. Coumarin has been demonstrated to have anti-biofilm activity in *P. aeruginosa*, particularly in hydroxylated coumarins.[9] It has also been shown to reduce swarming motility.[10] Zhang et al. (2018)[11] have recently shown that in coumarin-treated *P. aeruginosa*, integral genes involved in QS are downregulated, further demonstrating the potential application of coumarin as a QSI.

Curcumin (a bright yellow compound found in turmeric) also has potential as a QSI.[12] Bahari et al. (2017) showed that *P. aeruginosa* QS is inhibited by sub-inhibitory concentrations of curcumin with azithromycin and gentamicin. Promisingly, curcumin has similar effects in the bacteria *Aeromonas sobria*[13] and *Streptococcus mutans.*[14] In keeping with this, in 2014 Packiavathy demonstrated that curcumin enhanced the susceptibility of a marker strain and uropathogens to conventional antibiotics.[15] On a side note, the antibiotic azithromycin has been shown to prevent *P. aeruginosa* ventilator-associated pneumonia by inhibition of QS.[16]

P. aeruginosa is also known to form biofilms in the cystic fibrosis lung. QS controls biofilm maturation. In a pilot trial, Smyth et al. (2010)[17] randomised over 30 patients to garlic or olive oil capsules (both 656 mg daily) to ascertain the QS inhibitory activity of garlic. In general, the clinical trial showed that garlic inhibits *P. aeruginosa* QS in cystic fibrosis – a result which should be further investigated in a larger trial. Intriguingly, Jakobsen et al. (2012)[18] determined that it is the sulfur-rich molecule ajoene in garlic that inhibits genes controlled by QS.

In another investigation, Rajkumari et al. (2018)[19] studied the pentacyclic triterpenes betulin and betulinic acid. Betulin, found in the bark of birch trees, can be converted to betulinic acid, which is a more active compound than betulin itself. In this study, the researchers reported that these two triterpenes, at sub-lethal concentrations, attenuated biofilm formation and the production of QS-regulated virulence factors in *P. aeruginosa*.

Lee et al. (2011)[20] showed that, at low concentrations (0.5% v/v), acacia and multifloral Korean honeys reduce biofilm formation in an *Escherichia coli* strain. Truchado et al. (2009)[21] also showed that chestnut honey and its aqueous extract inhibit QS in the bacteria *Aeromonas hydrophila*, *Erwinia carotovora*, and *Yersinia enterocolitica*. Specifically, these compounds degraded AHLs and inhibited AHL production by the bacterial strains.

Adonizio et al. (2008)[22] assessed six south Florida medicinal plants for their anti-QS activities against *P. aeruginosa*. Interestingly, each plant had a different effect on the *las* and *rhl* QS genes and their corresponding signals. In addition, all extracts inhibited QS genes and QS-controlled factors, with negligible effects on bacterial growth.

Furthermore, the essential oils of rosemary and tea tree, as well as resveratrol and extracts of bee pollen, pomegranate, and propolis were tested for their QS inhibitory activities.[8] Overall, the results revealed that the essential oils of rosemary and tea tree have the highest inhibitory activity, whereas pomegranate extract and resveratrol have the lowest anti-QS activity.

The list goes on and indeed, other sources are also being investigated like extracts from aquatic fungi.[23] However, in addition to natural QSIs, numerous synthetic compounds are being developed to target and disrupt genes vital to QS systems. For example, Qiu et al. (2019)[24] have synthesised compounds derived from quinoline that inhibit biofilm formation and virulence in *P. aeruginosa*, and disrupt *rhl* expression. In a different investigation, Welsh et al. (2015)[6] screened synthetic N-acyl l-homoserine lactones and identified compounds that can change the production of two *P. Aeruginosa* virulence factors: pyocyanin and rhamnolipid. Overall, their results suggest that designing chemical agents to disrupt QS signalling could be a functional strategy to combat this common opportunistic pathogen.

CONCLUSION

Although new synthetic and natural compounds are continually being tested for their QSI efficacy, existing drugs and compounds may also serve as prospective QSIs. Yang et al. (2009)[25] used a computer-aided screening method - on a database comprised of both natural compounds and existing approved drugs that share similar structural properties to known QSIs - to detect previously unidentified potential QSIs. Many QSIs have been recognised in recent years, and the number of QSI-related patent applications is rapidly increasing.[26] However, the potential of QSIs as future therapeutic strategies will rest upon the results of clinical trials in humans; this is the next step in QSI research but is to date effectively unexplored.

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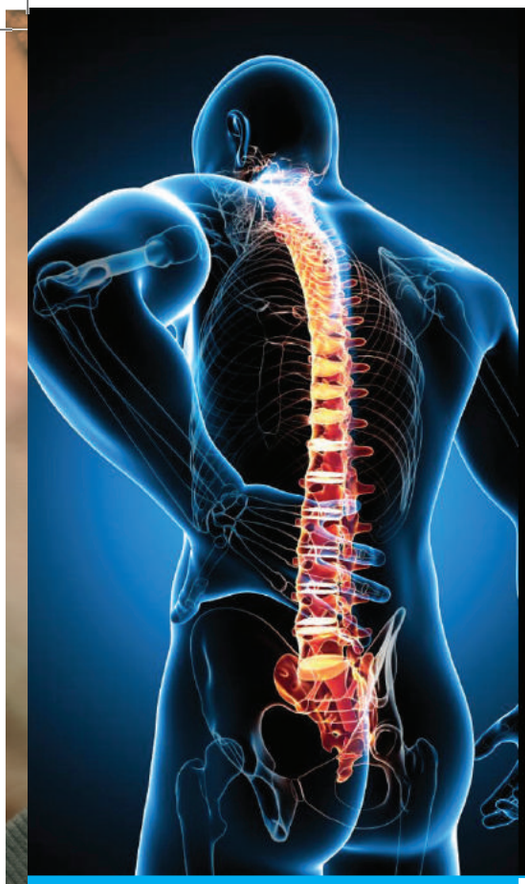

THESYNAPSE your Way eLEARNING

Management of Acute Pain

Dr Carmel Abela
Consultant Anaesthetist

DR CARMEL ABELA

Dr Abela is a Consultant Anaesthetist at Mater Dei Hospital who completed specialist training at the College of Anaesthetist in Dublin Ireland in 2002 after a 7 year specialist training program. During this period he also completed additional training in Intensive Care Medicine and in Pain Medicine. Dr Abela runs a Pain Clinic at Mater Dei Hospital that treats patients with chronic painful conditions and performs interventional pain procedures and neuromodulation therapies. Dr Abela is also an Intensive Care Consultant and for the last ten years held the position of ITU Lead Clinician. He also has a special interest in transplantation and in Patient Safety and chairs a committee for patient safety and quality of care.

Dr Abela graduated as Doctor of Medicine and Surgery from the Malta Medical School in 1991 and held positions as Secretary and then President of the Association of Anaesthetists Malta and also similar positions at the European Board of Anaesthesiology UEMS. Dr Abela was recently appointed deputy chairman of the Department of Anaesthesia, Intensive Care and Pain Medicine.

Acute pain is a symptom of disease that may be of new onset or an exacerbation of a chronic condition. Diagnosis of the underlying condition and treatment of the acute pain should be dealt with concurrently using a multimodal analgesia model by utilizing drugs and therapies that interfere with pain perception at different aspects of the pain pathway. Various medications may be used, each with their special properties but limited by their respective side effects and contraindications.

The caring physician should know when to refer to hospital and when to refer to a specialist in a timely manner. Reference is also made to the treatment of the neuropathic component of acute pain and the treatment modalities available to the caring physician.

LEARNING OBJECTIVES

- To understand in simple terms the complexity of dealing with acute pain
- To discuss the various treatment options and their side effects and contraindications
- To highlight the need for referral to specialist care and further investigations

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Consultant Psychiatrist

DR NIGEL CAMILLERI

Dr Camilleri studied Medicine and Surgery at the University of Malta where he was awarded an MD in 2003. He then started practicing medicine at St. Luke's Hospital, Malta and eventually started his psychiatry training at Mount Carmel Hospital, Malta in 2006.

In 2008 he moved over to Newcastle, UK and pursued training in psychiatry in the North East of England. Since 2015 he started working as a Child and Adolescent Consultant Psychiatrist at Mount Carmel Hospital Malta and St James Hospital, Malta. He has worked as a consultant psychiatrist in an adolescent in-patient and adolescent forensic in-patient unit in Middlesbrough, UK and as a Consultant in Child and Adolescent Psychiatry in the Tees Esk and Wear Valleys NHS Foundation Trust, at the Child and Family Department in Durham.

He is also an Associate Clinical Researcher at Newcastle University, currently working with Paediatric Bipolar Disorder Team on research projects in this field. He is currently working as a consultant psychiatrist and is the clinical lead for child and adolescent psychiatry at Mount Carmel Hospital, Malta. He has recently completed and was awarded an MD Newcastle, University, UK for his research. This consisted of a case control study and 2 year follow up study on this cohort of young people compared with a young people who attended a community mental health team. Dr Camilleri is the clinical lead within TAASC.

In this e-learning session Dr Camilleri gives a detailed overview of Attention Deficit Hyperactivity Disorder (ADHD) including its definition, presentation, aetiology, diagnosis and treatment options.

Dr Camilleri describes and discusses the importance of the use of a multi-modal assessment for the diagnosis and tailored management of ADHD according to individual requirements including the use of both non-pharmacological and pharmacological treatment options. In this session attention is also given to the presentation of ADHD in adulthood and on the importance of its adequate management to prevent it from negatively affecting the individual's quality of life.

LEARNING OBJECTIVES

To present

- the most up-to-date research on Attention Deficit Hyperactivity Disorder, in a succinct complete way,
- a description of the multi-modal assessment for ADHD,
- a complete description of treatment methodologies available for people with ADHD, and
- to answer questions often asked on ADHD and its treatment,

ACCREDITATION

Malta College of Family Doctors *0.5 Credits*

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Eating Disorders

Dr Anthony Zahra
Specialist in Psychiatry

DR ANTHONY ZAHRA

Dr Zahra underwent his undergraduate studies as a medical student at the University of Malta. After working as a medical doctor for two years; he started working and training within the mental health sector, successfully completing postgraduate psychiatry training in Malta and being elected a member of the Royal College of Psychiatrists (UK).

This was followed with a Master's degree in Gerontology with the University of Southampton with research on the mental health risk factors associated with long term nursing home placement in older adults. He has also completed a postgraduate certificate examining the philosophical aspects of psychiatry with the University of Lancashire and also completed higher certification in the use of Transcranial Direct Current Stimulation (TDCS).

As part of his work at the National Eating Disorders Centre, he has also received specialised training in the treatment of eating disorders and obesity through various exchanges with Italian eating disorder centres. Dr Zahra was elected board member of the Maltese Association of Psychiatry.

In this e-learning session Dr Zahra gives an overview of a number different eating disorders including their relevance, prevalence and presenting features. He also gives information on screening tools available which can be used in the community to screen for certain eating disorders gives an overview of different services available locally for the care of patients suffering from eating disorders.

LEARNING OBJECTIVES

- To obtain an overview of different eating disorders and common presenting features of these different eating disorders in the community
- To appreciate the role of screening tools for eating disorders in primary care practice
- To obtain a clearer perspective of the services being offered to patients with eating disorders in the local setting

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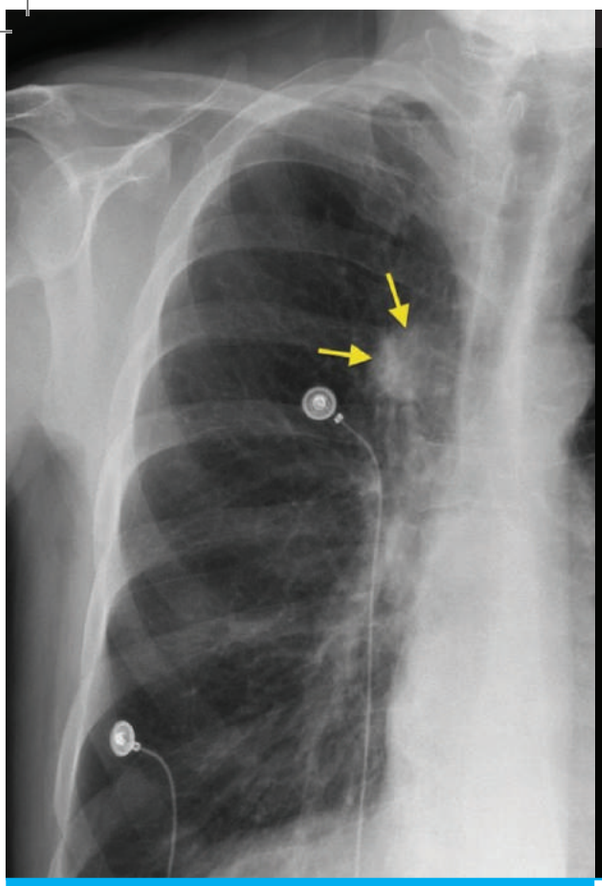

The Chest X Ray - a structured review

Dr Adrian Mizzi
Consultant Radiologist

DR ADRIAN MIZZI

Dr Mizzi obtained his medical qualification from the Malta Medical School in 1995 and pursued post-graduate training in Radiology in Glasgow, UK between 1999 and 2005.

He worked as a Consultant Radiologist at Hairmyres Hospital, Scotland between 2005 and 2007. He is presently a Consultant Radiologist at Mater Dei Hospital, a role which he has occupied for the past 10 years.

He is also a post-graduate training co-ordinator for radiology at MDH and is President of the Malta Association of Radiologists and Nuclear Medicine Physicians (MARNMP).

LEARNING OBJECTIVES

- To teach a systematic structured review system when looking at chest x-rays in order to minimize missing an important diagnosis e.g. lung cancer
- To appreciate the role which such a systematic review plays when assessing chest x-rays in the community
- To facilitate expedition of suspect cases to specialist services for formal work-up and diagnosis

ACCREDITATION

Malta College of Family Doctors *0.5 Credits*

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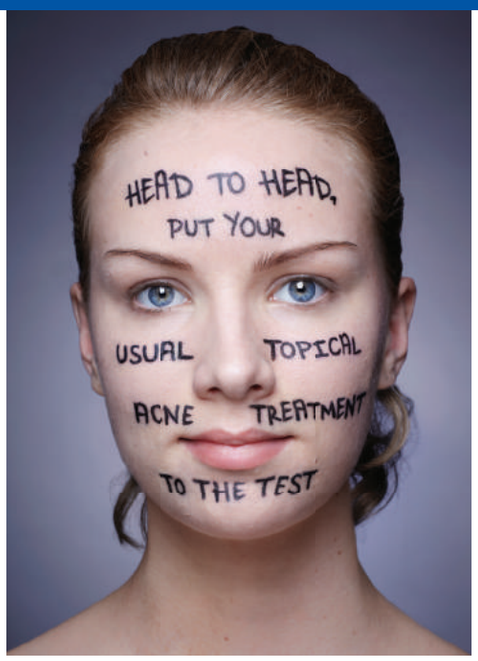
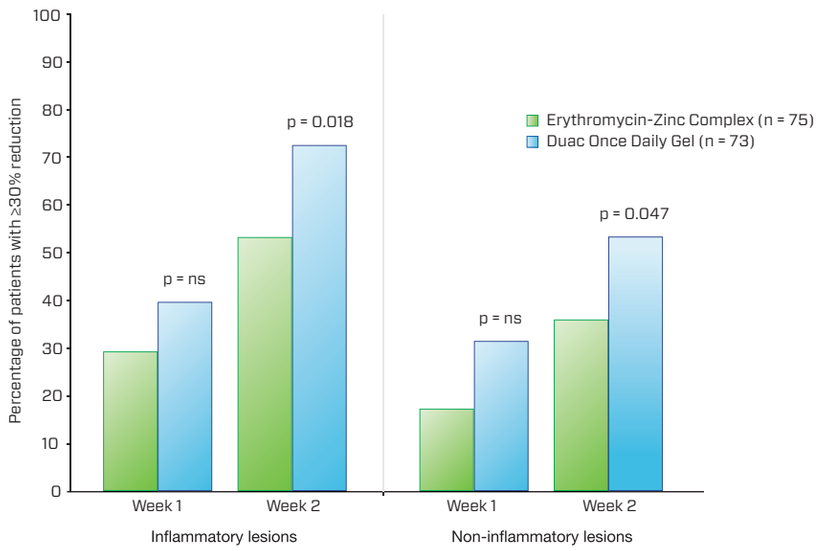
HEAD TO HEAD, DUAC WORKS FASTER THAN ERYTHROMYCIN-ZINC COMPLEX[1]





Graphs adapted from Langner A *et al.* JEADV 2007

- More patients with mild to moderate acne achieved at least a 30% reduction in inflammatory and non-inflammatory lesion counts at week 2 with Duac than Erythromycin-zinc complex[1]
- DUAC demonstrated a faster onset of action, reducing total lesion count in significantly more patients than Erythromycin-zinc complex at just 2 weeks[1]
- Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[4]

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[3]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin

• Gently pat dry

• Apply a thin layer of Duac gel on the affected area, not just the individual spots

TIPS[3]

If your patient's skin peels or becomes dry, they can try:
- Using an oil and fragrance-free hypoallergenic moisturiser
- Using Duac less often, or stopping for one or two days before starting again

DUAC ONCE DAILY GEL 10mg/g + 50mg/g ABRIDGED PRESCRIBING INFORMATION

Please refer to the full Summary of Product Characteristics (SPC) before prescribing

TRADE NAME: Duac Once Daily Gel 10mg/g + 50mg/g. **ACTIVE INGREDIENTS:** Clindamycin phosphate/anhydrous benzoyl peroxide. **PHARMACEUTICAL FORM:** Gel. **INDICATIONS:** Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. **POSOLOGY:** *Adults and Adolescents (12 years and over):* Once daily (evening) to affected area. Should not exceed more than 12 weeks. Applied in a thin film after washing gently with mild cleanser and fully drying. Was hands after application. **CONTRAINDICATIONS:** Hypersensitivity to active substances/lincomycin/excipients. **PRECAUTIONS:** Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated/broken skin. Caution in patients with a history of regional enteritis, ulcerative colitis, antibiotic-associated colitis, atopic patients, concomitant topical acne therapy. Increase in peeling and reddening will occur in most patients during first few weeks of treatment. If severe local irritancy, discontinue. Prolonged exposure to sun should be avoided. In patients with sunburn, this should be resolved before use. If significant diarrhoea/abdominal cramps occur, discontinue (symptoms may indicate antibiotic-associated colitis). May bleach hair or coloured fabrics. Patients with a recent history of systemic or topical clindaymcin and erythromycin are more likely to have pre-existing anti-microbial resistant *Propionibacterium acnes* and commmensal flora. Cross-resistance: May occur when using antibiotic monotherapy. **PREGNANCY/FERTILITY /LACTATION:** *Pregnancy:* only after careful risk/benefit assessment. *Fertility:* no data. *Lactation*: should not be applied to breast area. **UNDESIRABLE EFFECTS:** *Very common (≥1/10)*: erythema, peeling, dryness. *Common (≥1/100 & <1/10)*: burning sensation. *Refer to the SPC for full list of undesirable effects.* **LOCAL PRESENTATION:** 30g gel. **MARKETING AUTHORISATION NUMBER:** MA300/01401. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline UK Ltd. **Legal Category:** POM. **Date of Preparation:** September 2017.

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

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If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system: Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

References: 1. Langner A *et al.* JEADV 2007; **21**: 311-319. **2.** Duac 5% Summary of Product Characteristics, January 2015. **3.** Duac 5% Patient Information Leaflet, October 2014. **4.** Langner A *et al.* BJD 2008; **158**: 122-129

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For more information
https://gskpro.com/en-mt/products/duac/

Duac once daily gel
Clindamycin 1% and benzoyl peroxide 5%

Job no.: MLT_GIB/CBP/0002/17 Date of preparation: November 2017

AT THE CROSSROADS OF CHEMICAL PATHOLOGY AND BARIATRICS

DR MICHELLE MUSCAT,
ATTACHMENT WITH MR BENEDICT AXISA

Obesity afflicts a high number of individuals worldwide. Also, looking further into the local situation in Malta, there are alarming national statistics with regards to Maltese prevalence of obesity. This in turn poses a significant burden on health care given obesity is associated with multiple co-morbidities. Notable examples include type 2 diabetes, dyslipidemia, atherosclerosis, non-alcoholic steatohepatitis and sleep apnoea. When dietary, exercise and pharmacological regimes fail, certain patients may meet the criteria for Bariatric surgery which usually encompass those with morbid obesity having a BMI greater or equal to 40kg/m^2 or a BMI greater or equal to 35kg/m^2 which is medically complicated. Bariatric surgery has the potential to result in remission of type 2 diabetes.

During my bariatrics attachment at Mater Dei Hospital with Mr Benedict Axisa's bariatric team between October to November 2018 I had the pleasure of meeting the bariatric multidisciplinary assessment team which involved the surgical team, psychologist, dietician, anaesthetic teams, members of the sleep apnoea studies team and nursing teams who provide holistic patient management. The lead bariatric dietician and lead psychologist also host joint support groups on Mondays. During my attachment the Health Promotion and Disease Prevention Directorate and the European Association for the Study of Obesity (EASO) hosted a training course for health care professionals in the management of adult obesity which was very well received.

This short article looks further into relevant biochemical blood tests at the crossroads of chemical pathology and bariatrics. Standard biochemical laboratory tests such as lipid panels, LFTs and HbA1c, amongst others, guide general assessment and management of obesity. Clinical biochemistry tests may also be used to rule out secondary causes of obesity such as for example Cushing's syndrome, hypothyroidism and polycystic ovarian syndrome. These could include TFTs and a urinary 24-hour collection for free cortisol and hormonal assessments including LH, FSH and testosterone levels. Post-operative assessment of micronutrient and vitamin deficiencies may also rely on clinical biochemistry laboratory input. These deficiencies are even more likely to occur in malabsorptive procedures.

Certain other substances that are found in a person's blood may serve as biomarkers to guide diagnosis, management and occasionally help make prognostications. A brief literature review was conducted on PubMed articles in October 2018 taking as inclusion criteria articles having concurrently both the terms 'biomarker' and 'bariatric' in the title. Six publications are outlined below. This in turn looks at the crossroads of bariatrics and chemical pathology from a more academic perspective.

The body has various apolipoproteins that participate in lipoprotein metabolic pathways. Apolipoprotein C3 (Apo-CIII) has been described as acting as an inhibitor of lipoprotein lipase and hepatic lipase and is known to play a role in the regulation of metabolism of triglycerides. Apo-CIII glycoisoforms after bariatric surgery were assessed in relation to glycomic changes. Bariatric surgery appears to alter the isoform distribution in the direction of the non-obese.[1] Most health care professionals know of *Helicobacter pylori* and its association with gastric ulceration and gastritis. Biomarkers such as *Helicobacter pylori* antibodies, basal and stimulated gastrin-17 and pepsinogen I and II have also been investigated as potential replacements of preoperative esophagogastroduodenoscopy for bariatric surgery, where they showed promise as surrogate markers.[2] The complement pathways such as the classical and alternative pathways are well known for their role in immune regulation. Plasma complement factor 3 showed a strong association with post-bariatric surgery insulin resistance.[3] Epithelial intermediate filament proteins or cytokeratins are useful for immunohistochemistry and tumour detection diagnostics. In 2008 levels of cytokeratin 18 fragments have been suggested to potentially be useful as a novel biomarker of non-alcoholic fatty liver disease (NAFLD) in bariatric patients.[4] The receptor for advanced glycation end products or RAGE has been implicated in various diseases. The soluble form of RAGE (sRAGE) has been investigated in various clinical scenarios for associations and diagnostic utility. sRAGE may help identify those individuals who are expected to gain greater benefit from bariatric surgery.[5] Neutrophil gelatinase-associated lipocalin or NGAL is a newer marker for the diagnosis of kidney disease and in general

has been advocated as playing a role in the earlier detection of kidney injury. A paper was also written in 2013 about the putative benefit of using urinary NGAL in earlier detection of acute kidney injury in specifically bariatric patients.[6]

A separate literature review was again conducted via PubMed database this time expanding inclusion criteria to the terms 'biomarker' and 'obesity' in the title. This in turn yielded a far more extensive range of published papers in the literature. To date numerous papers were published detailing potential associations between biomarkers and obesity.

Leptin has been extensively studied as a hormone that regulates hunger together with energy consumption. Adiponectin is an adipokine produced by adipose tissue and plays a role in glucose and fatty acid metabolism. Larsen et al. suggest that the leptin to adiponectin (L:A) ratio can be used as a surrogate marker to uncover at an earlier stage metabolic derangements in obese individuals.[7] In another publication Tacke et al. discussed adipokine Wnt1 inducible signalling pathway protein 1 (WISP-1)/CCN4 as a potential novel obesity biomarker.[8] N-Acylethanolamines play various roles in energy expenditure. Fanelli et al. wrote about the usefulness of N-Acylethanolamine profiling in obesity.[9] Identification of miRNA biomarkers as a differentiation factor between obesity and metabolic syndrome would provide greater insights into pathophysiology. O'Neill et al. identified miR-758-3p, as related to cholesterol efflux regulatory protein/ ATP-binding cassette transporter expression, which could aid diagnosis of developing metabolic syndrome in the setting of obesity.[10]

Other interesting assessment methods have also been reported such as the measurement of the islet amyloid polypeptide, amylin, via the use of an amperometric immunoassay screen-printed carbon electrode and electropolymerized carboxylated polypyrrole.[11] In keeping with this, the immunohistochemical expression of PGC1 alpha was assessed from fat tissue specimens collected during bariatric surgery to elucidate patterns. The authors concluded that PGC1alpha may potentially constitute a therapeutic and preventive marker in obesity-related comorbidities.[12]

This is just a snapshot of some implicated biomarkers since other candidate substances have been described earlier in the literature.

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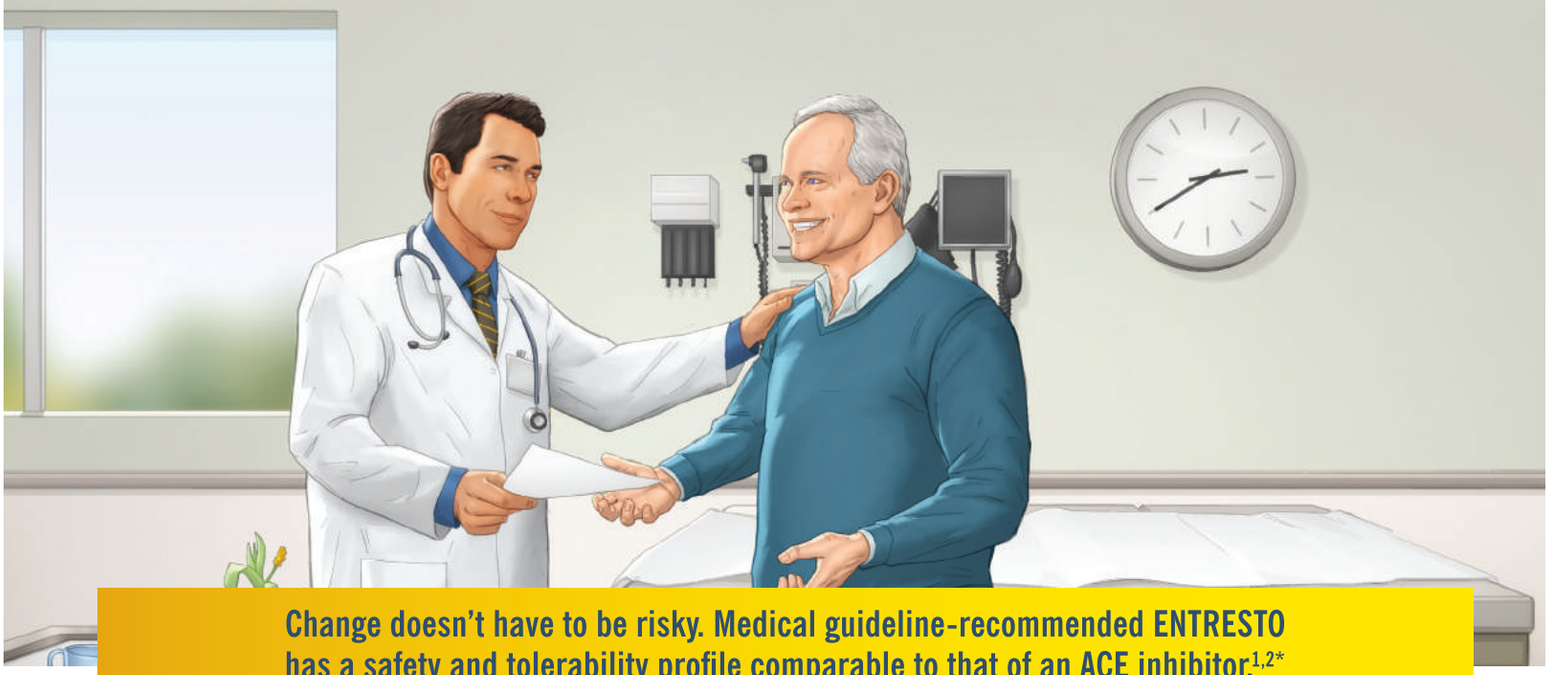

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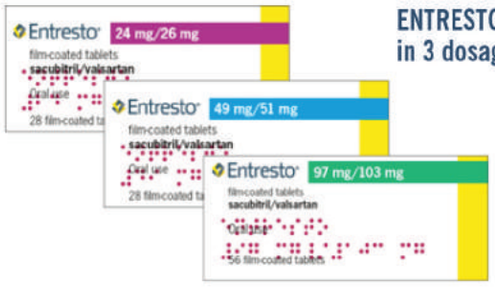

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Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Contraindications: 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 m2). 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. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing 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 Entresto 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 Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto 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. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto 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 of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto 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 Entresto because it is a neprilysin substrate. 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 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto 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 Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto 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 Entresto 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 Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto 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 Entresto 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 Entresto 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. 2018-MT-ENT-30-APR-2018

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IS ANTI-AGEING THERAPY MEDICAL FICTION?

PROF. ALBERT CILIA-VINCENTI

The quest for an immortality elixir has been around for centuries. Is anti-ageing, regenerative medical intervention, still in the realm of science fiction? We're not talking of cosmetic surgery here, obviously. Some scientists believe that human immortality is possible in the future. If all our tissues have stem cells for replacement of worn out ones, why do we age and die? Even if immortality is not ultimately possible, are there any recent advances in understanding ageing and deteriorating function at cellular level? Extending useful, healthy life without added strains on health systems, would be a significant medical advance.

For some time we believed that longevity was directly related to the telomeres at both ends of chromosomes and that the rate they wear down determined longevity. A more recent theory explains the ageing process in terms of the deterioration of the process by which aged, worn-out, *senescent* cells are removed to make way for stem cell-derived new ones.

In young tissues, senescent cells are quickly broken down and their constituent parts taken up and used by surrounding healthy cells by the combined processes of apoptosis (programmed cell death) and autophagy, in a similar way that an old car is dismantled and many of its parts used in other cars.

It appears that the organ changes we associate with ageing are related to an accumulation of senescent cells, which secrete protein-degrading enzymes that damage nearby healthy cells and produce chronic low-grade inflammation, damaging mitochondria and DNA and causing telomere dysfunction.[1-4]

Senescent cells also damage stem cells, limiting a tissue's regenerative capacity.[5] If accumulation of senescent cells causes age-associated diseases, could their removal improve health and slow ageing? We now have laboratory animal studies answering that question in the affirmative.

For the first time, it has been possible to remove senescent cells to make way for stem cells to replace them with new ones. The compounds used are now called *senolytics*. Mayo Clinic researchers, in a series of elegant experiments, have made almost unbelievable discoveries about the impact of senescent cells on normal healthy tissue.[1,3] They found that transplanting just a few senescent cells into young mice triggered accelerated ageing processes seen in older animals. The greater the number of senescent cells, the greater the deterioration.[1] Also, just a few senescent cells produced a snowball effect, triggering senescence in a large number of previously healthy cells. Senescent cells accelerated the ageing process and its associated problems.

Interestingly, a high-fat diet appeared to amplify the negative impact of senescent cells. With the mice on such a diet, even fewer senescent cells were needed to produce age-related ailments. It had been known that a high-fat diet and obesity induced cellular senescent in laboratory animals. But a dramatic finding was that the mice with senescent cells had a 5-fold higher risk of death compared to control mice.[1]

The researchers sought a solution to this identified senescent cell problem by testing a combination of two compounds with senolytic action, *quercetin* – a flavonoid found in apples, onions and other plants – and *dasatinib*, a tyrosine kinase inhibitor licensed for myeloid leukaemia treatment. This combination had a remarkable senolytic action, reducing senescent cell numbers and decreasing their production of proinflammatory signalling factors.[6]

When elderly mice were given the senolytic combination for four months, it increased their walking speed, improved their endurance, boosted grip strength and enhanced daily activity levels.

Giving the senolytics to elderly mice also increased their life span by 36% and reduced their risk of dying by 65%, compared to controls. The animals lived longer and healthier. The Mayo Clinic researchers referred to this result as "remarkable", indicating that senolytics can improve survival and reduce overall disability – with interesting potential implications for humans.

A second Mayo Clinic study focused on another serious consequence of ageing – dementia.[3] A strain of mice bred to produce tau protein was used. Tau protein build-up in the brain is a structural hallmark of Alzheimer's disease, and this animal model exhibited high levels of neurofibrillary tangles, neurodegeneration and loss of cognitive function by early middle-age.[3]

The presence of senescent cells in the brain was found to increase neurodegeneration and, the larger the number of senescent cells, the higher the levels of tau and neurofibrillary tangles. The brain size was also smaller with marked neuronal degeneration in the hippocampal memory centre.

Amazingly, the combination quercetin-dasatinib senolytic agent was found to remove these senescent cells from the brain, including the hippocampus, with a consequent reduction of neurofibrillary tangles and tau aggregation. Removing the senescent cells lessened short-term memory loss and prevented the neurodegeneration seen in control untreated animals.

These remarkable findings in an animal model will inevitably trigger pharmaceutical research into safe anti-ageing senolytic drugs for humans. Extrapolation of the animal experiment results to humans would suggest an average healthy lifespan of 110 years and beyond.

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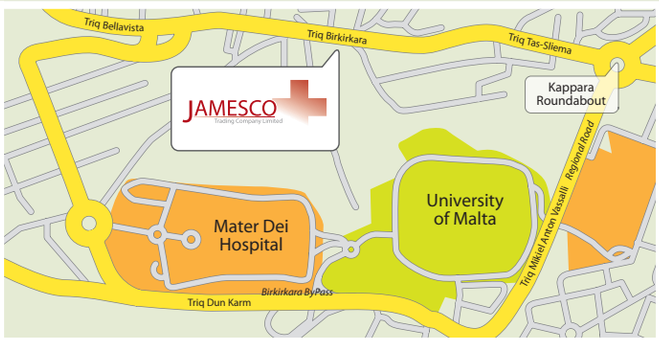

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IL-POLITIKU

Dr Ian Ellul catches up with **DR DEO DEBATTISTA**, a family doctor and Parliamentary Secretary for Consumer Rights, Public Cleansing and Support for the Capital City within the Ministry for Justice, Culture and Local Government.

TS: THIS YEAR YOU WILL BE 56 YEARS. DESCRIBE DR JUDE TADDEO DEBATTISTA IN ONE SENTENCE.

I have not heard my full name for a long time ... Jude Taddeo Debattista. You compel me to delve into my past. My mother had a very bad obstetric history. She gave birth to her first two sons who died immediately after birth. However, my mother did not lose hope and made a pledge to the patron saint of lost causes, Saint Judas Taddeus, that if she ever managed to give birth without any complications she would name that child after him. So when I was born – delivered with the now obsolete high forceps procedure – she kept her promise and named me Jude Taddeo. After my birth, my mother also had a set of twins, also boys, of whom only one survived.

Returning to your question, I would describe myself as a doctor who evolved into a politician to behave like a doctor.

TS: YOU INITIALLY WANTED TO BECOME A LAWYER. HOWEVER, YOU BECAME DOCTOR SIMPLY BECAUSE YOUR MOTHER ADVISED YOU TO FOLLOW THE ADVICE OF FR DOMINIC SCERRI – THE RECTOR OF YOUR SECONDARY SCHOOL. WHAT ARE YOUR REFLECTIONS ON THIS?

Being born and bred in Valletta, it was natural that I receive my primary and secondary education at St Albert the Great college in Old Bakery Street. In Form 3 we had to choose between science and arts. Now, I remember watching a popular TV series - in the seventies - whose protagonist was a very skilled lawyer, Dr Tony Petrocelli, who used to defend the weak and oppressed. This character, interpreted by Barry Newman, convinced me to choose arts to pursue the profession of Doctor of Laws. However, when I spoke to Fr Dominic Scerri - who was my Rector - of my choice, he cajoled me to pursue sciences to become a doctor instead. My mother echoed his advice. And so be it. I became a Doctor of Medicine.

Looking back I must admit that Fr Scerri's foresight was correct since studying medicine was probably my best decision ever. Indeed, after graduating I started training in surgery since I aspired to specialize as surgeon. I even made the necessary exams to further my studies in the US. Nonetheless I had to relinquish this move for medical and personal reasons. Thus I chose to specialize as family doctor in Malta. Fast forward to 2013, when I was planning to cross the sea again, this time to Canada to practice as family doctor; I felt that I needed a change. However, I was elected to parliament. Again in 2017, my family decided that if I were not elected, we would move to Canada. But here I am!

TS: YOU HAVE COME A LONG WAY FROM YOUR HUMBLE ORIGINS. YOUR FATHER WAS A MOST INDEFATIGABLE COOK AND YOUR MOTHER A HOUSE-WIFE. HOWEVER, BOTH YOU & YOUR BROTHER – A BANK MANAGER - HAVE CLIMBED EXTREMELY WELL THE SOCIAL LADDER ...

My father was a workaholic, working split shifts. His father - my grandfather - was captured and made prisoner of war in North Africa and when he was released and returned to Malta, he suffered from what may be known now as post-traumatic stress disorder. He died shortly after. My father was thereby forced to leave school and start work; they lived during the second World War. On the other hand, my mother also lost her mum at a young age and being the eldest, was expected to go out to work. This she did.

Both parents, due to the aforementioned life events, were early school leavers. In keeping with this, the first books which our house saw were *Janet and John*, which was a series of reading books for children. I was, and still am, an avid reader.

TS: AM I CORRECT TO SAY THAT YOU GOT YOUR STAMINA FROM YOUR FATHER AND AMBITION FROM YOUR MOTHER?

I guess so.

TS: YOU LIKE READING, DANCING, PLAYING FOOTBALL ... WHAT ELSE DO YOU ENJOY DOING?

I simply live for those few hours during the week when I go out for a good meal with my wife, just the two of us.

TS: HOW DO YOU DEFINE A GOOD POLITICIAN? DO YOU CONSIDER YOURSELF AS SUCH?

In my opinion, a good politician is one who remembers to be good despite being a politician; however, how can I judge myself? Only the electorate can.

TS: IS THERE A PERSON WHO IS YOUR ROLE MODEL?

It might sound obvious but I would definitely mention Dr Joseph Muscat. In my opinion he is a political genius. Having worked closely with him I must say that Dr Muscat has outstanding analytical skills in that he manages to analyze thoroughly any situation or challenge which presents itself. Experiencing him at work is similar to seeing a dissection; he manages to conduct a 360-degree analysis in a short period of time. I am lucky to work with him since his strategic skills are a constant learning experience.

TS: YOU HAVE TWO CHILDREN. WILL THEY FOLLOW ANY OF YOUR FOOTSTEPS?

My daughter currently studies medicine whilst my son has entered a different field and is doing a post-grad.

TS: IF YOU WERE TO EXIT POLITICS TODAY, WHAT DO YOU THINK WILL BE YOUR LEGACY?

The first is the introduction of medical cannabis, that is still picking up. We launched a consultation process on two important pieces of legislation, which eventually were passed in parliament, [1] *The Production of Cannabis for Medicinal and Research Purposes Act [Chapter 578]* and [2] *Act No. XXXII of 2018 to amend the Criminal Code, Cap. 9, the Drug Dependence (Treatment not Imprisonment) Act, Cap. 537 and to provide for other matters dealing with them or ancillary thereto.*

I would also mention *The Disposal and Collection of Waste in Valletta Regulations, 2018 [SL 206.02].* Amongst other things these regulations state that commercial waste collection can only be done between 3pm and 5pm and 12am and 3am from designated spaces. Before this legislation, refuse collection trucks being paraded through Republic Street during commercial hours was a common eyesore.

At this stage, I must add that Valletta has improved drastically during these last five years or so, most notably from the investment poured in it as part of the European Capital of Culture project. In all fairness the bid was made by the previous administration but the current administration managed to successfully sail the boat in port. Today we have more than 250 catering outlets and 30 boutique hotels. For comparison's sake, five years ago not even one boutique hotel was present.

TS: COMING TO POLITICS, YOU ENTERED POLITICS IN 2013, MAYBE MOTIVATED BY YOUR PREVIOUS DISCUSSIONS WITH THE LATE DR KARL CHIRCOP. IN KEEPING WITH THIS, BETWEEN 2013 AND 2017 YOU HAVE INCREASED YOUR TOTAL VOTE COUNT FROM 4473 TO 5734. ANY REFLECTIONS?

This is multi-factorial. I continued to practice as doctor which is something which patients appreciate. Also, the leader of the Labour Party traditionally contests the 1st district, which is the district from where I get elected. Although in 2013, the deputy leader Louis Grech contested the 1st district, I was lucky enough that in 2017 both the leader and deputy leader chose to contest other districts. I reaped the benefit of this, especially since many people seemed to wish to elect someone who was born and bred in Valletta.

You mentioned Dr Karl Chircop. If he were still amongst us, I would certainly not have stepped into politics; I would have chosen to help him instead. We were best of friends. Following his steps into politics is also my own way to commemorate this fine gentleman and true friend.

TS: ARE YOU ALWAYS IN AGREEMENT WITH YOUR DIRECT MINISTER, DR OWEN BONNICI?

Always. Dr Bonnici is pragmatic, a good mentor and allows you to work under your own steam. It is common practice for a newly-elected MP to first become a back bencher, then become appointed to a parliamentary secretary role and then eventually Minister. So, being elected for the second time running, I was lucky enough to be promoted to a parliamentary secretary role and assigned to work with Dr Bonnici as Minister.

TS: YOU COME FROM A VERY CATHOLIC BACKGROUND... EDUCATED AT ST ALBERT'S IN VALLETTA, A REGULAR CHURCH-GOER... ISN'T THE LABOUR PARTY TOO PROGRESSIVE FOR YOU? AFTER ALL THE LABOUR PARTY INTRODUCED, FOR EXAMPLE CIVIL UNIONS FOR SAME-SEX COUPLES AND THE MORNING-AFTER PILL. ON THE OTHER HAND, IF A FREE VOTE IS TAKEN ON ABORTION, HOW WILL YOU VOTE?

I am against abortion in all circumstances and without any exception; this is also the stance of the Labour Party, as of today. I am also a firm believer in justice. As politicians we must act in a just manner so that no-one gets hurt or is left lagging behind which is why we introduced legislation, which although may be viewed by many as progressive, is fair and just. Ultimately, the introduction of such 'progressive' measures was only a matter of time. Abortion is a totally different matter both to myself and the Labour Party; I reiterate that both myself and the Labour Party are against abortion.

I WILL READ THE SYNAPSE JOURNAL BECAUSE...

Your medical journal keeps me up-to-date. I also appreciate your professional CME videos which I must say are of the same standard of other accredited medical websites such as Medscape and BMJ Learning. However, in your case it is more pleasing since I see familiar faces like Dr Herbert Felice, Dr Robert Xeureb and the like. Keep up your good work!

DR PIERRE VASSALLO

ULTRASOUND ASSESSMENT OF RIGHT UPPER QUADRANT ABDOMINAL PAIN

• PART II •

Part 1 of this article discussed the importance of having an efficient diagnostic algorithm for right upper quadrant (RUQ) abdominal pain, since it is one of the most common presenting complaints to any clinic or emergency department. While acute cholecystitis is the most frequent cause of RUQ pain, more than a third of cases are due to other conditions. The same article also showed that abdominal ultrasound (US) is the imaging modality of choice because it is easily accessible, rapid, cost-effective, and safe since it involves no ionising radiation or potentially nephrotoxic intravenous contrast agent.[1] Abdominal US visualises multiple upper abdominal organ systems that could be the source of the patient's pain.

Part 1 of this article also described the US findings related to the biliary and hepatic causes of RUQ pain. The present Part 2 will discuss US findings seen with pancreatic and gastrointestinal causes, while a final forthcoming Part 3 will deal with adrenal, renal, thoracic and vascular causes of RUQ pain.

PANCREATIC CAUSES OF RUQ PAIN

Pancreatitis usually presents with epigastric pain radiating to the back, but it may also present with RUQ pain. Pancreatitis is best imaged with computed tomography (CT) and magnetic resonance imaging (MRI). However, US is often the first investigation to suggest that there is a pancreatic problem particularly where symptoms are atypical.

Acute pancreatitis may be due to an obstructing gall stone, alcohol use or use of certain drugs such as steroids and sulpha-containing medications. It may also be idiopathic. Visualisation

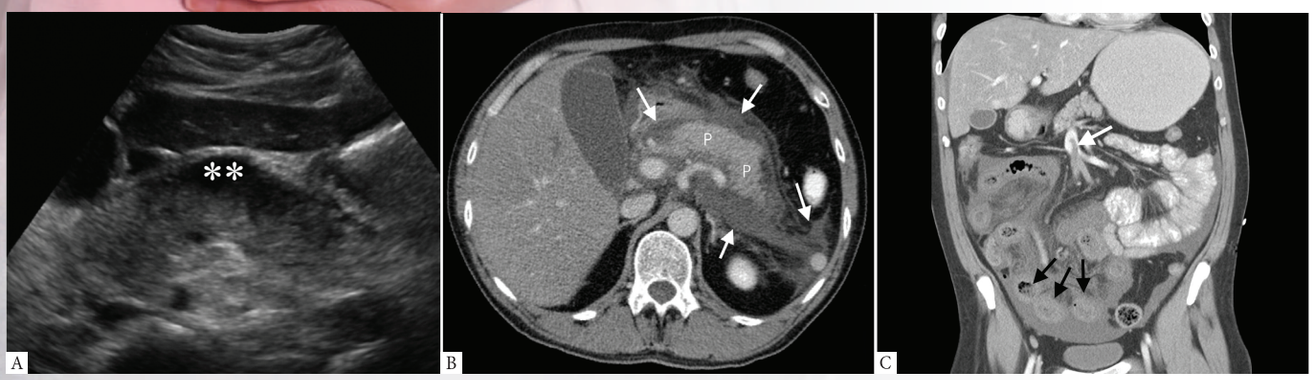

Figure 1a. Transverse US scan of the pancreas (**) showing a hypoechoic focus in the neck of the pancreas. This was confirmed on CT to be due to focal pancreatitis. CT or MRI is needed to distinguish focal pancreatitis from a pancreatic neoplasm and to assess the proportion of necrotic versus viable pancreatic tissue. **1b.** Contrast-enhanced CT scan showing enhancing viable segments of the pancreas (P) from necrotic components/peripancreatic fluid (arrows). **1c.** Contrast-enhanced CT coronal reconstruction showing thrombus in the superior mesenteric vein (black arrow) and oedematous small bowel loops (white arrows).

of the pancreas in US may be limited by an overlying gas-filled stomach or transverse colon. However, the head and neck of the pancreas are visible on US in most cases and acute pancreatitis can readily be detected and referred for further evaluation with CT or MRI.

In acute pancreatitis, the pancreas may appear enlarged, hypoechoic and shows ill-defined margins often with peripancreatic fluid collections. Pancreatitis may be focal (Fig 1a) and further evaluation with CT or MRI is needed to distinguish this entity from a pancreatic neoplasm. CT or MRI is also required to assess the extent of pancreatic damage as both exams distinguish viable (perfused) pancreatic segments from non-perfused/necrotic components (Fig 1b). Mesenteric vein thrombosis may complicate acute pancreatitis and may be seen on US. However, this complication may be more readily evident on CT or MRI (Fig 1c).[2] In contrast, gall stones that could be causing the pancreatitis are more readily visualised with US.

Pancreatic cysts are asymptomatic in 70% of cases. They are mostly benign, and when they cause pain, are more likely to be malignant. Acute RUQ pain may be the presenting feature in case of intra-cyst haemorrhage, infection or secondary to obstruction of the pancreatic or biliary tree. Pancreatic cysts can be readily visualised with US if located in the head and neck of the pancreas (Fig 2). CT or MRI will usually be required to detect cysts located in the pancreatic body or tail; CT and MRI are more accurate for monitoring cyst size and for distinguishing cysts from tumours.

Pancreatic neoplasms may be solid or cystic. Adenocarcinomas are the most common solid tumours of the pancreas and are a leading cause of death due to tumor aggressiveness and often late diagnosis. Other solid pancreatic tumours include neuro-endocrine tumours, solid pseudopapillary tumours, pancreatic lymphoma and metastases. Cystic pancreatic neoplasms include serous cystadenomas, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms.[3]

Since most pancreatic adenocarcinomas are in the pancreatic head, the typical clinical presentation is painless jaundice, which occurs due to obstruction of both pancreatic and biliary trees. Pain often develops late and is due to dorsal infiltration into the splanchnic plexus and the spine. On US, a pancreatic neoplasm generally appears as a hypoechoic and hypovascular mass (Fig 3a) that may impinge upon the portal venous vessels, the biliary tree and main pancreatic duct. Changes in the biliary and pancreatic ducts are best assessed with MR imaging using MRCP (magnetic resonance cholangio-pancreatography) sequences (Fig 3b). CT or MRI is required to evaluate vascular encasement as well as local and distant metastatic disease, all of which determine resectability of the tumour (Fig 3c).

GI CAUSES OF RUQ PAIN

While many radiologists consider US as being of limited use for the analysis of the stomach and bowel, many gastrointestinal conditions are readily detected by US. These include neoplasms, bowel obstruction, bowel perforation, subacute appendicitis and hepatic flexure colitis.

In 14% of patients presenting in an emergency department with abdominal pain, the cause is subacute appendicitis. While the pain from a normally-located appendix usually presents around the umbilicus and the right iliac fossa, pain from a superiorly displaced appendix, such as may occur with a high-riding caecum, prior surgery or pregnancy, will be located in the RUQ. Acute appendicitis is the most common surgical emergency during pregnancy. Early detection is crucial as there is a 10-15% perforation rate with an associated 35-55% foetal mortality rate. US or MRI must be used to avoid exposure of the foetus to ionising radiation. Reported mean sensitivity and specificity of US for the detection of acute appendicitis during pregnancy is 87% and 97% respectively.[4] The full thickness measurement (outer wall

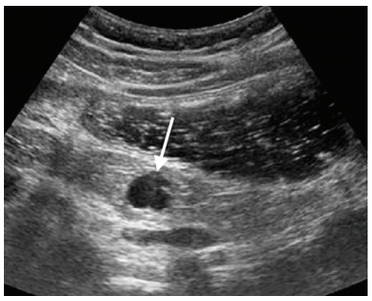

Figure 2. Transverse abdominal US scan through the pancreas showing a small cyst in the pancreatic neck (arrow).

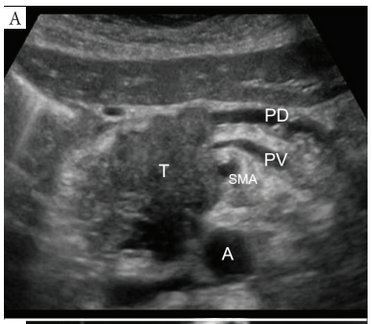

Figure 3a. Transverse US scan through the pancreas showing a pancreatic head tumour (T) with a dilated main pancreatic duct (PD). PV is the portal vein, SMA superior mesenteric vein and A aorta.

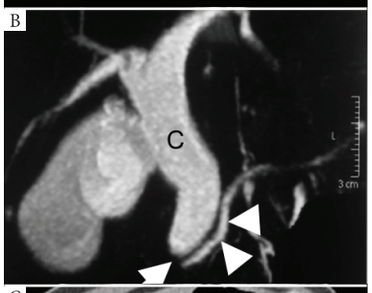

Figure 3b. MRCP sequence showing a dilated common bile duct (C) and main pancreatic duct (arrowheads). Abrupt obstruction of the main and pancreatic ducts (arrow) correlates with the site of the pancreatic head tumour.

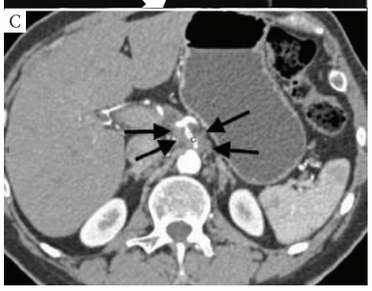

Figure 3c. Transverse arterial-phase contrast-enhanced CT scan showing the coeliac artery (C) encased in tumour (arrows) that has spread by contiguous extension from a pancreatic neoplasm (not shown here).

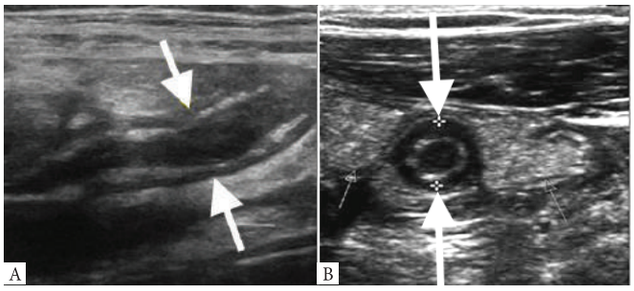

Figure 4a: US scan through the long axis of an inflamed (thickened) appendix (arrows). **4b:** US scan through the short axis of an inflamed appendix (arrows) demonstrating a targetoid appearance.

to outer wall) of a normal appendix should not exceed 7mm; thicknesses in excess of this, measured on US, are suggestive of appendicitis (Fig 4a). The appendix also shows a targetoid appearance (Fig 4b), absent peristalsis and non-compressibility on US. Tenderness over the appendix elicited by the compressing US probe is also a sign of appendicitis. US may also demonstrate an appendicolith, inflammation of the adjacent caecum and mesentery and para-appendiceal fluid. Abundant para-appendiceal fluid or a discontinuous wall of the appendix should raise the suspicion of perforation.

Hepatic flexure colitis, whether in isolation or as part of diffuse colitis, may result in RUQ pain; it may be due to infectious, inflammatory or ischaemic causes or as part of diverticular disease. On US, the normal anterior colonic wall is thin and abuts intestinal contents which are hyperechoic; the latter usually obscure the posterior wall due to dorsal shadowing (Fig 5a). Colitis leads to concentric thickening of the bowel wall with a central echogenic mucosal lining and a visible posterior wall (Fig 5b). Paracolic fluid may be present and the possibility of abscess formation must be considered. Distinction of infective colitis from that related to inflammatory bowel disease (e.g. Crohn's disease

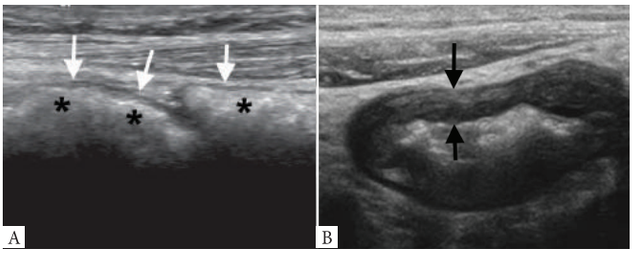

Figure 5a: Longitudinal US scan through a normal ascending colon. The anterior wall is thin and hypoechoic (arrows). Deep to the anterior wall, echogenic gas (*) obscures the posterior wall. **5b:** Transverse US scan through the ascending colon showing a thickened bowel wall with central echogenic mucosa (targetoid appearance) and visibility of the posterior wall.

or ulcerative colitis) is not possible based on US findings, but the clinical history and symptomatology my assist in distinguishing these entities. CT or MRI is more useful for detecting skip lesions, transmural extension of inflammation, strictures, fistulae and abscesses, which are characteristic of Crohn's disease.

While diverticular disease is best diagnosed and its extent best assessed with CT or MRI, US may be the first step to detect an inflamed colonic diverticulum that presents with

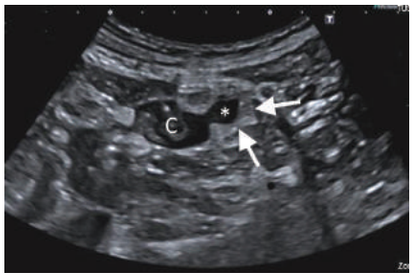

Figure 6. Transverse US scan through the RUQ showing the ascending colon (C) and an inflamed fluid-filled diverticulum (*) surrounded by inflamed echogenic omental fat (arrows). Tenderness was elicited during compression with the examining US probe.

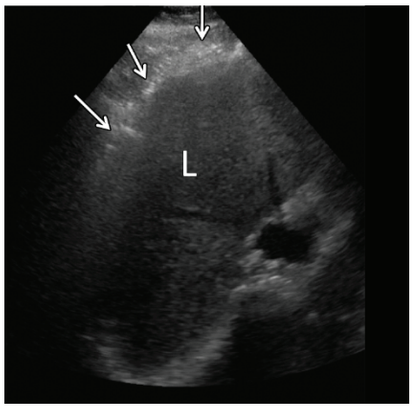

Figure 7. Transverse US scan through the right hypochondrium showing the liver (L) and echogenic gas bubbles (arrows) between the liver and the diaphragm.

RUQ pain. Diverticulae are most common in the sigmoid colon (75%) with only 5% occurring in the ascending colon.[5] However, an inflamed diverticulum close to the hepatic flexure of the colon will present with localised tenderness and can be detected on US (Fig 6).

Free peritoneal gas originating from a perforated visceral organ may be evident on US and should be actively sought in the presence of acute clinical peritoneal signs and a thickened visceral organ seen on US (Fig 7). Any suspicion of intestinal perforation should lead to further urgent evaluation with CT. CT will help to confirm the presence of free peritoneal gas and to identify the location and cause of the intestinal perforation. It will also distinguish free gas from gas in the bowel wall (pneumatosis intestinalis), which occurs in necrotizing enterocolitis due to bowel infection or ischaemia.

CONCLUSION

Pancreatic and gastrointestinal causes of RUQ pain are common, and their presence can be readily detected or at least suggested by US. Further evaluation with CT or MRI is often required to confirm the diagnosis and to detect complications. The next and final part of this article will discuss adrenal, renal, thoracic and vascular causes of RUQ pain.

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A TOUCH OF THE *'DEVIL'S BREATH'*

DR MICHELLE MUSCAT

Plants from the Solanaceae family such as *Datura* and *Brugmansia* are sources of anticholinergic alkaloid drug scopolamine. Scopolamine, or 'burundanga' can be obtained from extracts of the so called 'Borrachero' tree found mainly in Colombia for example. Scopolamine poisoning is known to cause amnesia and is thought of by some as the scariest drug in the world.[1]

Many describe the victims on whom it is used as hypnotized and are allegedly described by some sensationalized stories to act like zombies. Once under the influence, these people are prone to suggestion of what to do from anyone, although appearing lucid to others around them. It is less associated with recreational use but it has reportedly been ascribed many criminal uses[2] such as robberies, assaults and even sensationalized stories of organ trafficking. The drug is odorless and tasteless and also may leave the person without any memories the following day.[3] Excess consumption may result in fatalities. The name attributed to scopolamine is 'devil's breath' stemming from an urban legend which narrates that during episodes of intoxication, your soul temporarily drifts away.

The drug also has a colorful past of being tried as a truth serum in criminal interrogations. However it also has hallucinogenic potential.[4]

Scopolamine, or hyoscine does have legitimate medical uses. The BNF details such uses for the hydrobromide or butylbromide salts. For example, in very small quantities scopolamine transdermal patches have been used as medication for motion sickness. Other uses include symptomatic relief of muscle spasm and as premedication. It is also cytoplegic and mydriatic. [5-10]

Dr Camilo Uribe from San Jose University Hospital, a toxicology expert on scopolamine describes the drug as acting 'like chemical hypnosis'.[11]

The drug has been exploited by criminal groups in view of the potential for effortless manipulation of victims whilst under the influence and subsequent amnesia.

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