THESYNAPSE

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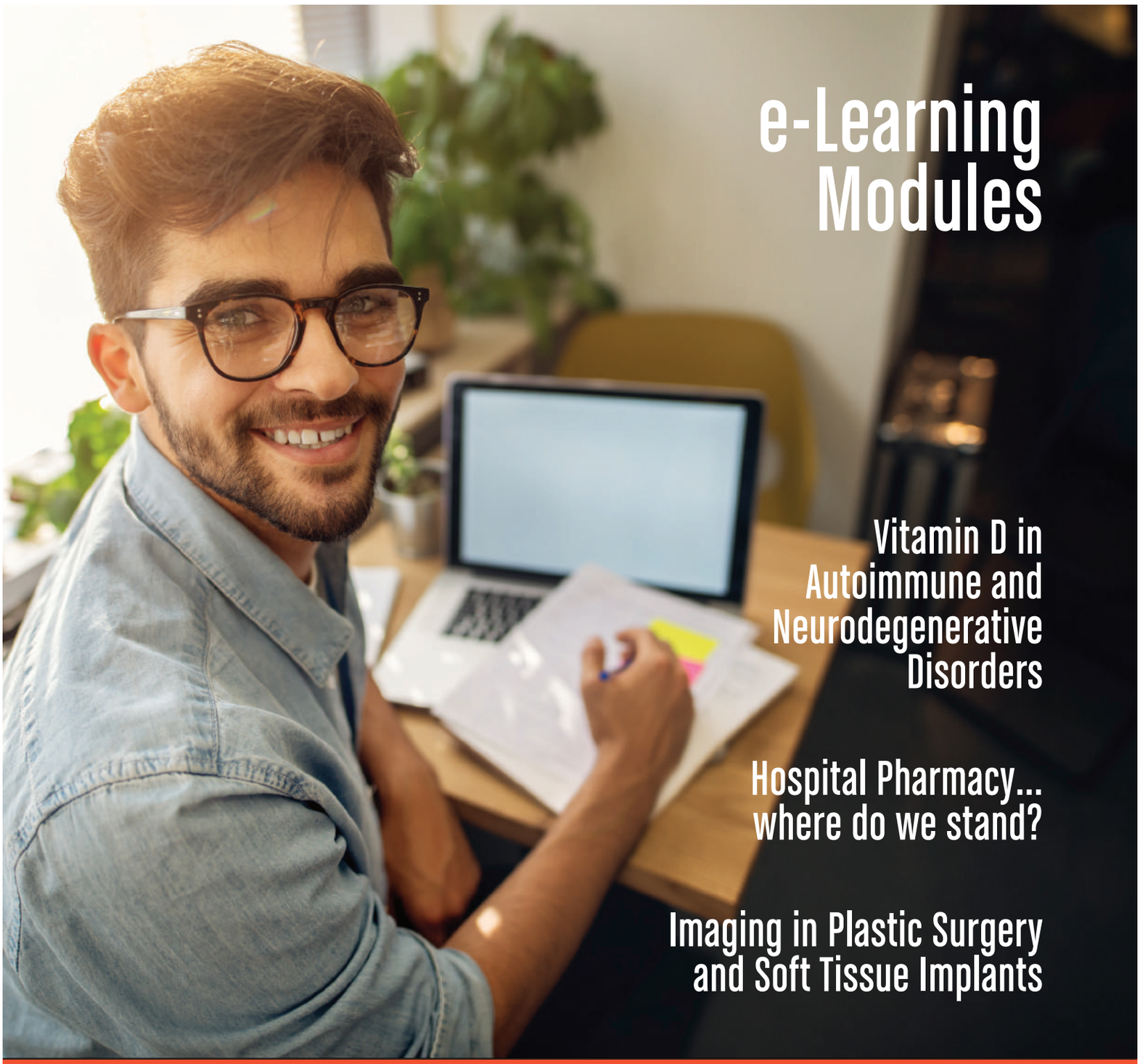

e-Learning Modules

Vitamin D in Autoimmune and Neurodegenerative Disorders

Hospital Pharmacy... where do we stand?

Imaging in Plastic Surgery and Soft Tissue Implants

Augmentin® ES

600 mg/42.9 mg/5 ml

Amoxicillin/Clavulanate Potassium

Powder for oral suspension

- Provides extended antibacterial coverage to include the most penicillin-resistant strains.[1]
- Recommended by leading Guidelines as first line treatment in AOM.[2,3]
- Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.[4]
- Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.[4]

Spreading infectious energy!

Abridged Prescribing Information: *Please refer to the full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAMES:** Augmentin ES. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PHARMACEUTICAL FORM:** 600mg/42.9mg/5ml powder for oral suspension. **INDICATIONS:** Treatment of acute otitis media & community acquired pneumonia in children aged at least 3 months and less than 40kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **POSOLOGY:** 90/6.4mg/kg/day in 2 divided doses. Oral use. Administer with a meal. **CONTRAINDICATIONS:** Hypersensitivity to active substances/penicillins/ excipients. History of: severe immediate hypersensitivity reaction to another beta-lactam agent, jaundice/hepatic impairment due to amoxicillin/clavulanic acid. **PRECAUTIONS:** Enquiry of previous hypersensitivity reactions to beta-lactams. Switch to an amoxicillin-only preparation (to be considered for infections proven due to amoxicillin susceptible organism). Convulsions may occur in patients receiving high doses or impaired renal function. Should be avoided if infectious mononucleosis is suspected. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Overgrowth of non-susceptible organisms with prolonged use. Occurrence of a feverish generalised erythema associated with pustula at treatment initiation may be symptom of AGEP (reaction requires discontinuation, contraindicates subsequent administration of amoxicillin). Caution in patients with hepatic impairment. Hepatic events may be associated with prolonged treatment. Antibiotic-associated colitis. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Appropriate monitoring when anticoagulants are prescribed concomitantly. Creatinine clearance less than 30 ml/min (not recommended). Possibility of amoxicillin crystalluria. Potential of incorrect diagnostic test results during treatment *(refer to full SPC for details)*. Contains 2.72mg of aspartame (E951) per ml (source of phenylalanine). Contains maltodextrin (glucose). *Refer to the SPC for full details of precautions.* **PREGNANCY/FERTILITY/LACTATION:** Pregnancy: Use should be avoided unless considered essential by the physician. Lactation: benefit/risk assessment to be considered. **UNDESIRABLE EFFECTS:** Common (≥1/100 to <1/10): mucocutaneous candidosis, diarrhoea, nausea, vomiting. Refer to the SPC for full list of undesirable effects. **LOCAL PRESENTATION:** 100ml glass bottle with plastic measuring spoon. **MARKETING AUTHORISATION NUMBER:** AA1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** November 2017. In order to ensure that this product information reects 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). Alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal

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1. Anthony R. White *et al.* Augmentin® amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent Journal of Antimicrobial Chemotherapy (2004) 53, Suppl. S1, i3–i20.
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Prepared: June 2018 Job No: MLT_GIB/AES/0001/18a

For more information and dosing instructions:
https://gskpro.com/en-mt/products/augmentin/

UK's BREAST CANCER SCREENING GLITCH

Last May, Health Secretary Jeremy Hunt announced that 450,000 women between the ages of 68 and 71 in the UK failed to receive invitations for a final routine breast cancer screening. Of note, women in the UK from the age of 50 who are registered with a family doctor are automatically invited for screening with a letter every three years until their 71st birthday. Patients cannot ask for an appointment themselves until that age; after that, screening requests can be made every three years.

As a result of the 450,000 failed invitations it has been estimated that up to 270 women succumbed to the disease. This gross mistake spanned over a period of almost ten years, between 2009 and 2017. The first question is posed … who is to blame? To put it mildly, a computer algorithm failure, involving the programming of people's ages. The second question arises naturally … how was this glitch revealed? Following an upgrade to the breast screening invitation IT system, which allowed for improved data on the actual ages of the women receiving screening invitations.

Further to this, Sheikh and Sasieni studied data from the screening programme between 2004 and 2017,[1] which included looking at the number of eligible women who were sent invitations each year from the ages of 45 to 70. In a letter to *The Lancet*, they claim that over 502,000 women may have actually been affected.

It is indeed bewildering how such a grave error went unnoticed for all these years. Obviously this has opened a pandora's box of medico-legal issues which I will not delve into. However, one needs to clearly discuss how this and related problems can be prevented from happening again through periodic independent audits; this is of special importance considering our gradual increasing reliance on intelligent analytics within the internet of things [it is estimated that 26 billion things will be connected to the internet by 2020]. At this stage, artificial intelligence [incorporating failsafe automation systems] within the realm of blockchain may have a pivotal role in reducing the incidence of this and similar algorithm failures.

The application of artificial intelligence in blockchain also has another important application relating to diagnostic accuracy. In keeping with this, in February of 2018, Skychain Global, a blockchain startup, has successfully conducted a medical diagnostics test in Russia, reviewing the number of errors committed by doctors vs the number of errors generated by AI. The test related to the accuracy of melanoma and breast cancer diagnosis as well as the interpretation of ECG results. The challenge may be viewed at www.youtube.com/watch?v=NeqnhaghfrI. Of note is the considerable reduced false positive and false negative results by AI; in real life, the utilization of such AI-powered diagnostic software in clinical practice would possibly translate in a reduction in financial burden of further diagnostic workup, reduction of patient morbidity, etc.

As Nicholson Price notes in his piece *Black Box Medicine*,[2] medicine "already does and increasingly will use the combination of large-scale high-quality datasets with sophisticated predictive algorithms to identify and use implicit, complex connections between multiple patient characteristics." This will allow doctors to increase the precision and accuracy of health care diagnosis and decision-making, thereby reducing medical errors. Obviously, an increased reliance on artificial intelligence and machine learning could complicate potential malpractice cases arising from improper treatment as the result of algorithm errors. However, on the other hand, diagnosis and decision-making algorithms may help reduce the costs associated with defensive medicine.

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MPSA
MADS Malta Association of Dental Students

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†Based on 2016 ESC HF Guidelines and 2017 ACC/AHA/HFSA Guideline Update.

‡Primary end point.

§Secondary end point that measured the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

ENTRESTO™▼(sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Indications:** In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. **Dosage & administration:** The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. **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 coadministered 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% and28%, 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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ISSUE GUIDE

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TheSynapse

FOCUS ON

VITAMIN D
IN AUTOIMMUNE & NEURODEGENERATIVE DISORDERS

THERESA MALLIA & THERESE HUNTER

ABSTRACT

Vitamin D, a secosteroid exhibiting a pleiotropic action, plays important functions in the nervous system and immune system. By suppressing dendritic cell survival, it impairs the activation of allo-reactive T-lymphocytes. It induces apoptosis of B-lymphocytes, reducing the production of autoantibodies. Its neuroprotective roles are linked with its influence on neurotrophin production, calcium ion homeostasis and in controlling oxidative damage. It is therefore not surprising that hypovitaminosis D is linked to both autoimmune and neurodegenerative disorders.

Keywords: Vitamin D, autoimmunity, neurodegeneration.

INTRODUCTION

Vitamin D is a secosteroid existing in two major forms: ergocalciferol and cholecalciferol. The most recognized function of this vitamin is in maintenance of calcium homeostasis.[1] However more recent evidence supports a role of vitamin D in brain development and function, in regulation of insulin production, in controlling immune responses and in cardiovascular and musculoskeletal health.[2]

1. VITAMIN D AND ITS MODULATORY FUNCTION

A. THE NERVOUS SYSTEM

Vitamin D alters the synthesis and secretion of neurotrophic factors, nerve growth factors and the neurotrophin receptor p75NTR. Its deficit results in decreased expression of neurotrophins and p75NTR, leading to a loss of the survival, differentiation and maintenance function that these exert in nerve cells, contributing to neurodegeneration.[3]

By interacting with and reducing reactive oxidative species (ROS), vitamin D prevents oxidative stress-induced neuronal damage. Even nanomolar concentrations of vitamin D (0.1-100 nM) help to protect neurons from such damage.[4] Vitamin D inhibits γ-glutamyl transpeptidase and nitric oxide synthase. This leads to lower levels of intracellular hydrogen peroxide and nitric oxide respectively, further exerting anti-oxidant effects.[5]

Vitamin D is also involved in sustaining intracellular calcium ion (Ca^{2+}) homeostasis by suppressing L-type Ca^{2+} channels. Physiologically elevated levels of Ca^{2+} ions in the cytosol lead to exocytosis of various stimulating amino acids neurotransmitters, resulting in excitotoxicity.[5]

B. THE IMMUNE SYSTEM

Inhibition of memory- and plasma- cell production, as well as promotion of apoptosis of B-lymphocytes are direct effects exerted by vitamin D on B-cells. By controlling B-lymphocyte activation and proliferation, vitamin D reduces the production of autoantibodies, which are involved in the pathophysiology of autoimmune disorders.[5]

Vitamin D suppresses T helper cell (Th) proliferation and differentiation. Through down regulation of the major histocompatibility complex-II (MHC-II) antigen and the production of interleukin (IL)-23 and IL-12, vitamin D shifts the polarization of T-lymphocytes from a Th17 and Th1 phenotype towards a Th2 phenotype. This results in reduced production of pro-inflammatory cytokines like IL-17 and interferon-γ and promotes the synthesis of anti-inflammatory Th2 cytokines, including IL-3 and IL-10. By suppressing dendritic cell survival, vitamin D further promotes the development of T regulatory cells and Th2 cells.[6]

Lucas *et al.*[7] have shown that vitamin D helps in maintaining the ratio of activated Th1/Th17 cells in the systemic circulation and prevents their movement across the blood-brain barrier. This reduces the expression of the chemokine receptor CXCR3. Increased expression of this receptor increases intracellular Ca^{2+} levels by activating the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase pathways, leading to excitotoxicity.[8]

Another target through which vitamin D mediates suppression of self-reactive T-lymphocytes is the Fas ligand. The Fas-FasL pathway regulates activation-induced cell death in T-lymphocytes, thereby maintaining central and peripheral

IN UTERO LEVELS OF VITAMIN D ALSO AFFECT THE RISK OF DEVELOPMENT MS LATER IN LIFE

tolerance to self-antigens. Through downregulation of this ligand vitamin D alters the immune response at various levels, preventing the development of autoimmune diseases.[9]

This shows that vitamin D is an environmental factor, related to both autoimmune and neurodegenerative disorders. In fact, studies suggest that hypovitaminosis D, which is defined as a vitamin D serum concentration of being less then 25nmol/L, negatively impacts such disorders.[10]

2. VITAMIN D AND AUTOIMMUNITY

With insufficient vitamin D serum levels, the immune system allows the up-regulation of B-cells and self-reactive T-cells. The production of inflammatory cytokines, together with increased production of immunoglobulin producing B-cells, contributes to the development of autoimmune diseases.[11]

Vitamin D deficiency has also been implicated in facilitating the progression of existing autoimmune disorders. In a study carried out by Zold *et al.*[12] 161 patients with an early connective tissue disorder were followed for about 2 years. There was no progression of the disease in most of the patients. However 21% of the patients developed a specific rheumatologic disorder including systemic lupus erythematous (SLE). Lower vitamin D levels were present in the population in which the disease progressed to a definitive state.[12]

Hypovitaminosis D is linked to several autoimmune disorders, including multiple sclerosis (MS), type 1 diabetes mellitus (T1DM) and inflammatory bowel disease (IBD).[5] MS is the only autoimmune disease in which the effects of vitamin D have been well-established.

A. MULTIPLE SCLEROSIS

MS is an autoimmune neurodegenerative disease, driven by myelin auto-reactive T- lymphocytes, which leads to the recruitment of macrophages, with subsequent myelin destruction and axon degeneration.[5]

Vitamin D deficiency leads to loss of balance between the inflammatory and anti-inflammatory pathways. This is because activation of immature dendritic cells results in mature dendritic cell production, leading to reduced differentiation of immunosuppressive regulatory T-cells and increase in Th1 cells. These synthesize and secrete inflammatory cytokines, including IL-23 and interferon-γ, leading to demyelination. Prolonged toxic insults to neurons results in the release of neural antigens, stimulating further inflammatory responses, enhancing demyelination .[13]

Vitamin D acts as a specific inhibitor of osteopontin, a pro-inflammatory cytokine involved in the progression of MS. Osteopontin increases the production of IL-12, tumor necrosis factor and interferon-γ by T-lymphocytes, inhibits IL-10 production and lengthens the life-span of activated T-lymphocytes. In fact, higher levels of osteopontin transcripts are found in patients suffering from MS.[5]

In utero levels of vitamin D also affect the risk of development MS later in life. Eyles *et al.*[14] showed that in utero vitamin D deficiency led to the dysregulation of various mRNA transcripts, including the enzyme calcineurin and FK506 binding protein 1a in the brain tissue of the offspring. These function to limit the synthesis of IL-2, which results in cytotoxic T-cell activation and tissue damage.

IN A STUDY INVOLVING 10,366 CHILDREN ... DAILY SUPPLEMENTATION OF 2000IU OF VITAMIN D IN THE FIRST YEAR OF LIFE REDUCED THE RISK OF DEVELOPING T1DM ... BY ABOUT 80%

Genetic Risk Factors

Vitamin D receptor gene

The *FokI* polymorphism of the vitamin D receptor (VDR) gene affects in vitro vitamin D-mediated inhibition of IL-12 transcription and protein production by dendritic cells and monocytes. IL-12 induces Th1 cells, contributing to neuronal inflammation.[15] The *TaqI* variant of the VDR gene is also weakly related to MS.[16]

HLA-DRB1 gene

The *MHC* gene on chromosome 6 provides the single largest contribution to disease susceptibility in the entire genome. The classical human leukocyte antigen (*HLA*)-*DRB1*15:01* allele has been documented as the strongest genetic association to the risk of developing MS.[17] The vitamin D response element in the *HLA-DRB1* promoter, corresponding to the *HLA-DRB1*15* haplotype, binds VDR with higher affinity than other elements. Vitamin D stimulation of B-lymphocytes transfected *with HLA-DRB1* gene constructs, including the *HLA-DRB1*15* sequence, doubles the expression of *HLA-DRB1*15:01*. This suggests that the *HLA-DRB1*15:01* haplotype greatly contributes to the effect exerted by vitamin D in MS.[18] A lack of vitamin D during the early life of *HLA-DRB1*15*-bearing individuals could allow autoreactive T-cells to escape thymic deletion, increasing the risk of the development of autoimmune disorders.[19]

Epigenetic changes in the genes encoding cytochrome P450 reductase (CYP) 27B1 and CYP24A1, which are involved in vitamin D metabolism and catabolism respectively, also affect vitamin D serum levels, contributing to the pathogenesis of the disease.[17]

B. OTHER AUTOIMMUNE DISORDERS

i. Type 1 Diabetes Mellitus

T1DM results from immune-mediated destruction of β-pancreatic cells. Apart from acting at a peripheral level and controlling the cellular-mediated pathogenesis of this disease, vitamin D reduces the selection of self-reactive T-cells in the thymus.[20] Vitamin D supplementation also decreases the risk of developing T1DM. In a study[21] involving 10,366 children carried out in Finland, daily supplementation of 2000IU of vitamin D in the first year of life reduced the risk of developing T1DM in the next 31 years by about 80%.[21]

ii. Inflammatory Bowel Disease

IBD includes ulcerative colitis and Crohn's disease, both of which are characterized by chronic inflammation of the intestine. Reduced levels and/or dysfunctional auto-phagocytosis have been implicated as contributing factors in IBD.[22] By enhancing the co-localization of pathogen-harboring phagosomes with autophagosomes in a

cathelicidin-dependent manner, vitamin D increases the basal levels of autophagy.[23] Vitamin D down-regulates the expression of the protein kinase mammalian target of rapamycin (mTOR), a negative regulator of autophagy.[24] Furthermore, through the activation of the PI3K signaling pathway, it enhances beclin-1 expression, which stimulates auto-phagocytic processes.[23]

3. VITAMIN D AND NEURODEGENERATION

Insufficient levels of vitamin D results in increased levels of Ca^{2+} ions and ROS, which together with reduced neurotrophin levels, contribute to neuronal degeneration. Hypovitaminosis D also contributes to immune-mediated degeneration. Interactions between Th1, Th17 cells and inflammatory cytokines result in microglia activation and inflammation, resulting in cytotoxicity and neuronal damage.[5] Apart from MS, low levels of vitamin D are linked to several neurodegenerative disorders including amyotrophic lateral sclerosis (ALS) and Alzheimer's dementia (AD).[5,25]

A. AMYOTROPHIC LATERAL SCLEROSIS

Multiple effector pathways contribute to ALS pathology including deficiency of neurotrophic factors, glutamate toxicity and damage from ROS, all of which are kept in control by vitamin D. An abnormal calcium-parathyroid hormone-vitamin D level has been detected in patients with ALS, with vitamin D serum concentrations being significantly lower in ALS patients than in transgenic mouse control models of ALS. Such patients showed improvements in their functional capacity following dietary vitamin D supplementation.[25]

Several of the ALS susceptibility genes with related VDR-binding sites have been indicated in salient brain functions such as neuritogenesis and axonal growth.[26] In fact, the Gc2 polymorphism of vitamin D-binding protein was recorded in the plasma of a cohort of Portuguese patients with familial ALS.[27]

B. ALZHEIMER'S DEMENTIA

Given the role of vitamin D in facilitating neurotransmitter synthesis, protecting against oxidative stress, reducing pro-inflammatory responses, and maintaining neurite outgrowth,[5] a biological basis exists that supports the role of vitamin D in the pathogenesis of cognitive impairment and AD. 72% of the 25 cross-sectional studies analyzed by van der Schaft *et al.* report a statistically significant worse outcome on one or more cognitive function tests or a higher frequency of dementia with lower vitamin D levels or intake. 66.7% prospective studies show a higher risk of cognitive decline after a follow-up period of 4–7 years in participants with lower vitamin D levels at baseline.[28]

CONCLUSION

Vitamin D exhibits the main characteristics of a true neuroactive steroid, with clinical and experimental evidence that vitamin D deficiency is an important factor involved in autoimmune and neurodegenerative disorders. However little is still known whether its supplementation helps in the prevention and treatment of such disorders.

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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/1/07/414/003. **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

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) angioderma: 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

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NOVARTIS

GAL AD1 06/18 MT

Galvus vildagliptin

Eucreas vildagliptin/metformin

SHORT ACCOUNTS OF INTERESTING CASES, SOME MEDICAL DISASTERS, INVOLVING PATHOLOGY AND CLINICAL PRACTICE, FROM THE RECOLLECTION OF PROF. ALBERT CILIA-VINCENTI.

WE'RE PLANNING TO AMPUTATE THIS CHILD'S TOE

This is still the mid-1980s and the medical scene in Malta is still "under duress", with the MAM strike still on and with many specialist procedures requiring visiting consultants from the UK.

A clinician from my year at medical school, practicing in Malta, has two infant daughters, the younger of whom has had a recurrent nodule in one of her toes. I was sent the recurrent nodule for opinion – the first nodule was probably not referred to pathology. Local recurrence raised a suspicion of possible malignancy.

As luck would have it, I had just come across a scientific paper describing *recurrent digital fibroma of infancy*, a lesion that had also been called *digital neurofibrosarcoma*. The paper described a small fibrous lesion involving skin and subcutaneous tissue in fingers and toes of infants not older than three years, with high recurrence rate after excision, but no tendency to malignant transformation and, interestingly, spontaneous regression after age three. It also described characteristic intracytoplasmic inclusions within the fibroblasts, which could be mistaken for red blood cells, and which consist of actin filaments.

This lesion is derived from the myofibroblast, the cell with a principal role in granulation and reparative tissue, scar tissue, keloidal scars and the various superficial and deep fibromatoses. The digital lesion in question has therefore also been called *infantile digital myofibroblastoma*. It is now most commonly referred to as *infantile digital fibromatosis*. Some authors have also claimed this lesion can be made to regress by injecting with corticosteroid.

I transmitted the information of its benign nature in spite of local recurrence tendency to the Maltese surgeon that had referred me the case, together with a recommendation for conservative management. The parents were understandably anxious and consulted both another Maltese surgeon and a visiting British surgeon from Oxford's Nuffield Orthopaedic Hospital. They discussed amputating the toe but, before doing so, Oxford asked me to send them the histological sections for their pathologist to review.

Their pathologist was an author of an orthopaedic pathology book but, when he phoned me on receipt of the slides, it was obvious that he was unaware of this peculiar digital lesion of infants and said he couldn't see the inclusions I had claimed as characteristic. I therefore had to take micrographs, with arrows pin-pointing the inclusions, and posted them to him. I heard no further from Oxford. The parents eventually told me that the toe had been preserved and the girl had no further problems at the site. I understand she is now an established lawyer.

Her older sister read medicine in Malta and, close to her last medical school year, her father asked me whether I could recommend her to a clinician in UK for a summer clerkship. It so happened that because surgical senior registrars from London's St George's Hospital rotated with our surgical department in Winchester, I had become well-acquainted with the likes of Merion Thomas, subsequently oncological surgeon at The Royal Marsden, hepatic surgeon Melvin Rees at Basingstoke, and our own Winchester surgeon Dick Rainsbury who has gone on to become principal tutor at London's Royal College and the subject of a Daily Mail article detailing him as the top breast surgeon in the UK.

I asked Merion Thomas whether he would accept this Maltese female medical student to join his firm for a month or so. He did and reported back how bright she was. I understand she's now a consultant gynaecologist in London. Happy endings all round, for a change.

Augmentin SR

1000 mg/62,5 mg

Amoxicillin/Clavulanic Acid Prolonged-Release Tablets

- Unique bilayer tablet with immediate and sustained release delivery of amoxicillin provides superior efficacy against resistant pathogens[1,2]
- Recommended by leading Guidelines in the treatment of Community Acquired Pneumonia[3,4]
- Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis[5]
- Indicated for use in adults & adolescents aged ≥16 years; 2 tablets BD for 7-10 days[5]

Spreading infectious liveliness!

Abridged Prescribing Information: Please refer to the full Summary of Product Characteristics (SPC) before prescribing. **TRADE NAME:** Augmentin SR. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate), potassium clavulanate. **PHARMACEUTICAL FORM:** 1000 mg/62.5 mg prolonged-release tablets. **INDICATIONS:** Treatment of community acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **POSOLOGY:** *Adults and adolescents ≥16 years:* Oral use. 2 tablets, twice daily for seven to ten days. Administer with a meal. **CONTRAINDICATIONS:** Hypersensitivity to active substances/penicillins/excipients. History of: severe immediate hypersensitivity reaction to another beta-lactam agent, jaundice/hepatic impairment due to amoxicillin/clavulanic acid. **PRECAUTIONS:** Enquiry of previous hypersensitivity reactions to beta-lactams. Switch to an amoxicillin-only preparation (to be considered for infections proven due to amoxicillin susceptible organism). Convulsions may occur in patients receiving high doses or impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Overgrowth of non-susceptible organisms with prolonged use. Occurrence of a feverish generalised erythema associated with pustula at treatment initiation may be symptom of AGEP (reaction requires discontinuation and contra-indicates subsequent administration of amoxicillin). Caution in patients with hepatic impairment. Hepatic events may be associated with prolonged treatment. Antibiotic-associated colitis. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Appropriate monitoring when anticoagulants are prescribed concomitantly. Creatinine clearance less than 30 ml/min (not recommended). Possibility of amoxicillin crystalluria. Potential of incorrect diagnostic test results during treatment *(refer to full SPC for details)*. Contains 29.3 mg (1.3 mmol) of sodium per tablet. *Refer to the SPC for full details of precautions.* **PREGNANCY/FERTILITY/LACTATION:** *Pregnancy:* Use should be avoided unless considered essential by the physician. *Lactation:* benefit/risk assessment to be considered. **UNDESIRABLE EFFECTS:** *Very common (≥1/10): diarrhoea. Common (≥1/100 to <1/10):* mucocutaneous candidosis, nausea, abdominal pain. *Refer to full SPC for the full list of adverse reactions.* **LOCAL PRESENTATION:** 28 tablets/pack. **MARKETING AUTHORISATION NUMBER:** AA1051/00102. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** November 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)** *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). Alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal

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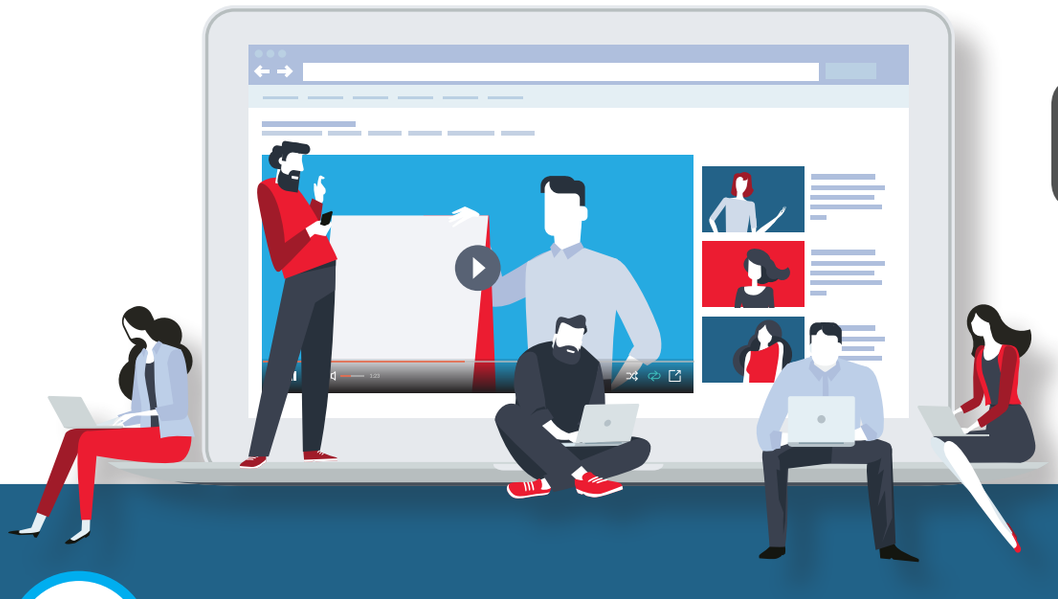
Prepared: June 2018 Job No: MLT_GIB/AES/0002/18

For more information and dosing instructions:
https://gskpro.com/en-mt/products/augmentin/



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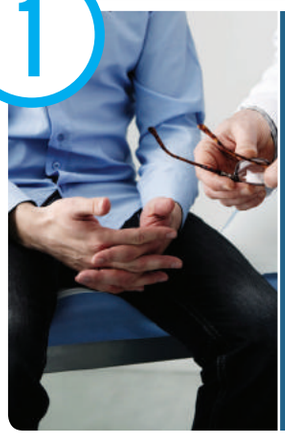


INVESTIGATING AND MANAGING THE PATIENT WITH MALE FACTOR INFERTILITY - A CASE BASED APPROACH

LEARNING OBJECTIVES

- Understanding the role of the urologist in diagnosing and treating male factor infertility
- Review a number of cases related to male factor infertility
- Appreciate the myriad of presentations related to this clinical condition
- Appreciate the prevalence of male factor infertility in the local population

E-LEARNING SESSION DELIVERED BY MR ANDREW MERCIECA [M.D., M.R.C.S, F.E.C.S.M, F.E.B.U]

ACCREDITATION: Medical Association of Malta *0.5 Credits*
Malta College of Family Doctors *Applied for*

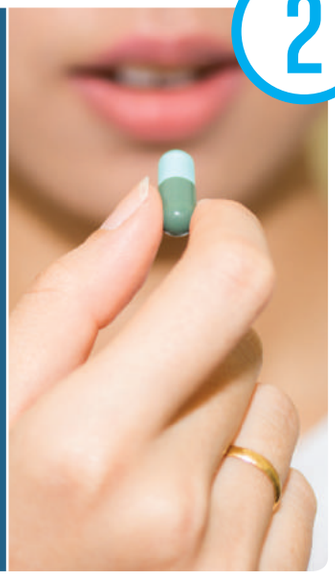
2

ANTIBIOTIC STEWARDSHIP - 1

In this eLearning episode, Prof. Michael Borg, Consultant in infection Control, discusses common antibiotic prescription errors, taking into account contemporary epidemiological data and how this should direct clinical decisions when confronted with infectious diseases.

LEARNING OBJECTIVES

- To highlight current practices and their impact on resistance epidemiology
- To advocate for better antibiotic prescribing in the community
- To appreciate the local epidemiological data related to common infectious pathogens
- To raise awareness on the infectious disease support services available for community practitioners



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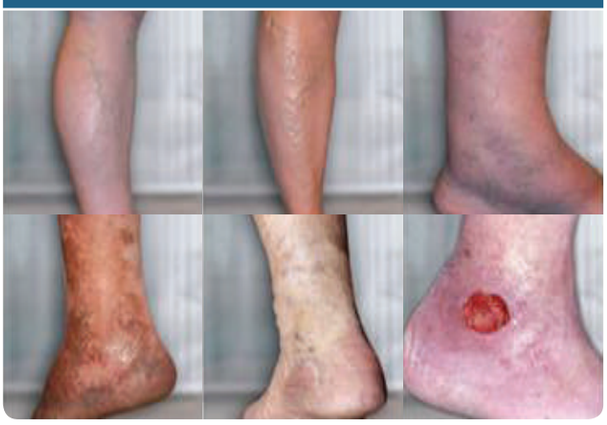

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CHRONIC VENOUS INSUFFICIENCY

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Session delivered by **Prof. Kevin Cassar** MD(Malta), FRCS (Ed), FRCS (Gen Surg), MMEd (Dundee), MD(Aberdeen), FFSTEd

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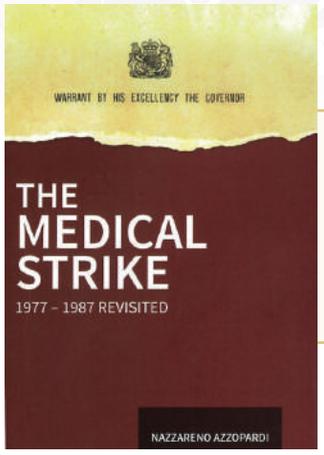

DR NAZZARENO AZZOPARDI

Publishers: BDL
Pages: 144
Hardback Price: €15
Published: 2017

Forty years ago Malta and Gozo were faced with a serious crisis because the Medical Association of Malta (MAM) clashed with the incumbent Labour Government headed by Mr Dominic Mintoff A. & C. E. and organised a general medical strike. The strike stemmed from the:

1. Inadequate salary structure of government employees doctors and specialists;
2. Lack of agreement on the shortening of the three-year obligatory work in government hospitals medical graduates had to perform before being granted the warrant to practice medicine.

A MAM account of the action, ably authored by Mr Lino German FRCOG, had long been published.

Dr Nazzareno Azzopardi FFARCS felt that posterity should acknowledge the efforts of the Forty-Five Signatories' who kept performing their medical duties within the government service during the action despite a professional boycott and even physical threats; in fact, one of the participants lost his daughter in a letter bomb.

It was also the first time that medical doctors and specialists from neighbouring Mediterranean states and Pakistan arrived to bolster the efforts of the sorely tried 'Forty-Five Band of Brothers'. It was also the first and last time that the Medical Council had its prerogative of granting warrants to practice lawfully subverted by the incumbent Minister of Health.

It was the first time that Maltese graduates enjoyed the experience and qualifications of European post-graduate medical schools.

The duration of the action, a full ten years, lasted as long as the Labour Government was in power and ended on the day when finally, a change of administration to a Nationalist one occurred.

As a final word the author cautions MAM to forego politics in dealing with Trade Union issues.

HOSPITAL PHARMACY... WHERE DO WE STAND?

ALISON BRINCAT
KATHLENE CASSAR
MARIO BARBARA
& RUTH BORG THEUMA

Hospital pharmacy is a specialised field of pharmacy within the healthcare service which entails the procurement, storage, compounding and dispensing of medications and medical devices. It also involves advising healthcare professionals and patients on their safe, effective and efficient use. In accordance to the European Association of Hospital Pharmacists (EAHP), the mission of each hospital pharmacist is to enhance the safety and quality of all medicine-related processes affecting patients whilst ensuring that the seven "rights" are respected: right patient, right dose, right route, right time, right drug with the right information and right documentation. Being part of the medication management within a hospital, each hospital pharmacist must strive to optimise the use of medicines such as ensuring the correct dosage regimen and promote adherence to prescribed treatment by patients.

The Malta Association of Hospital Pharmacists was set up in 2013 with the prime aim to promote and aid in the professional development of hospital pharmacy in the Maltese archipelago. The local organisation has then joined EAHP. The latter incorporates over 19,000 pharmacists working in 35 European countries representing hospital pharmacists in European and international fora.

A consensus has been reached on the vision for hospital pharmacy services within EAHP with the collaboration of patients and healthcare professional groups. During the European Summit of Hospital Pharmacy in Brussels in May 2014, forty-four statements were agreed upon. These were divided into six overarching sections:

- Introductory statements and governance;
- Selection, procurement and distribution;
- Production and compounding;
- Clinical pharmacy services;
- Patient safety and quality assurance;
- Education and research.

Statement Implementation Ambassadors have been appointed for each country in a drive to implement the statements by acting as a link between EAHP, member associations and work conducted within the countries. The European Statements of Hospital Pharmacy are supported by various stakeholders including education providers, patients, pharmaceutical industry groups and even by other healthcare providers such as nurses organisations.

THE MISSION OF EACH HOSPITAL PHARMACIST IS TO ENHANCE THE SAFETY AND QUALITY OF ALL MEDICINE-RELATED PROCESSES AFFECTING PATIENTS WHILST ENSURING THAT THE SEVEN "RIGHTS" ARE RESPECTED

National strategies will be designed and discussed with the relevant stakeholders. The degree of implementation will be assessed by an online self-assessment tool and action plans will be developed accordingly. Due to the varied systems and necessities of the different countries, EAHP will liaise with the national associations and ambassadors to comprehend the needs and priorities of the local scenario and compile specific national strategies accordingly.

Further information regarding the European Statements and the project of implementation may be obtained from http://statements.eahp.eu/statements/european-statements-hospital-pharmacy. If a healthcare association would like to endorse these statements, the EAHP implementation team may be contacted through http://statements.eahp.eu/about/support-us.

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THE VOCATION OF BEING A PHARMACIST

The Mayor presenting the Għarfien il-Ħila award to Simone Fenech on Qormi day

Marika Azzopardi interviews pharmacist **SIMONE FENECH** who was recently presented with an award by the Qormi Local Council.

WHEN DID YOUR CAREER AS A PHARMACIST BEGIN?

I graduated in December 1982 and over the years worked in varied pharmacies. Today I work at Pinto Pharmacy in Qormi which is now a family-run business.

IS THIS A VERY OLD PHARMACY?

Indeed it is. The name is directly connected with the history of Qormi and Grandmaster Pinto. It is a very old pharmacy which was run by a veteran chemist. Our son bought it recently and we worked in it, in its old state, for a while. This was up until we relocated to small premises close by whilst the building underwent intensive restoration works. These will be ready soon and, once it is inaugurated, we will start operating from within it again.

On the graduation day with my sister Germaine, 11 Dec 1982

CAN YOU SHARE WITH THE SYNAPSE READERS SOME INFORMATION ABOUT YOUR AWARD?

This came as a complete surprise. I received an invitation in the post, whereby I was invited to attend a ceremony at the Local Council. I must admit that initially I did not intend to attend, due to the fact that we work long hours at the pharmacy; I try to avoid attending events after hours whenever possible. But then, at the last minute, I decided to attend. And sure enough, during the ceremony, my name was called and I was presented with the award dedicated to 'Għarfien il-Ħila - Servizz lill-Komunità.' Basically the Local Council felt I deserved appreciation for my work with clients who come to our pharmacy and for my ability to serve them well. I decided to dedicate this award to the memory of my late father, Pio Sciriha, who was a highly talented maths and physics teacher. He taught many people who would otherwise have floundered in these topics, including myself. He had a gift of teaching such complex subjects most effectively. Above all, he taught me respect, discipline and how to take a serious approach to responsibility.

WHAT WOULD YOU SAY MADE YOU STAND OUT AND BE ELIGIBLE FOR THIS AWARD?

I must make it clear that I was absolutely in the dark about all of this. But from what I gather, people feel I am a helpful person. To be honest I love to work with a passion, and when

On the wedding day with my husband George, 5 February 1984

The graduation day of my son Sean, together with my late father Pio Sciriha, to whom I dedicate my Għarfien il-Ħila award, 2010.

I am speaking to a client, I do my best to dedicate my full attention to his or her questions and health problems. I like to listen well, and try to give samples where possible to help people who need to try out a product before they actually purchase a probably costly full-size, that might not be helpful to their particular case after all.

HOW HAVE PEOPLE CHANGED IN THEIR ATTITUDE TO PHARMACISTS OVER THE YEARS?

A great deal. There was a time when a pharmacist was a highly respected professional in all senses - remember that in the past we used to prepare tinctures, medicines and potions ourselves. Sometimes I still mix medicines for clients but very rarely indeed. Nowadays, clients tend to be disrespectful, behave as if they are speaking to a glorified salesgirl. They will insist on being given certain products without a prescription, even when you explain these can be dangerous and must be prescribed by a doctor.

WHAT ARE THE MAJOR PROBLEMS YOU FACE IN SUCH INSTANCES?

Clients who want to be given an antibiotic or a steroid cream, 'like the one used last year'. Elderly patients tend to be the most challenging. On the other hand, in general, clients tend to be better informed. They listen to radio or TV programmes with great attention and will come back to me to ask more information about something that interests them.

ARE THERE ANY HEALTH ISSUES WHICH YOU ARE AMAZED TO STILL SEE OR WHICH YOU HAVE SEEN ON CLIENTS RESURFACE AFTER MANY YEARS?

Oh yes … STDs are definitely on the rise. Recently I was amazed to see a case of scabies, something we only associated with deprived conditions of wartime.

WHAT WOULD YOU SAY ARE RISKS OF THE JOB WHICH YOU MUST WATCH OUT FOR?

Working in a busy pharmacy such as Pinto Pharmacy brings us face–to-face with episodes of blatant theft. We have to be quick and efficient, yet careful at the same time, especially when the pharmacy is full of clients, each demanding attention. Then there is contagion - people with bad bouts of flu come to the pharmacy as the first resort to help themselves get better. Still, we know these are our risks of the job, so to say, and we learn to protect ourselves as best we can.

IF YOU HAD TO DO IT ALL AGAIN, WOULD YOU STILL BECOME A PHARMACIST?

Most definitely. I love what I do, I love my job. I am at the pharmacy everyday at 6am, doing the paperwork, re-stocking shelves, preparing for the moment we open our doors to welcome clients. I cannot envisage a day in my life when I am not at the pharmacy anymore.

My sons, Francis and Sean

I READ THE SYNAPSE BECAUSE...

For the past 21 years it has been a source of information updating me on the latest medical news and educating each and every one of us on so many fields of science. Over the years, the journal has acquired a permanent and prominent position in my library. The minute I receive it, I read it from cover to cover. When the front cover image shows a historic location or building, I like to make time to go and visit it. My heartfelt compliments go to the managing editor, Dr Ian Ellul, for his sterling work.

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- 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.

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Relvar Ellipta was developed in collaboration with INNOVIVA

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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.
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IMAGING IN PLASTIC SURGERY & SOFT TISSUE IMPLANTS

PIERRE VASSALLO

The demand for plastic surgery procedures with or without the use of implants or soft tissue fillers has increased dramatically over the years. In 2017, 17.5 million cosmetic surgical procedures were performed in the US; 1.8 million were cosmetic surgical procedures, while 15.7 million were minimally invasive procedures. The most common surgical procedures were breast augmentation, liposuction, rhinoplasty, eyelid surgery and tummy tucks; the most common minimally invasive procedures included Botulinum Toxin Type A (Botox) injection, soft tissue fillers, chemical peel, laser hair removal and microdermabrasion.[1] Although there are no available statistics for Malta, the demand for such procedures has grown locally as well.

Despite the large number of procedures performed, complications are uncommon. However, the number of requests for imaging to exclude such complications is increasing so the radiologist must be familiar with the related imaging findings. Irrespective of the location and type of plastic surgery, complications are mostly minor and display common themes; these include seromas, haematomas, infection, migration, vascular and nerve compression, fibrosis, foreign body reaction and rupture or breakdown of the implant.[2] Some imaging findings noted after plastic surgery procedures are not complications at all; they are anatomical changes related to the procedure that will not cause any detriment to the patient.

BREAST AUGMENTATION

The subject of breast implant assessment and the value of MRI and US have already been discussed in the last issue of this Journal.[3] Besides implant breakdown, there are other findings that may be noted on cross-sectional imaging that may be of clinical importance particularly in breast cancer patients who have had breast reconstructions.

Peri-implant fluid collections are the most common findings on breast US; they may be simple or complex. Most fluid collections are small and require only observation. Large fluid collections will need US-guided aspiration (Fig 1), while recurring fluid collections may require sclerotherapy. Aspirated fluid must be analysed for the presence of infection (e.g. non-tuberculous mycobacterial infection) or malignancy (particularly anaplastic large cell lymphoma - ALCL), since these would influence further management. Although infections are rare, they may be caused by unusual bacteria as indicated above; they may require testing of multiple sequential fluid aspirations with repeated cultures and complex polymerase chain reaction (PCR) tests for confirmation.

Fluid around the silicone implant may be due to implant rupture; most ruptures remain within the fibrous capsule that the body creates around the implant (intracapsular) and may be difficult to distinguish from other fluid collections (Fig 2).

Extravasation of silicone outside the capsule is known as extracapsular rupture. MRI is the best imaging tool to detect intra and extracapsular ruptures; the features of implant rupture have been described in previous issues of *The Synapse Journal*.[3,4] Detection of implant rupture should prompt implant replacement. The use of MRI will confirm the presence and type of rupture and will help exclude other complications, particularly cancer recurrence in breast cancer patients.

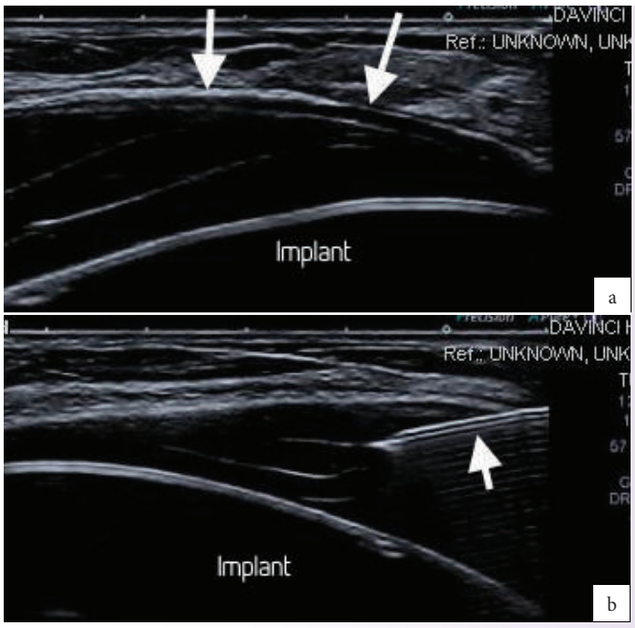

Figure 1: a. Breast US showing a fluid collection (arrows) superficial to an implant. **b.** US-guided aspiration showing the needle tip (arrow) within the fluid collection.

A further complication of breast augmentation surgery is fibrosis or capsular contracture; it is uncommon, occurring in less than 5% of cases.[5] Like any foreign body, breast implants result in the formation of a fibrous layer around them that represents the implant capsule. Excessive fibrous reaction results in capsular contracture with tightening around the implant that may lead to a misshapen implant that rides high in the chest wall resulting in a hard and immobile breast and may cause pain (Fig 3). There is an increased likelihood of capsular contracture in the presence of fluid collections or abscesses, an implant leak, after radiation therapy and following breast trauma. Contractures are also likely consequences of a foreign body reaction to the implant. New textured implants have been developed that reduce the likelihood of capsular contracture, however the FDA is currently investigating reports relating these implants to ALCL. The treatment for contracture is capsulectomy with implant replacement.[6]

ABDOMINOPLASTY

Commonly known as "tummy tuck", abdominoplasty may be performed to adjust disproportional fat distribution, to correct abdominal skin redundancy or myofascial laxity/diastasis, or for weight loss with or without bariatric surgery. Abdominoplasty has been performed since the 1980s, but it has evolved considerably since then. It is now a complex procedure that involves an incision from hip to hip, subcutaneous release of the umbilicus, dissection of the subcutaneous soft tissues along the rectus sheath superior to the costal margin, midline muscle plication, and resection of redundant skin, followed by skin closure. Plication of the rectus muscles, which is done to reduce outward protrusion of the abdomen, results in changes that are easily identified on CT and MRI (Fig 4).

The most common complication of abdominoplasty is a seroma that results from accumulation of fluid between the deep fascia and the skin/subcutaneous fat flap. These are readily confirmed with US or CT (Fig 5). Smaller seromas may be observed while larger ones will require needle aspiration that is best performed under US guidance. The use of specifically designed compression garments reduces the risk of seromas.

LIPOSUCTION

Liposuction was initially described in the 1970s, but the technique was revolutionised in the 1980s and remained largely unchanged since then. This is the most common form of plastic surgery after breast augmentations. It is commonly combined with abdominoplasty in a procedure termed lipoabdominoplasty. It essentially involves insertion of blunt cannulas through small skin incisions to aspirate fat from the deep subcutaneous tissues; it has been used in all parts of the trunk and limbs to reduce unwanted subcutaneous fat. Following liposuction, CT and MRI show linear cannula tracks in the deep subcutaneous tissues (Fig 4).

Although uncommon, wound infection may occur with liposuction, which consists mostly of uncomplicated cellulitis. Seroma and haematoma formation may also occur following liposuction, however these rarely require intervention. Rare complications include abdominal wall perforation and venous thromboembolism, both of which can be avoided by careful technique.

AUTOLOGOUS FAT GRAFTING

Autologous fat grafting involves harvesting fat from one site where removal is aesthetically desired, such as the abdomen or thighs, and transferring it to other areas for augmentation in the same patient, commonly to the buttocks and breasts. Other terms used for this procedure include lipografting, liposculpture, lipotrasfer and lipofilling.

Different techniques for harvesting fat are being developed to maximise the viability of harvested tissue. Effectiveness at the receiver site depends on the location of injection, which may be subcutaneous, subdermal or intramuscular with surgeons often using a combination of injection sites.

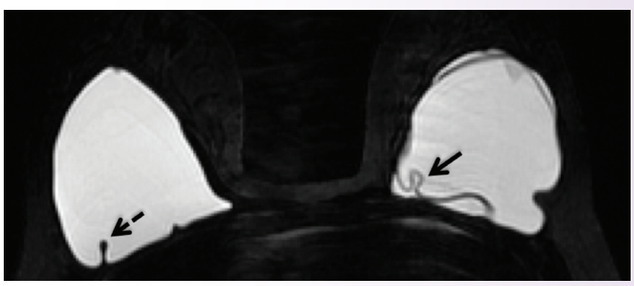

Figure 2. Silicone-selective MRI image showing a simple fold in the elastomer shell of the right implant (dashed arrow) and an intracapsular rupture in the left implant (solid arrow) with fluid outside the folded implant shell.

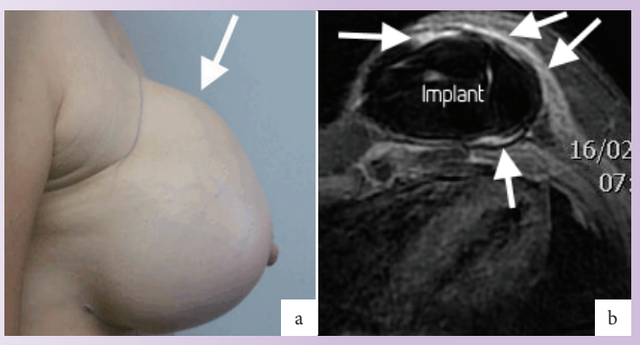

Figure 3. a. High-riding implant (arrow) is a feature of capsular contracture; pain, hardness and immobility represent other common clinical features. **b.** Silicone and fat-suppressed contrast-enhanced MR image showing a misshapen implant (globular) and an enhancing thickened fibrous capsule (arrows).

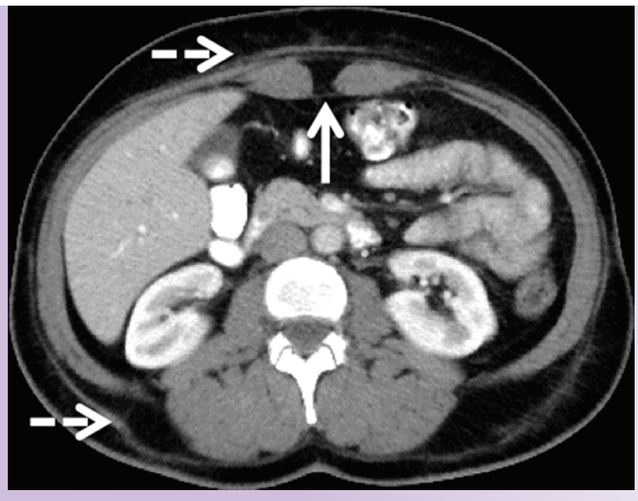

Figure 4. Transverse CT image of the abdomen shows linear subcutaneous fat stranding (dashed arrows) along the anterior and posterior abdominal wall, which represents the cannula tracks from liposuction. The characteristic midline inward protrusion of the rectus abdominis muscles (solid arrow) results from rectus muscle plication.

At the harvest site, cannula tracts are seen on CT and MRI, while at the graft site injected fat may not be discernible from native fat. Linear stranding may be present in subcutaneous graft sites, while fat is readily visible if injected intramuscularly (Fig 6).

Complications related to fat transfer sites include infection and nerve or vascular compression and are best imaged with MRI. Contrast-enhanced MR images will show enhancement within the compressed nerve resulting from neuritis and within the walls of abscess cavities (Fig 7).

SOFT TISSUE FILLERS

Soft tissue fillers are among the most popular minimally-invasive plastic procedures performed today. They can be used anywhere but are most often employed in the face and hands. The most commonly used fillers are collagen, hyaluronic acid, calcium hydroxyapatite or poly-L-lactic acid based. Fillers are best evaluated by MRI, but CT and US are also useful (Fig 8). Complications related to the use of fillers are uncommon. Early complications that occur in the first few weeks include overcorrection, hematoma, infection, and transient erythema and/or oedema. Late complications occur more than 6 months after the procedure and include foreign-body granuloma formation, infection, compound migration, and cross-reactions between different fillers. If placed under aseptic conditions by licensed and experienced medical professionals, soft-tissue fillers have a low incidence of complications.

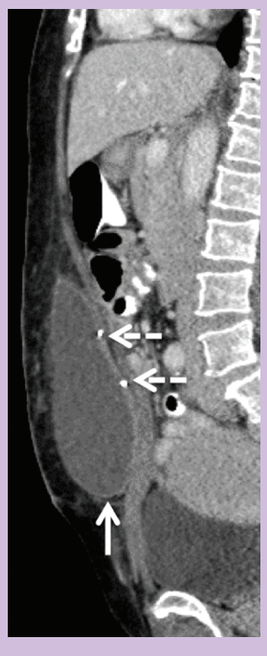

Figure 5. Sagittal CT image of the midline of the abdomen showing a seroma (arrow) occurring 3 weeks after abdominoplasty. Typical inward protrusion of the rectus muscles and surgical clips (dashed arrows) due to rectus plication are also depicted.

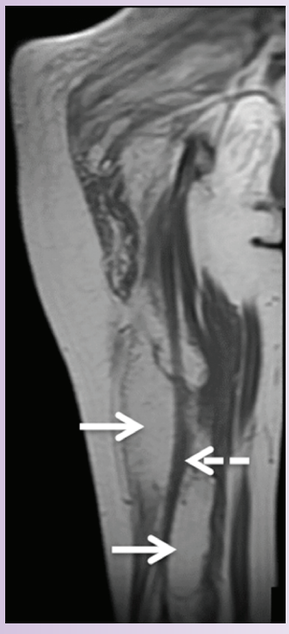

Figure 6. Coronal T1-weighted MRI scan following augmentation gluteoplasty showing a large area of fat signal intensity in the right gluteal musculature (arrows). The linear low signal structure (dashed arrow) represents the sciatic nerve.

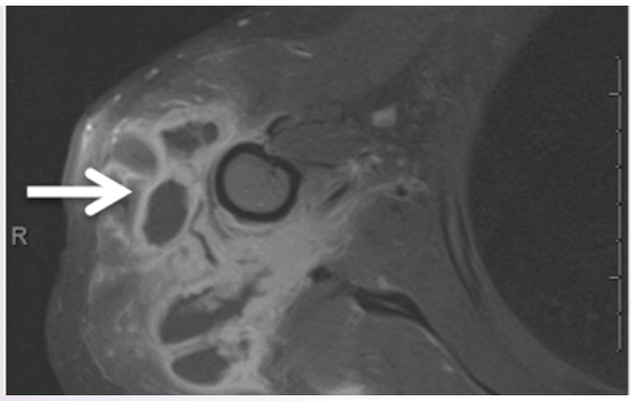

Figure 7. Fat-suppressed contrast-enhanced T1-weighted image of the deltoid region showing multiple thick-walled abscess cavities (arrow) following deltoid augmentation with fat transfer.

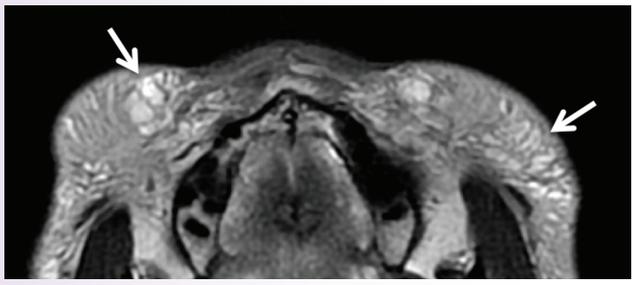

Figure 8. Collagen filler injections for malar augmentation seen on an axial T2-weighted MR image as increased subcutaneous infiltration and areas of lobular T2 hyperintensity (arrows).

CONCLUSION

Soft-tissue augmentation and implants are used frequently in plastic surgical procedures. The associated imaging findings must be readily recognised by the radiologist. These procedures may be performed purely for cosmetic reasons or for reconstruction after cancer surgery or other chronic illnesses. Complications, although rare in expert hands, must be readily recognised on diagnostic imaging and distinguished from normal post-operative findings.

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SEROXAT

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