

Tech & Innovation,
Shaping Foot Care
of the Future:

The DRIFT Project

Metabolomics

Fatalities Avoidable
with Antibiotics

Nutritional
Assessment in

New
Admissions
at SVPR

IMAGING
The
Fallopian
Tube



As a strong complement
to a maximally tolerated statin¹

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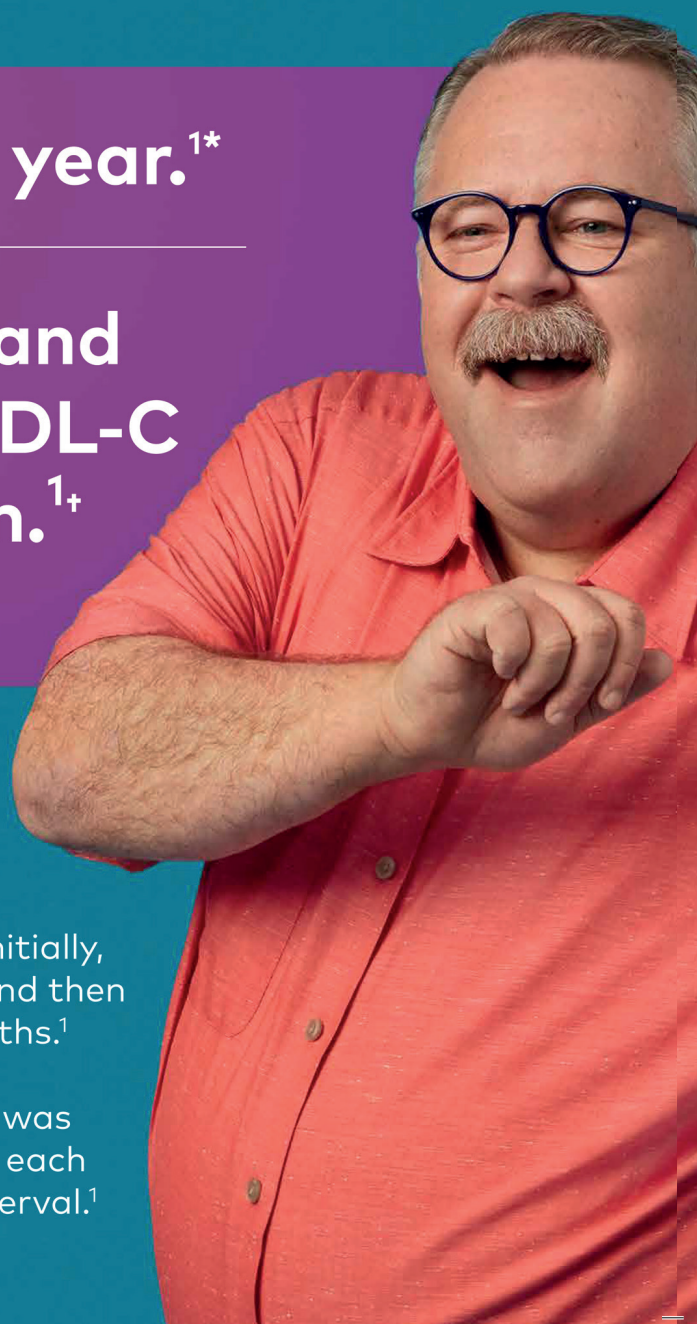
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Two doses a year.^{1*}

Effective and
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reduction.^{1†}

*LEQVIO is dosed initially,
again at 3 months, and then
once every 6 months.¹

†LDL-C reduction was
maintained during each
6-month dosing interval.¹



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TWO DOSES A YEAR^{1*}

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PRESENTATION: Leqvio 284 mg solution for injection in pre-filled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

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

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

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

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

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

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

LEGAL CATEGORY: POM PACK SIZES: Pre-filled syringe: x1 pre-filled syringe. Pre-filled syringe with needle guard: x1 pre-filled syringe with needle guard.

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

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001-2
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.

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

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hospital, live longer, and feel
better right from the start¹⁻⁴

Entresto®
sacubitril/valsartan
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**1st-line
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**The 2021 ACC ECDP Update
recommends ARNI as a first-line
treatment for all appropriate HFrEF patients¹**

ACC—American College of Cardiology; ARNI—angiotensin
receptor–neprilysin inhibitor; ECDP—Expert Consensus
Decision Pathway; HF—heart failure; HFrEF—heart failure with
reduced ejection fraction.

ENTRESTO® (sacubitril/valsartan)

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

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

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

Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 mL/min/1.73 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. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co-administered with another ARB containing medicinal product. **Hypotension:** Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended. **Impaired or worsening renal function:** Limited clinical experience in patients with severe renal impairment (estimated GFR <30 mL/min/1.73m²). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended. Use of sacubitril/valsartan may be associated with decreased renal function, and down-titration should be considered in these patients. **Impaired renal function:** Patients with mild-moderate renal function

are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. sacubitril/valsartan is not recommended in patients with end-stage renal disease. **Hyperkalaemia:** Treatment should not be initiated if the serum potassium level is >5.4 mmol/L. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoadrenalism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation if serum potassium level is >5.4 mmol/L discontinuation should be considered. **Angioedema:** Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartan immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It must not be re-administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification Tu.: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. **B-type natriuretic peptide (BNP):** BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate. Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered.

Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 mL/min/1.73 m²). Should not be co-administered with another ARB. Use with caution when co-administering sacubitril/valsartan with statins or PDE5 inhibitors. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartan is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of sacubitril/valsartan and furosemide reduced C_{max} and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co-administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin),

OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

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

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

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

Legal classification: POM.

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

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

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

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sacubitril/valsartan

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Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health for these last 30 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-authors of the article are Dr Mario Farrugia and Dr Michael Balzan



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ERRATA CORRIGE

The article 'Role of Hop Extract in Menopause' published in Issue 03 of Volume 21 (2022) included a typographical error. Estrogen receptors alpha were sometimes abbreviated as Er β instead of ER α . The correct version is found online on thesynapse.net. The error is regretted.



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Dr Mark Abela |
| Session 4 | Low T and other hormonal issues in Men
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| Session 5 | Men and GU Problems
Dr Donia Gamoudi |
| Webinar | Opportunistic Screening in Men |
| Planned Date | 1st February 2023 @ 20:00 Hrs |

Malta's Health Budget, a Princess & a Tin of Peas

I read with interest Chapter 6 of the Maltese Budget 2023 relating to health. I will analyse this with the eyes of a patient and also, those of a carer, as well as a healthcare provider.

It is very encouraging to see a Health Budget teeming with brilliant proposals. However, is it possible that the yellow brick road which it purports indeed makes us miss the forest for the trees?

Whilst we are advocating new technologies and new treatments, are we acknowledging the harsh reality of patients when they face out-of-stock medicines and medical devices on a regular basis? Let us consider cataract operations. These were largely postponed during the COVID-19 pandemic ... only to hit another brick wall in the second half of 2022. Lenses and custom packs were repeatedly out-of-stock for months on end. Will you believe me when I tell you that frail octogenarian oncology patients were summoned to MDH at 7:30am for the cataract operation ... only to be told that the required lens is out-of-stock, after the A-Scan was performed? Is this fair and just on vulnerable patients (and their carers)? And is this fair and just on our dedicated surgeons and nurses who waste precious time trying to juggle around out-of-stock items? Regretfully this is what our healthcare system offers to our vulnerable patients. I understand that securing stock may be geopolitically challenging for a small island at the periphery of Europe. But is it possible that we cannot plan and manage to procure lenses and custom packs for our patients who have been waiting for the operation for months on end?

The budget document also refers to the flagship Regional Centre in Paola, named after the late Dr Vincent Moran. I knew Dr Moran through my studies. He was a stalwart socialist whom I admired immensely. I believe that if he were still with us, he would question how the Ministry intends to attain the required manpower for the Centre, including specialists and nurses, when as we speak MDH is understaffed. The chronic understaffing has in turn churned various industrial actions from trade unions in the past years. In keeping with this, even a child will understand that ultimately, having your hospital appointment postponed either because of understaffing or because of an industrial action does not really matter. The end result is the same.

Chapter 5 of the budget document also trumpets the increase in investment in e-Health and the digitalization of the

Pathology department. This is commendable. But at times what the patient actually needs is that he reaches out to a particular department at one of our centres and someone picks up the other end of the telephone and addresses his or her queries. Getting through to specific departments in our hospitals is tantamount to performing a tracheostomy on oneself with bare hands.

It is also nice to hear that urgent oncology patients will receive treatment within 12 weeks from diagnosis. It is equally nice to have navigator nurses at SAMOC. However, wouldn't it be even nicer if we manage properly the repeated shutdown of one, two or all three linear accelerators at SAMOC which invariably occur periodically. Sometimes it is because of annual servicing, and other times because of 'water seepage', and other times still, because of other breakdowns. When one or two accelerators are not functioning, patients get called in for radiotherapy sessions, nauseated and tired of living, at ridiculous times, even at 11pm. When all three accelerators are not functioning ... [Dear Reader, this is not an assumption; this actually happened last July] ... Malta's radiotherapy sessions at SAMOC are brought to a halt.

It seems that Hans Christian Andersen's fable of the Princess and the Pea is still relevant today. Seeing something which is seemingly appealing and first-class [twenty mattresses and twenty eider-down duvets] in reality could translate in the most unpleasant experience for those who are vulnerable in specific settings ...

We have seen great improvement in health services since 2013. But they need to improve much more. If there is the correct *forma mentis* in the application of the Goldilocks principle, problems become challenges which can and should be overcome.

Fortunately, my life journey made me encounter many brilliant healthcare professionals at our hospitals and centres who offer a sterling service. It is these dedicated surgeons and specialists who help mitigate the gargantuan shortcomings of our health service.

This narrative has been written through my tired eyes of carer, patient, as well as healthcare provider. It may be subjective but it is a reality, nonetheless.

I wish you a peaceful Christmas and a serene New Year firmly rooted in Ubuntu values. Keep well.

Pan Ellis

Tech & Innovation, Shaping Foot Care of the Future: The DRIFT Project

KEY WORDS

Diabetic foot, foot ulceration, health-tech, innovation, foot screening

BACKGROUND

Diabetes Mellitus (DM) affects 8.5% of the global population, while in Malta, approximately 37,800 individuals (11.2% of the Maltese population) are affected by the condition.¹ Individuals living with diabetes are at risk of developing foot complications, such as foot ulceration, which can lead to amputations followed by permanent disability and reduction in quality of life and independence.² This is set to increase in the coming years, because of an aging population, sedentary lifestyle, and an altered dietary pattern. In Malta alone, diabetes leads to more than 400 lower limb amputations every year, with more than half of these amputees losing their lives within 5 years of the intervention.³ However, through research we know that 85% of these amputations can be prevented with proper screening, prevention programmes and timely management of the disease.⁴ Current foot screening programs require the individual to attend the hospital on routine basis, with such services being harshly impacted during the months due to the COVID-19 pandemic.⁵ This was not only witnessed locally, but also at a global level. This unprecedented situation has been well documented in a retrospective study published by Rastogi et al. in 2021.⁶ Furthermore, the WHO (2020a) reported that out of 155 countries, half of them had partially or completely disrupted health services related to diabetes care and management during May 2020.⁷ Apart from the disruption of non-emergency foot care services, high-risk patients themselves were reluctant and fearful to seek medical assistance during this period.⁸ This may account for the increase in lower limb complications witnessed during the COVID-19 period. In fact, more severe presentations of peripheral arterial disease (PAD) were observed during this time with individuals living with DM being 10.8 times more likely to undergo any level of amputation, while risk for a major amputation (transfemoral or transtibial) stood at 12.5 times higher.^{9,10}

RETHINKING THE PROVISION OF HEALTHCARE

These circumstances have shed light on the many challenges faced in the delivery of care, and the importance for a healthcare system to adapt and remodel itself to address and meet the current demands. The COVID-19 pandemic has necessitated a switch from the traditional way of providing foot care services to other innovative methods care. A good example of this is teleconsultations and remote patient monitoring, which have been widely and increasingly utilized in the past months with success.¹¹

A digital transformation of diabetes foot care has the potential to empower individuals living with diabetes to manage their care by improving the quality and continuity of care provided in the hospital setting and extended in the home and work environment. Enabling people living with diabetes or those at high risk of developing diabetes-related foot complications to manage their condition with integrated digital solutions should be highly considered.

INNOVATION IN THE PREVENTION OF DIABETIC FOOT COMPLICATIONS

Recent advances in the diabetes care paradigm have brought us into a new era of care. Among these are digital medicine products, including continuous glucose monitors, connected insulin pens, and advanced hybrid closed-loop insulin pumps – all targeted at keeping stable glucose levels.

An area that has in recent years attracted significant interest for the prevention of foot ulcerations, is the monitoring of foot temperatures. Elevated skin temperature has been associated with pressure ulcer development in several studies, with any condition that increases skin temperature being suggested to increase the susceptibility to tissue breakdown.¹²⁻¹⁵ It is known that prior to skin breakdown and ulceration, the temperature of the designated area in the foot increases due to localised inflammation – this is known as a ‘warm spot’. This is often brought about by footwear with increased friction between the skin and the shoe interface.



Consequently, the monitoring of skin foot temperature has been used, and proved to be an effective approach in determining the health status of the foot and in preventing foot complications. For example, one study found that 97% of non-traumatic diabetic foot ulcers (DFU) were properly detected through foot temperature assessment around 5 weeks before any visual signs of such DFUs appeared on the foot.¹⁶ Hence, foot temperature monitoring at home could greatly help individuals living with diabetes to identify the 'pre-ulcerative' foot and to predict complications at a much earlier stage.

Over the years, this has led to the development of various foot temperature measurement systems. While some are used solely as research tools in controlled lab environments, others have been made available as clinical tools for use by medical professionals, and a few are also commercialised as consumer products for home use by the patients.¹⁷

THE DRIFT (DENSE RECORDING OF IN-SHOE FOOT TEMPERATURES) PROJECT

Reducing the risk of developing foot complications in diabetes is the logical first priority. Researchers at the University of Malta (UM) in collaboration with Mater Dei Hospital are currently developing smart insoles with embedded thermal sensors that interact with the sole of the foot. This wearable sensor-rich in-shoe monitoring system consists of a dense array of sensors for foot condition and patient activity monitoring, developed to detect arising problematic foot conditions at an early stage. The system will provide users with real-time alerts and suggestions for remedial actions, and can also be used to provide clinicians and consultants with access to regular objective data relating to the patient's condition. This innovative technology aims to transform care for people with diabetes, will aid the clinician to better devise preventive care management, and will significantly reduce the financial burden on the healthcare system by not only reducing the number of ulcerations and amputations, but also improving patients' quality of life.

CONCLUSION

The COVID-19 pandemic has highlighted possibilities and the need for technological advancement products and solutions to support diabetes care. Embracing the change in the delivery of care, will not only be of benefit for the user (patient) but will also provide the clinician with easily available objective data to better devise management care programmes to prevent injury and

reduce the number of ulcerations and amputations in this specific population. This novel approach will bring a paradigm shift in diabetic foot care, bridging self-care and health care.

ACKNOWLEDGMENTS,

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Metabolomics

ABSTRACT

Metabolomics is the process whereby metabolites are profiled in biofluids, cells and tissues. With the advance of informatics and other analytical technologies, metabolomic profile analyses are being used to understand physiological and pathophysiological mechanisms. Thus with other -omics, research into metabolomics is showing potential to be another useful tool in understanding health and disease, and help in their management.

INTRODUCTION

By definition, a metabolite is an organic molecule with a molecular weight (MW) of less than 1500 Da (Dalton).¹ Metabolites encompass many different chemical families. Examples include peptides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, alkaloids, foods, food additives, toxins, pollutants, drugs and their metabolites. The spectrum also includes human and microbial products.

Metabolomics is a field of life science research that identifies and/or characterises metabolites in many matrices² like saliva, serum, urine, exhaled air, cells, tissue or organism. The total profile of the metabolites is called the metabolome.

About 50,000 metabolites have been identified in humans. Slowly but surely, this number is likely to expand as other metabolites which as yet cannot be detected or unknown will make this number higher. Indeed, these undetected or unknown metabolites have been nicknamed the 'dark matter of the metabolome'.

Broadly, metabolites can be categorised into endogenous or exogenous metabolites. Endogenous metabolites are far more numerous than exogenous ones. Besides being the most abundant, the endogenous metabolites also span the greatest concentration ranges. Indeed, their concentration varies from low picomolar up to almost molar levels. They can be located in a database called the 'Human Metabolic Database'. Urea is the most abundant in terms of its concentration in the body. Endogenous metabolites are generally further divided into primary metabolites and secondary metabolites. Primary metabolites are generated in primary pathways of metabolism, like the Krebs's cycle or glycolysis. On the other hand, secondary metabolites are metabolites that are generated from primary metabolites.

Exogenous metabolites are those that are derived from an outside source. Examples include food, drugs and their metabolites, toxins, and environmental pollutants. Drugs

span typically a lower range in concentration, around micromolar levels. Toxins and environmental chemicals (pollutants) hopefully range in the nano-molar concentration or below. Higher concentration spells trouble.

Metabolism has been basically 'understood' and worked in the 1950's and 60's and one can connect many metabolites to many genes. Indeed, metabolism is exquisitely detailed far more than any other biology field. So by knowing well the metabolome, researchers end up connecting it with the proteome and the genome to bring together the concept of systems biology.

Innovation is still happening in metabolomics and it is moving more forward from the back room to the front room. Having said this, it is still falling behind the other -omics. This is because of the involved chemistry. Genomics deals with 4 bases while proteomics deals with 20 amino-acids, in different combinations, but metabolomics deals with thousands of different chemicals, which have different behaviour and different features. Even though metabolomics is the endpoint in the 'omics' flow (genomics–transcriptomics–proteomics–metabolomics), it comes with its own important advantages which are listed in table 1.

TABLE 1. ADVANTAGES ASSOCIATED WITH THE STUDY OF METABOLOMICS.

Advantage	Reference
Levels of several metabolites could be profiled and their perturbation could be connected to a pathophysiological condition.	3
Small alterations in gene expression or protein synthesis result in bigger changes of metabolite levels.	4
Compared with the genome or proteome, the metabolome is more sensitive to pathophysiological changes.	5
The metabolome is dynamic and it changes rapidly with the cell status. This allows the cell state to be evaluated temporally.	3
Metabolome profiling could decipher pathways of disease progression.	6
Metabolome perturbations are intimately linked with the phenotype.	6

Metabolomic profiling can be done through an 'untargeted' or a 'targeted' approach. In the untargeted



method the aim is to detect as many metabolites as possible.⁴ In the targeted approach, specific metabolites from a particular metabolic pathway are profiled and quantified. The targeted approach can be used to confirm results obtained by the untargeted method.^{4,6}

Along the years, several branches emerged from metabolomics. Amongst these are 'lipidomics' and 'volatilomics'. The latter analyses 'volatile organic compounds' (VOCs), like ketones, aldehydes, alcohols, hydrocarbons and aromatic compounds.⁷ These VOCs are end products of biological processes in the human body and can be found in blood, sweat, urine, faeces, saliva or breath.^{7,8} It was observed that trained sniffer dogs could 'smell' these VOCs in urine or skin samples of patients with specific cancers. This led to their investigation as possible cancer biomarkers.⁹ Indeed, it was found that VOC composition was different in different types of cancer¹⁰⁻¹² and could be used clinically using what is called an 'electronic nose' (e-nose), which is a technological biological sensor.⁷

Lipidomics involves qualitative and quantitative metabolic profiling methods that analyse lipid metabolites in biological samples.¹³ The interest in lipidomics has increased because cancer cells exhibit perturbations in the lipidome signatures and thus offer the possibility of using lipids in theranostic applications, like finding lipid-based biomarkers and lipid therapeutic targets.^{14,15} Also, research in lipidome profiles is helping to understand carcinogenesis and cancer progression. Mammalian cells have around 10,000 lipid species¹⁶ which can be classified into classes and subclasses, of which glycerophospholipids (GPLs), sphingolipids (SL), and lysophospholipids (LPLs) (a subclass of GPLs) are the most studied in cancer research.

METABOLICS AND DRUGS

The field of metabolomics has its specific strengths in the landscape of drug repurposing, especially when used integrally with other-omics like genomics, epigenomics, transcriptomics, and proteomics.

Combination therapies have the potential to offer new opportunities in fighting antibiotic resistance. Using high-throughput metabolomics, Campos et al.¹⁷ designed an approach to predict drug-drug interactions and opened insights for repurposing compounds to be used in combination therapies. Specifically, the authors predicted some novel drug combinations like sulfamethizole (a sulfonamide antibiotic) and zidovudine (a dideoxynucleoside used in the treatment of HIV infection) against *E. coli*.

Lima et al.¹⁸ also used metabolomics to understand the mode of action of the anti-depressant sertraline when used against *Leishmania infantum*. The authors found that sertraline kills *Leishmania* by targeting essential metabolic pathways of the parasite. They propose that sertraline can be a valuable drug against visceral leishmaniasis.

Metabolomics has also been utilized to predict the efficacy of antivirals in Covid-19.¹⁹ Indeed, metabolomics showed that antiviral efficacy could depend on the metabolic phenotype of the patient. It was found that the most important metabolomic perturbations were increased metabolites associated with *de novo* NAD (nicotinamide adenine dinucleotide) production, mitochondrial function and ATP production. This could explain the decreased effectiveness of nucleoside-based antivirals used or tried for treating SARS-CoV-2 (e.g., remdesivir, ribavirin, and favipiravir) as these need host enzymes to be activated by endogenous ATP, changing them into the active triphosphate kind. Thus one can propose clinical trials of antivirals or other drugs, to monitor the metabolotypes of patients (stratified by viral load, outcome, sex, age, day/s of treatment, and so on). This could be potentially critical in optimizing their efficacy, like what drugs can be used and when.

METABOLOMICS IN CANCER

Generally, early detection of many neoplasms is very important in their management. Several approaches have been suggested and such potential candidates are metabolomic-based biomarkers. This is because metabolites are closely related to the neoplastic phenotype and also because metabolomic profiling can be easily done on different human bio-fluids, like blood, urine, and faeces. Indeed, such metabolomic biomarkers are being investigated for several neoplasms.

Erben et al.²⁰ did a literature search in 'PubMed' and 'Web of Science' for potential metabolomic biomarkers for the early detection of colorectal neoplasms. They analysed 41 studies and concluded that single metabolites are of limited use to discriminate people with or without colorectal neoplasm. However, metabolite panels are potential candidates; specifically, amino acid panels in blood samples and nucleosides in urine samples.

Using a multi-centred study (ClinicalTrials.gov NCT01486745), Eisner et al.²¹ investigated and assessed the possibility of using urine metabolomics for the screening of colorectal cancer (CRC). They were able to create an automated diagnostic test using a urine sample to differentiate those patients who need a colonoscopy from those who do not.

Prostate-specific antigen (PSA) is an essential biomarker for prostatic cancer diagnosis. Nevertheless, when it comes to levels of 4-10ng/ml, dubbed the 'gray zone', PSA is not accurate. Xu et al.²² used serum metabolomic profiling to differentiate between benign prostatic hyperplasia (BPH) and prostate cancer (PCa) in patients with PSA levels in the gray zone. They identified 18 lipids and lipid-related metabolites as potential biomarkers that could discriminate between patients with BPH and PCa with PSA levels in the gray zone.

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TRADE NAME: Utrogestan 100 mg, soft oral or vaginal capsule

COMPOSITION: Progesterone 100mg per soft capsule.

PHARMACEUTICAL FORM: Soft oral or vaginal capsule

INDICATIONS

Oral route: Disorders associated with progesterone deficiency, in particular:
• Premenstrual syndrome • Menstrual irregularities due to dysovulation or anovulation • Benign mastopathy • Perimenopause • Hormone replacement therapy for menopause (in addition to oestrogen therapy)

Vaginal route: • Progesterone support during ovarian insufficiency or complete ovarian failure in women lacking ovarian function (oocyte donation)
• Supplementation of the luteal phase during in-vitro fertilisation (IVF) cycles
• Supplementation of the luteal phase during spontaneous or induced cycles, in cases of sub-fertility or primary or secondary infertility, particularly due to dysovulation • In cases of threatened miscarriage or prevention of recurrent miscarriage due to luteal phase deficiency, until week 12 of pregnancy. For all other indications of progesterone, the vaginal route represents an alternative to the oral route in cases of:
• Side effects caused by progesterone (drowsiness following absorption via the oral route).

POSLOGY The dosage must not exceed 200 mg per dose, regardless of the indication and route of administration (oral or vaginal). Oral route: For progesterone deficiency, an average dose of 200-300 mg of micronised progesterone per day is recommended. • For luteal insufficiency (premenstrual syndrome, benign mastopathy, irregular menstruation and perimenopause), the usual therapeutic regimen is 200-300 mg per day. A single dose of 200 mg in the evening, upon going to bed, or 300 mg split over two doses Ten days per cycle, usually from day 17 to day 26, inclusive. • When used as a hormone replacement therapy for menopause: oestrogen therapy alone is not advised (due to the risk of endometrial hyperplasia). Instead, progesterone should be incorporated at a dose of 200 mg per day: Split over two 100 mg doses, or as a single 200-mg dose in the evening, upon going to bed, either from day 12 to day 14 of the month, or during the last two weeks of each treatment course. Following this treatment, all replacement therapies should be suspended for approximately one week, during which time it is normal to

observe withdrawal bleeding. For these indications, the vaginal route should be used, at the same dosage as for the oral route, in the event of side effects caused by progesterone (drowsiness following oral absorption). Vaginal route: • Progesterone replacement therapy in cases of ovarian insufficiency or complete ovarian failure in women lacking ovaries (oocyte donation). The therapeutic regimen (in addition to appropriate oestrogen therapy) is as follows: 100 mg of micronised progesterone per day on days 13 and 14 of the transfer cycle, then 200 mg of micronised progesterone per day on days 15 and 25 of the transfer cycle, split over one or two doses per day, then From day 26 of the cycle, and in cases of an incipient pregnancy, the dose may be increased up to a maximum of 600 mg per day, split over three doses. This dosage should be adhered to until day 60, or until week 12 of pregnancy at the latest. • Supplementation of the luteal phase during IVF cycles: The recommended dosage is 400-600 mg per day, over two to three doses per day, from the date of HCG injection until week 12 of pregnancy. • Supplementation of the luteal phase in cases of spontaneous or induced cycles, in subjects with sub-fertility or primary or secondary sterility, particularly due to dysovulation: the recommended dosage is 200-300 mg per day, over two doses, for ten days, from day 17 of the cycle. If menstruation does not resume and pregnancy is diagnosed, treatment should be quickly resumed until week 12 of pregnancy. • Threatened early miscarriage or repeated miscarriage due to luteal phase insufficiency: the recommended dosage is 200-400 mg per day, split over two doses, until week 12 of pregnancy. Method of administration: Oral route: It is recommended to use this medicinal product sometime after eating, preferably in the evenings upon going to bed. Vaginal route: Each capsule should be inserted deep into the vagina.

CONTRAINDICATIONS This medicinal product is contraindicated in cases of severe liver impairment.

SPECIAL WARNINGS AND PRECAUTIONS OF USE: More than half of all early miscarriages are due to genetic disorders. Early miscarriages can also be caused by infectious phenomena or mechanical disorders. The administration of progesterone should therefore have the sole effect of delaying the release of a dead ovum (or interrupting a non-progressing pregnancy). • The use of progesterone should be reserved for cases of insufficient secretion by the corpus luteum. • Under the recommended conditions of use, this treatment

is not contraceptive. • The use of UTROGESTAN 100 mg during pregnancy is restricted to the first trimester via the vaginal route. UTROGESTAN 100 mg is not a treatment for the threat of preterm birth. • Exceptional cases of cytolytic hepatitis and intrahepatic cholestasis of pregnancy have been reported in patients using micronised progesterone, during the second and third trimesters of pregnancy.

FERTILITY, PREGNANCY AND LACTATION: Several epidemiological studies in more than one thousand patients have found no association between progesterone and foetal malformation.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: It is important, particularly for those driving or using machines, to be aware of the risks of drowsiness and/or feelings of dizziness connected with the use of this medicinal product via the oral route.

UNDESIRABLE EFFECTS: Oral route: • Drowsiness or transient feelings of dizziness, occurring one to three hours after ingesting the product. In this event: Reduce the dosage of each dose, or adjust the timing of doses (e.g., for a dose of 200 mg per day, take the full 200 mg in a single dose in the evening, sometime after eating), or Adopt vaginal administration. • Shortened menstrual cycle or intercurrent bleeding: Delay the start of treatment until later in the cycle (e.g., start on day 19 of the cycle instead of day 17). These effects most commonly indicate an overdose. Vaginal route: No local intolerances (such as burning, pruritus or fatty discharge) have been observed during various clinical trials. No general side effects, including drowsiness or transient feelings of dizziness, have been reported during clinical studies, at the recommended dosages.

MARKETING AUTHORISATION HOLDER: Laboratoires Besins International 3, Rue Du Bourg L'Abbe 75003 Paris

MARKETING AUTHORISATION NUMBER: 323 275-1

LEGAL CATEGORY: POM

DATE OF REVISION OF THE TEXT: May 2017.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from PAC3 Ltd. 91, Triq i-Siggiewi, Siggiewi, SGW2021 Malta. Tel. +356 462326.

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TRADE NAME Utrogestan Vaginal 200 mg Capsules, soft

COMPOSITION Each capsule contains 200 mg progesterone (micronised).

PHARMACEUTICAL FORM Vaginal Capsule, soft. Ovoid and slightly soft yellow capsules, containing whitish oily suspension.

INDICATIONS

Indicated in women for: Supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles. Prevention of preterm birth in women with a singleton pregnancy who have a short cervix (mid-trimester sonographic cervix ≤ 25 mm) and/or a history of spontaneous preterm birth.

POSLOGY For supplementation of the luteal phase during Assisted Reproductive Technology cycles - the recommended dose is 600 mg/day, given in three divided doses, one in the morning, one at midday and the third at bedtime. The treatment is started not later than the third day after oocyte retrieval. If pregnancy has been confirmed, continue treatment until at least the 7th week but no longer than the 12th week of pregnancy. For prevention of preterm birth in women with a singleton pregnancy who have a short cervix and/or a history of spontaneous preterm birth, the recommended dosage is 200 mg per day in the evening at bedtime from around week 20 to week 34 of pregnancy. Paediatric population: There is no relevant use of Utrogestan in the paediatric population. Elderly patients: There is no relevant use of Utrogestan in the elderly. Method of Administration: Vaginal. Each capsule of Utrogestan must be inserted deep into the vagina.

CONTRA-INDICATIONS

Hypersensitivity to the active substance or to any of the excipients; Severe hepatic dysfunction; Undiagnosed vaginal bleeding; Mammary or genital tract carcinoma; Thrombophlebitis; Thromboembolic disorders; Cerebral haemorrhage; Porphyria; Missed abortion; Premature rupture of membranes (PPROM); Allergy to peanuts or soya.

WARNING AND PRECAUTIONS FOR USE

A complete medical examination must be performed before starting and regularly during the treatment; Utrogestan is not suitable as a contraceptive; In rare cases, the use of micronised progesterone during the second and third trimester of pregnancy may lead to the development of gravidic cholestasis or hepatocellular liver disease; Treatment should be discontinued upon diagnosis of a missed abortion. Precautions: Any vaginal bleeding should always be investigated. *Warning specific for supplementation of the luteal phase during Assisted Reproductive Technology cycles:* Utrogestan should only be used during the first three months of pregnancy and must only be administered by vaginal route. *Precautions specific for prevention of preterm birth in women with a singleton pregnancy who have a short cervix and/or a history of spontaneous preterm birth:* Before treatment is initiated: The risks and benefits of the options available, should be discussed with the patient. The physician and patient should make a shared decision on which treatment is most suitable. Premature rupture of membranes (PPROM) should be excluded. Should rupture of membranes occur during treatment, further treatment with Utrogestan should be discontinued. Utrogestan contains soybean lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Utrogestan.

FERTILITY, PREGNANCY AND LACTATION: Natural progesterone may be given orally, vaginally or by the intramuscular route to treat luteal phase deficiency until at least the 7th week of pregnancy and not later than the 12th week of pregnancy. Natural progesterone may also be given vaginally for prevention of preterm birth, from the 20th week of pregnancy to the 34th week of pregnancy.

Pregnancy: No association has been found between the maternal use of natural progesterone in early pregnancy and fetal malformations.

Breastfeeding: Utrogestan is not indicated during breast-feeding. Detectable amounts of progesterone enter the breast milk.

Fertility: As this medicinal product is indicated to support luteal deficiency in sub-fertile or infertile women, there is no deleterious known effect on fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Utrogestan has negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Local intolerance (burning, itching or oily discharge) has been observed in clinical studies and has been reported in publications, but the incidence is extremely rare. When used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine. Pruritus, vaginal haemorrhage, vaginal discharge, burning sensation.

MARKETING AUTHORISATION HOLDER:

Besins Healthcare SA, Rue Washington 80, 1050, Ixelles, Belgium.

MARKETING AUTHORISATION NUMBER: MA727/00205.

LEGAL CATEGORY: POM

DATE OF REVISION OF TEXT: June 2022.

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PAC3



Ovarian cancer (OC) is another cancer where metabolomic profiling is being investigated and proposed as a potential biomarker of this silent killer. As other cancers, ovarian cancer causes metabolic perturbations to maintain its growth and metabolomic analyses can unveil these perturbations and detect cancer in its early stages. Yang et al.²³ studied these metabolic alterations of OC, aiming to find potential metabolomic-based biomarkers and potential targets for treatment. As biomarkers they proposed two metabolites that showed a sensitivity of 96.7% and a specificity of 66.7%. The two metabolites were 2-piperidinone and 1-heptadecanoylglycerophosphoethanolamine. They also found metabolic perturbations in fatty acid β -oxidation, phospholipid metabolism, and bile acid metabolism, which are associated with proliferation and metastasis of OC cells.

METABOLOMICS IN AUTISM SPECTRUM DISORDER (ASD)

ASD is a complex heterogeneous disorder. In order to reduce this complexity and heterogeneity, the 'Children's Autism Metabolome Project' (CAMP) (ClinicalTrials.gov Identifier: NCT02548442) was embarked on using a quantitative metabolomic approach. Metabolomic perturbations in ASD patients were identified and these subjects were classed into subpopulations with similar 'metabotypes' (metabolic phenotypes). Smith et al.²⁴ with their metabolomic screening method detected more than 50% of the autistic subjects. They propose that if their approach can be developed further to increase its sensitivity and specificity, it could help in earlier referral and diagnosis of ASD. They also claim that their method gives insight to possible targets for treatment.

METABOLOMICS IN PSYCHIATRIC DISORDERS

The molecular pathophysiological pathways of psychiatric disorders are still incomplete. Due to this fact, the treatment and diagnosis of each disorder relies on a uniform approach, despite the fact that within each disorder there is heterogeneity. This limits the ultimate goal of 'precision psychiatry' based on phenotype stratification of patients. Metabolomics is being used towards this end by detecting and investigating perturbations in metabolomic signatures which give insight of underlying mechanisms.

For example, an untargeted serum metabolomic profiling of a cohort of subjects carried out by Tasic et al.²⁵ could differentiate schizophrenic patients from the healthy subjects. Besides, the investigation pointed to the glycolysis pathway and confirmed the 'hyperglutamate hypothesis'.²⁶ The results of Yang et al.²⁷ implicated perturbations in fatty acid metabolism, carbohydrate metabolism, and amino acid metabolism.

Metabolomics can also be used to identify patients with mental illness who are at risk of metabolic co-morbidities related to their treatment. For example, mentally ill patients often gain weight during their treatment. Metabolomic and

lipidomic profiling show that certain perturbations in lipid signatures are associated with this weight gain.²⁸

Metabolomic profiling can also be used to tackle the inconsistency of patient's response to treatment.²⁹ It can also be used to predict recovery from depression,³⁰ or as a biomarker in anxiety disorders.³¹

All this shows that metabolomic biomarkers have the potential in theranostics, helping in diagnosis, patient stratification in a heterogeneous population, monitoring treatment response and disease progression, and lastly in finding targets, like eicosanoids, for novel treatments.³²

METABOLOMICS IN CARDIOVASCULAR DISEASE

Jiang et al.³³ used serum metabolomics to try and find biomarkers in acute coronary syndrome (ACS). Their results fished four metabolites, namely betaine, acetylcarnitine, isoundecylic acid and 1-heptadecanoyl-sn-glycero-3-phosphocholine. They proposed that these differential metabolites could be used in the management of ACS.

From the ARIC study (Atherosclerosis Risk in Communities), Wang et al.³⁴ fished 19 differential metabolites and proposed a 'metabolite risk score' that can be used to better assess the risk of Coronary Heart Disease (CHD). They also highlight the fact that their findings point to novel causative pathways of CHD.

MICROBIOME-METABOLOMICS

Ya-Long Feng et al.³⁵ used a rat model for chronic kidney disease (CKD) to study the dysbiosis of the gut microbiome and CKD. A microbiome-untargeted metabolomic analyses showed decreased microbe diversity and richness and a substantial change in 291 serum metabolites. The altered metabolite profile pointed to dysregulation in the metabolism of amino acids, polyamines, bile acids and lipids. Giving the CKD rats poricoic acid A and poriacocos bettered the microbial dysbiosis and reduced renal fibrosis and hypertension. This study confirmed the association between CKD and dysbiosis of the gut microbiome, and importantly that through dietary manipulation one can improve the dysbiosis and the disarrayed metabolome, and also delay kidney disease.

Kanbay et al.³⁶ also suggest that gut microbiome modification can be used in CKD as prevention and treatment.

SINGLE CELL METABOLOMICS

High-throughput metabolomics is now even possible at the cellular level using 'single cell metabolomics' (SCM). Specifically, SCM is used to profile metabolites in individual cells. This makes it a very powerful tool to study cell heterogeneity. Thus, it can be used to identify cell types and their differentiation in cell colonies. Indeed, it is being applied in various fields like neurology and oncology.

In neuroscience research,³⁷ SCM is being used to analyse differences between similar cells in the brain (like oligodendrocytes) and also to study differences between different cell types (like neurons and astrocytes). The studies are also being applied to unveil changes, which occur in such cells, with diet, drugs and disease. As in other fields this will surely be helpful in the theranostics of brain diseases.

In any one type of tumour, the cells could have different phenotypes, a condition called cancer heterogeneity. In oncology research, SCM is being used to identify such cancer heterogeneity and this will in the future be translated into more precise cancer diagnosis and personalized treatment. For example, Tian et al.³⁸ propose a SCM platform to monitor drug resistance of non-muscle invasive bladder cancer (NMIBC) treated with intravesical chemotherapy (post transurethral resection). Specifically, they used SCM of urinary exfoliated tumour cells (UETCs).

CONCLUSION

Metabolomic profiling is showing great promise in theranostics. Indeed, it can help in disease diagnosis when used as biomarkers, in the stratification of patients (and hence in more personalized treatment) and in monitoring patient's response to treatment. It can also be applied to follow disease progression; and lastly, metabolomics can unveil targets for new treatment.

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Fatalities Avoidable with Antibiotics

The problem of antibiotic misuse and emergence of antibiotic-resistant bacteria has been around for several decades and strict dispensing of antibiotics by doctor's prescription, and only after microbiological sensitivity studies, particularly in hospital settings, was introduced early especially in north European countries such as the UK.

However, withholding antibiotic use pending identification of the infective agent involved and its antibiotic sensitivity profile may sometimes result in unwanted serious, even fatal, consequences. Here are some cases that came to my personal attention in the UK Coroner's investigations and also, two cases in Malta.

UK CASES

A previously healthy 33 year-old Englishman was suffering from flu-like symptoms, with cough and pyrexia, and his wife phoned their GP and her husband was prescribed paracetamol. Two days later he's worse, can hardly walk to the bathroom and his wife phones the GP again, who demands that her husband is referred to hospital. He dies soon after arriving at the emergency department. At the Coroner's autopsy his lungs were extremely congested and swabs from the lungs and pulmonary trunk blood grew pure cultures of *Streptococcus pneumoniae*. Diagnosis: septic shock from acute bacterial pneumonia.

A 9 year-old English girl returns from school feeling unwell and complaining of some tummy ache. She is feverish and her mother calls this young GP who attends and notes a soft non-tender tummy, is unsure of the diagnosis, recommends a "flu" anti-inflammatory oral medication and says he'll visit again next day. In the morning the mother finds her daughter dead in bed. The Coroner's autopsy finds a right lower lobar pneumonia with some purulent pleurisy and swabs from this lobe and from pulmonary trunk blood grew pure cultures of *Streptococcus pneumoniae*. Right pleural inflammatory irritation of the tenth intercostal nerve explained the referred pain around the umbilicus - the abdominal contents were normal. Cause of death: septic shock from acute bacterial pneumonia.

A 55-year-old menopausal English woman visits her GP surgery because of a very recent brownish vaginal discharge, is feeling a little unwell with some discomfort in the outer aspect of her left leg. A cervical smear is taken and she is given some paracetamol. Next day she deteriorates rapidly and dies at home. At autopsy there

is little of note apart from a vague skin discolouration on the outer aspect of the left calf and lower leg. However, swabs from the uterine cavity, subcutaneous tissue of the outer aspect of the left leg, and from pulmonary trunk blood, all grow pure cultures of group A *Streptococcus pyogenes*. Cause of death: septic shock due to *Streptococcal* infection including erysipelas.

An English teenaged boy develops a sore throat and after it persists for a few days a visit to the GP surgery recommended a simple analgesic as it must have been presumed to be of viral aetiology. The sore throat persists and he misses school for at least three weeks. There is history of his urine getting pinkish or dark and a decreasing need to urinate. He is eventually found dead at home. He lived with his single mother in a somewhat deprived area of the town. The main findings at post-mortem were swollen pale kidneys and a swab from his tonsils later identified a group A β -haemolytic streptococcus. Kidneys are normally congested at autopsy due to terminal cardiovascular failure but they are notably pale in death due to fatal bleeding (hypovolaemic shock) or in some types of acute glomerular disease. In this case the cause of death was acute renal failure due to post-streptococcal glomerulonephritis.

A Royal Marsden Hospital patient, an Englishman in his late sixties, previously treated for high grade lymphoma, is admitted because he's been recently unwell and tumour recurrence is suspected. He is feverish and has a cough but before investigations are carried out and results known, he dies less than 24 hours after admission. At autopsy no recurrent tumour could be found and his lungs are congested and bronchi are full of purulent secretions. Cause of death: bronchopneumonia.

MALTESE CASES

A 10-year-old Maltese boy first complains of a sore throat and after a couple of days develops abdominal pain. The family doctor fears this might be appendicitis and refers him to St Luke's Hospital. A consultant surgeon removes a grossly unremarkable appendix (later also reported as uninfamed by the laboratory) and also notes unremarkable abdominal contents. However, the boy doesn't make the usual speedy recovery after surgery. It happens to be a long holiday weekend and his consultant has gone on vacation leave. His general condition deteriorates and pus is noted exuding from

A 16-YEAR-OLD MALTESE GIRL DEVELOPS A SEVERE FRONTAL HEADACHE ... THEIR GP DIAGNOSES FRONTAL SINUS PAIN AND RECOMMENDS PARACETAMOL. NEXT DAY SHE'S FEELING WORSE ... SO HER MOTHER TAKES HER TO MATER DEI WHERE AN EMERGENCY DEPARTMENT HO ALSO DIAGNOSES FRONTAL SINUS PAIN AND ADVISES TO CONTINUE WITH PARACETAMOL ... THE FOLLOWING DAY THE GIRL FALLS INTO A COMA AND DIES ...

the abdominal wound. He is eventually seen by a duty senior surgical registrar who takes him back to theatre and finds he has a purulent generalised peritonitis. The boy dies soon after. I was not directly involved with this case but what I know about it came from Professor Paul Cuschieri of the microbiology department and letters in the Malta Sunday Times.

The boy's parents were obviously distraught and took to the letters column of The Sunday Times insinuating, more than once, that some fault in the consultant's surgical technique, before leaving on holiday, was responsible for their son's tragic death. Perhaps foolhardily I took it upon myself to answer the parents' letters in the paper. I explained their son's case was a rarity and could have easily fooled any doctor. The microbiologist had confirmed with me that autopsy swabs from the boy's throat and peritoneal pus all grew the same type of streptococcus. So, streptococcus from the throat had found its way to the peritoneal cavity via the bloodstream, just as meningococcus finds its way from the nose or pharynx, via the bloodstream, to the meninges. I have also seen Klebsiella from an inflamed urinary bladder find its way to the meninges and causing death by purulent meningitis. In this boy's case whether appropriate type, timing and dosage of antibiotic had been used remained unclear as far as I could gather.

The medical defence lawyer acting for the consultant surgeon later thanked me for the help offered via the Sunday paper.

A 16-year-old Maltese girl develops a severe frontal headache. Because she doesn't normally suffer from headaches her mother calls their GP who diagnoses frontal sinus pain and recommends paracetamol. Next day she's feeling worse, then says she's seeing double, so her mother takes her to Mater Dei where an emergency department house office also diagnoses frontal sinus pain and advises to continue with paracetamol. No investigations are carried and no more senior doctor is consulted before discharging her. The following day the girl falls into a coma and dies soon after emergency admission to hospital. Before she dies a scan reveals thrombosis of major intracranial cerebral veins. Presumably an infective agent from the sinus found its

way intracranially. No autopsy was carried out. Her mother was a senior scientist at one of private laboratories I worked in. She was devastated by this tragic loss of her only daughter. When she recovered somewhat after a few months she asked me how to go about getting some form of redress from the hospital for what she regarded had been seriously inadequate medical attention contributing to her daughter's death. I recommended a lady lawyer with an interest in medical litigation and passed on the case to Dr Anthony Galea Debono. The health service and parents eventually settled outside court.

Readers may wonder how come some of the above UK cases could be allowed to happen by a reasonably competent primary healthcare system. Modern GP surgeries in UK are very similar to Malta's health centres. You would not normally expect home visits by your GP and you would normally need to book an appointment to visit the surgery. Some of the above cases are medical rarities and can be expected to fool even experienced doctors. However, it's hard not to admit that the now heavily censured immediate "blunderbuss" use of antibiotics may not have saved some of these lives.

The Coroner's Court in England is an old institution whose main purpose is to establish the events leading to death and to provide that information to close relatives. Family doctors cannot sign death certificates of patients they haven't examined two weeks before death and hospital doctors cannot either do that for patients dying shortly after hospital admission or after an operative procedure. In these circumstances doctors need to inform the Coroner's office which may order an autopsy and open a Coroner's Inquest.



Nutritional Assessment in New Admissions at St Vincent De Paul Residence

INTRODUCTION

Undernutrition leading to nutritional deficiency is a common problem which occurs in long term care facilities. This may in turn translate into an increase in morbidity and mortality and a decrease in the quality of life of the patients.

The aim of this audit is to research the current protocols used as a nutritional assessment at St Vincent De Paul Residence (SVPR). After identifying such protocols and comparing them with the standards set by the Nutritional Task Force of the International Association of Gerontology and Geriatrics (IAGG European Region) and the International Academy of Nutrition and Aging (IANA), this document sets out recommendations by which nutritional assessment of newly admitted patients at this long term care facility can be improved.

ETHICS

Before commencing the audit the management board of SVPR was contacted for data protection approval. The Faculty of Medicine and Surgery Research Ethics Committee's approval was also obtained.

This audit did not consist of interviews, recordings or photos of the patient population. The information gathered was from Mater Dei Hospital online softwares - Patient Dashboard and iSoft, which are linked to the SVPR admission database. After collection of data, only the authors of this paper had access to the information and results.

METHODOLOGY

New admissions to SVPR were automatically recruited for this study. Table 1 shows the recruitment criteria used. The SVPR records office was contacted to recruit such a population.

Table 1: Population recruitment criteria

Period	May 2021 - October 2021
Wards	42 wards were included (42 wards were open at the time)
Exclusions	Patients who passed away at time of recruitment were excluded from data collection

Every patient in this population was checked for any blood tests that were taken within a week of their admission, any anthropometric measures and any nutritional assessment forms that were filled in on admission in their appropriate file. This data was all transcribed and recorded on Google Sheets.

Blood tests were checked via iSOFT, which is the program currently being used by all local doctors to book routine tests for patients. The authors of this audit had already been given access to this program. For the patient cohort used for this audit, it was checked if the following specific blood tests were taken during the first week of their admission:

- Haemoglobin
- Cholesterol
- Albumin
- Iron profile
- Vitamin screening

According to Salva et al.,¹ these tests are important for the nutritional assessment of the patient.

RESULTS

303 patients were recruited in the audit. Figures 1 to 5 show what blood tests were taken on their admission as a percentage from the total. There was no standard blood test protocol which was noted during the audit, blood tests varied throughout. The commonest tests ordered were haemoglobin (81%) and albumin (61%) levels.

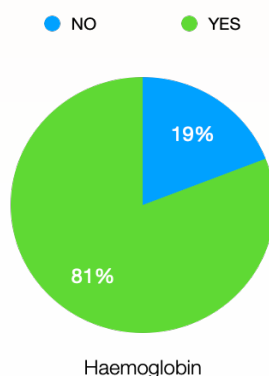


Figure 1: Haemoglobin

- Pie chart demonstrating percentage of patients tested for haemoglobin levels on admission [Yes - tested; No - not tested].

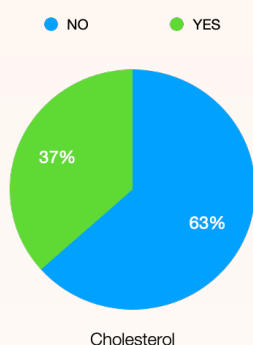


Figure 2: Cholesterol - Pie chart demonstrating percentage of patients tested for cholesterol levels on admission [Yes - tested; No - not tested].

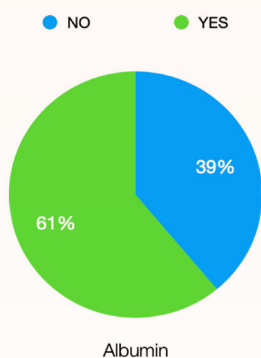


Figure 3: Albumin - Pie chart demonstrating percentage of patients tested for albumin levels on admission [Yes - tested; No - not tested].

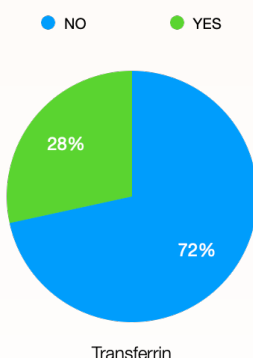


Figure 4: Iron Profile - Pie chart demonstrating percentage of patients tested for iron profile on admission [Yes - tested; No - not tested].

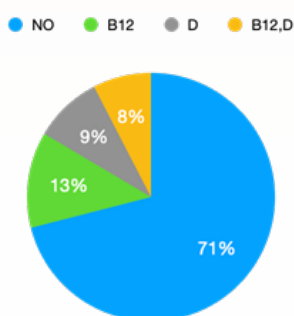


Figure 5: Vitamin Screen - Pie chart demonstrating percentage of patients tested for vitamin levels on admission [B12 - tested for vitamin B12 only; D - tested for vitamin D only; B12,D - tested for both; No - none tested for].

Table 2 shows a summary of what anthropometric measures are taken in each ward on admission. Whilst all wards measure weight on request, only 4 wards out of 42 take weights on admission. Weight was the only anthropometric measure mentioned by the wards. The reason outlined for not taking the weight on admission was the lack of resources to do so. Anthropometric assessment is done 6 monthly by all SVPR wards as this is requested by the SVPR nutritionist.

Table 2: Summary of new admission protocols per ward

Wards (Total - 42)	Anthropometric Measures
27 - 64.3%	Weight only on request
1 - 2.4%	Weight on admission + monthly + on request
3 - 7.1%	Weight on admission + on request
6 - 14.3%	Weight every Sunday + on request
5 - 11.9%	Weight monthly + on request

A nutritional assessment form developed by the SVPR nutritionist is available, however after auditing all 42 wards, only 1 ward fills this form for newly admitted patients.

CONCLUSION AND WAY FORWARD

An adequate population study was recruited to audit nutritional assessment effectively in a long-term care admission facility. Having wards using multiple strategies and fulfilling no specific criteria for primarily assessing nutrition in new admissions to this facility is suboptimal.

In relation to the above findings, the following is being proposed:

1. A blood test bundle has been developed by the authors for SVPR staff doctors to book for new admissions. A single list of tests will standardise level of care throughout the facility. This list, along with a justification of the tests can be seen in table 3. This will also be sent by email to all staff doctors. The appropriate staff at Mater Dei Hospital's IT department will be contacted to set up a 'Geriatric Bundle' to this aim.

2. New admission patients should have an appropriate nutritional assessment form filled in. A form has been prepared as seen in figure 6. To mitigate any problems relating to incomplete documentation, the following is being proposed:

- An email will be sent with a poster to inform ward staff to fill in the form – repeat emails may follow.
- Posters will be used in every ward to remind staff of the changes.
- Ward nursing officer's signatures will be required on the forms themselves.
- Multiple copies of the form will be printed and inserted into the new admission files that are used currently.

Table 3: New admission geriatric bundle

Test	Justification
Iron profile	Recommended for assessing nutrition ¹⁻³
Vitamin B12	
Vitamin D	
Albumin	
Full blood count	These tests, although not directly assessing nutrition, were found to be already booked during admission and will therefore be included in this bundle.
Magnesium	
Calcium and phosphate	
Liver function test	
Thyroid function test	
Folate	

Figure 6: Mini-Nutritional Assessment form

SVP Saint Vincent De Paul **MNA** Completed by Dr. Christina Cassar and Dr. David Borg under the supervision of Dr. Peter Ferry

New Admission Mini Nutritional Assessment Form

Name and Surname: ID no.: Sex: Age: Weight: Height: Date:

Complete the screen by filling in the boxes with the appropriate numbers. For the final score, total the numbers in each section.

A Has food intake declined over the past three months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
 0 = Severe decrease in food intake
 1 = Moderate decrease in food intake
 2 = No decrease in food intake

B Involuntary weight loss during the last 3 months?
 0 = Weight loss greater than 3 kg (6.6 pounds)
 1 = Does not know
 2 = Weight loss between 1 and 3 kg (2.2 and 6.6 pounds)
 3 = No weight loss

C Mobility?
 0 = Bed or chair bound
 1 = Able to get out of bed/chair, but does not go out
 2 = Goes out

D Has the patient suffered psychological stress or acute disease in the past three months?
 0 = Yes
 2 = No

E Neuropsychological problems?
 0 = Severe dementia or depression
 1 = Mild dementia
 2 = No psychological problems

F1 Body mass index (BMI)? (weight in kg / height in m²)
 0 = BMI less than 19
 1 = BMI 19 to less than 21
 2 = BMI 21 to less than 23
 3 = BMI 23 or greater

IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2. DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.

F2 Answer only if unable to obtain BMI
 0 = CC less than 31
 3 = CC 31 or greater

Total score (Max 14 points)

12 – 14 points	Normal nutritional status *
8 – 11 points	At risk of malnutrition **
0 – 7 points	Malnourished ***

* Rescreen according to request or 3 monthly
 ** Close weight monitoring ± nutritional intervention
 *** Nutritional intervention + in depth nutritional assessment + close weight monitoring

This form is to be completed in the first week of a new admission or transferred long term care patient. This form is not meant to correlate with any other monthly or weekly weight, it serves a purpose by itself and should be present in every patient's file for aid in nutritional assessment.

Name and surname of ward nurse in charge: Name and surname of ward staff filling in form: Signature of ward staff: Date:

A re-audit will be done in 2023 to ensure the required improvements have come into effect.

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Imaging the Fallopian Tube

A number of processes may affect the fallopian tube and early diagnosis and treatments may avoid severe and even life-threatening complications. This article will discuss the most common processes including pelvic inflammatory disease, tubal and tubo-ovarian torsion, endometriosis, ectopic pregnancy, and malignant diseases. Since all these conditions may block the fallopian tube, prompt management is important for preserving fertility. The role of fallopian tube neoplasms in the development of ovarian and serous peritoneal neoplasms will be discussed.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is the most common disease affecting the fallopian tube. Around one million cases are diagnosed yearly in the United States.¹ It spreads by direct upward extension from the vagina and cervix to the peritoneal cavity. It is associated with sexually transmitted infections, particularly *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium*, as well as gram negative bacteria.² Atypical bacteria such as tuberculosis (TB) and actinomycosis may also cause PID. PID is most common in young women (18-25yrs), those having multiple sexual partners or a history of pelvic surgical intervention including insertion of an intrauterine device.

The symptoms of PID typically include vaginal discharge, pelvic pain, fever, dyspareunia, and constitutional symptoms. Sometimes, PID may be asymptomatic and may be diagnosed based on imaging findings only.

Salpingitis is an acute form of PID and may involve one of both fallopian tubes. The inflammation may result in narrowing or obstruction of the lumen of the tubes and may lead to peritoneal adhesions. Consequently, salpingitis is associated with one of the highest rates of infertility and ectopic pregnancy.¹

Ultrasound (US) Imaging findings may be absent in PID, but a thickened tube (>5mm in diameter) (Fig 1a) and hyperaemia in the tubal wall may be present (Fig 1b). Contrast-enhanced Computed tomography (CT) may show mucosal hyperaemia in the tube.

Pyosalpinx is a complication of tubal infection, where obstruction leads to accumulation of pus within the tube. US shows a fluid-filled tube with internal echoes (Fig 2); fluid/debris levels may be seen. A distended coiled tube

may mimic the appearance of a cystic ovarian mass. Free fluid may be present in the cul-de-sac. CT and Magnetic Resonance Imaging (MRI) will show a cluster of thick-walled "cysts" containing debris with contrast enhancement in the walls and in the adjacent broad ligament. Wall thickness and wall enhancement may be used to differentiate non-infected hydrosalpinx or haematosalpinx (thin walls) from pyosalpinx (thick walls) (Fig 3).

A tubo-ovarian abscess (TOA) represents a progression of infection from a pyosalpinx into the adjacent soft tissue, the ovaries, and the peritoneal cavity. The fallopian tube and ovary can no longer be distinguished from each other since both undergo necrotic change forming a complex partially cystic partially solid mass (Fig 4). This appearance may mimic a necrotic tumour so imaging findings must be interpreted based on clinical grounds.

Fallopian tube involvement is seen in 34% of women suffering from TB and bilateral involvement is often present.³ Spread of TB to the pelvic organs may occur through haematogenous spread from the lungs or via lymphatic routes. Less commonly it can occur through peritoneal spread from adjacent bowel. Imaging findings are similar to PID caused by other micro-organisms. Progression to tuberculous peritonitis is seen in 50% of cases presenting with complex ascites with multiple septa and loculations and thickened contrast-enhancing peritoneum seen on CT and MRI, which may resemble peritoneal carcinomatosis. Pelvic lymph nodes may become necrotic and at a later stage may calcify (Fig 5).

HAEMATOSALPINX AND HYDROSALPINX

Haemato- and hydrosalpinx may occur when the fallopian tube is obstructed at its fimbrial end. Fluid that normally forms within the tube cannot be discharged into the peritoneal cavity. It accumulates within the tube and distends forming a hydrosalpinx. Endometriosis, PID, post-op adhesions, ectopic pregnancy and neoplasms all lead to tubal obstruction; the fluid in the distended tube is more likely to contain blood products resulting in a haematosalpinx.

Surgical interventions such as after endometrial ablation and tubal sterilisation (post-ablation and tubal sterilisation syndrome - PATSS) may result in haematosalpinx due to persistent islands of endometrium in the endometrial cavity.

Imaging findings include dilated tubes that become tortuous and fold over (Fig 6a). Usually, the fallopian tube wall is thin, however some thickening of the longitudinal mucosal folds within the tube may result in a cogwheel appearance (Fig 6b).

Thick hyperaemic walls are indicative of pyosalpinx as occurs with PID and other causes of tubal infections (such as TB or actinomycosis).

Peritoneal adhesions may occur secondary to endometriosis, PID and as post-op complications. Adhesions are best seen on MRI (Fig 7).

Characteristic findings on MRI of a haematosalpinx due to endometriosis include a tubal diameter >5mm, thin walls, high T1 signal due to high protein content fluid and T2 shading due to blood degeneration products within the fluid (Fig 7).

ECTOPIC PREGNANCY

Transvaginal Ultrasound (TVUS) is highly sensitive for detecting a tubal pregnancy.⁴ A tubal ring with thick walls and central cystic fluid are the most common US findings (Fig 8). An embryo, a yolk sac or a heartbeat may also be present. Intracystic haemorrhage may be present, while free peritoneal fluid indicates an increased likelihood of tubal rupture. Rising β HCG levels also support the diagnosis. Treatment options include systemic or local methotrexate, local potassium chloride injection, endoscopic excision, uterine artery embolization, tubo-cornual excision or hysterectomy.

PARATUBAL CYSTS

These are simple cysts arising from the fimbrial end of the fallopian tube. They are also known as hydatid or Morgagni cysts. They originate from the mesothelium lining, the mesonephric (Wolffian) duct or from the paramesonephric (Mullerian) duct. Those of mesonephric origin are attached to the fimbriae (Fig 9), while those of paramesonephric origin are located in the broad ligament. TVUS facilitates the distinction of hydatid cysts from ovarian cysts since pressure from the examining probe displaces hydatid cysts away from the ovary. Hydatid cysts are usually asymptomatic being discovered incidentally. They may however, cause infertility by limiting the ability of the fimbriae to catch the ovum at ovulation.

FALLOPIAN TUBE TORSION

Fallopian tube torsion refers to isolated rotation of the tube that may occur along its long or short axis (Fig 10). Risk factors for tubal torsion include endometriosis, PID, hydrosalpinx, tubal ligation, an ovarian mass and pregnancy. A torqued tube shows thickened walls that may be hyperaemic or avascular. Increased vascularity correlates with increased tubal viability, while avascularity is more indicative of tubal

necrosis. A hydro- or haematosalpinx is usually present and free fluid, a thickened broad ligament and fat stranding may also be noted.

FALLOPIAN TUBE / OVARIAN / PERITONEAL NEOPLASMS

It was traditionally thought that ovarian serous carcinomas arise de novo within the ovary. During the past decade however, it has become increasingly evident that serous carcinomas of the ovary and even peritoneum slough off from the fimbrial end of the fallopian tube starting as a serous tubular intra-epithelial carcinoma.⁵

There are two types of epithelial tumours, a type 1 or low-grade lesion that leads to low-grade serous carcinomas, low-grade endometrioid tumours, clear cell carcinomas, mucinous carcinomas and malignant Brenner tumours, and type 2 or high-grade lesions that cause high-grade serous carcinomas, high-grade endometrioid carcinomas, mixed mesenchymal tumours and undifferentiated carcinomas.

Benign deposits on the peritoneal surface, ovaries and in lymph nodes result in a condition known as endosalpingiosis. This is seen in association with PID, salpingitis and other tubal infections (Fig 11). It presents with multiple cystic structures seen on the peritoneal surface, in the ovaries and in the lymph nodes.

High grade tubal cancers are mostly composed of solid masses that show strong contrast enhancement on MRI (Fig 12). If they start in the tube, they may decompress into the uterus or into the peritoneal cavity resulting in cancer spread.

CONCLUSION

PID is the most common disorder of the fallopian tube. However, there are numerous other diseases affecting the fallopian tube, only some of which are mentioned here. TVUS is the first-line imaging modality for evaluation of the fallopian tubes. Distinction between thick or thin walls and vascular or avascular walls can diagnose different disease entities. The presence of solid components generally raises the question of malignant disease. MRI is an excellent tool for more challenging cases and for problem-solving. It also assists surgical planning.

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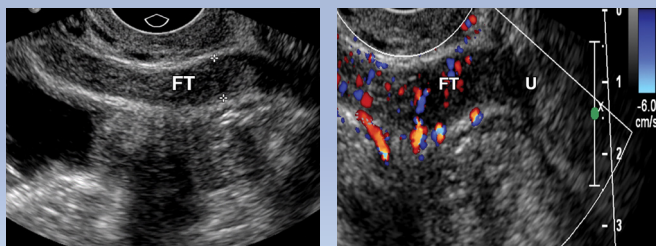


Figure 1. Salpingitis in a young woman with abdominal pain and vaginal discharge. US (a) shows a thickened (10mm) fallopian tube (FT), while (b) colour Doppler US shows hypervascularity in the wall (colour flow).

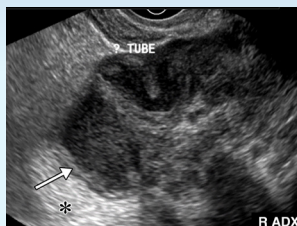


Figure 2. Pyosalpinx in a woman with fever and diffuse pelvic pain. US image shows a distended thick-walled tube (arrow) with internal echoes. Echogenic fat posterior to the tube (*) is due to inflammation.

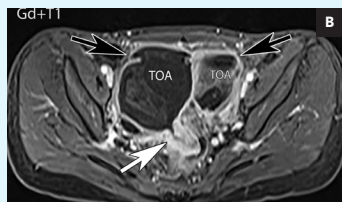


Figure 3. a. T2 weighted (T2w) MR image in a woman with PID, showing complex thick-walled cystic structures (black arrows) that represent distended bilateral fallopian tubes. Free fluid is present in the cul-de-sac (white arrow). b. Fat-suppressed contrast enhances T1 weighted (T1w) image showing TOAs with thick enhancing walls (black arrows) and enhancement in adjacent soft tissues (white arrow).

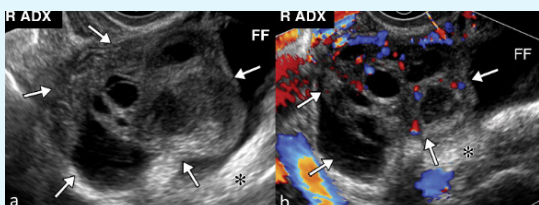


Figure 4. Transvaginal US images (a. grey scale and b. colour Doppler) in a 35 year old woman with pelvic pain and fever showing a complex mass (arrows) replacing the right ovary and fallopian tube. It is composed of both solid and cystic components and has thick hypervascular septa. There is free fluid (FF) and echogenic fat (*), the latter indicating inflammation.



Figure 5. Contrast-enhanced abdominal CT scan in a woman with abdominal and pelvic TB showing distended fallopian tubes (solid arrows) that show wall enhancement, multi-loculated ascites (*), thickened enhancing peritoneum (dashed arrows).

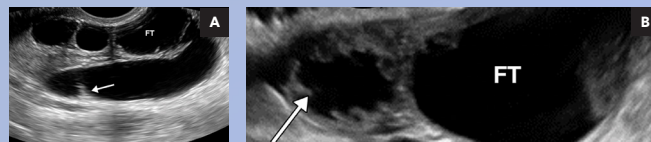


Figure 6. a. Hydrosalpinx in a young woman with PID. A long tortuous tube is seen (FT). Due to folding, incomplete septa (arrow) may be noted. b. A distended tortuous fallopian tube (FT) is present with a segment showing thickened longitudinal folds (arrow) that resembles a cogwheel.



Figure 7. Deep pelvic endometriosis in a young woman. This T2 weighted sagittal image shows a markedly dilated fallopian tube (arrow) with shading present in the tube fluid due to blood products. Also note a thick low signal band (dashed arrows) extending between the posterior aspect of the uterus and the rectosigmoid junction.

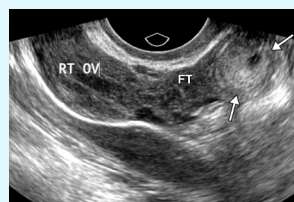


Figure 8. Uncomplicated tubal pregnancy in a young woman with a positive pregnancy test and crampy abdominal pain. The transverse TVUS shows a round hyperechoic structure (arrows) with central fluid located in the fallopian tube (FT). The right ovary (RT OV) is located more laterally.

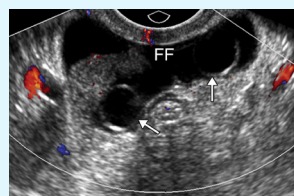


Figure 9. Hydatid (of Morgagni) cysts in a young woman noted as an incidental finding. TVUS shows two simple thin-walled cysts (arrows) which are noted within surrounding free fluid (FF).

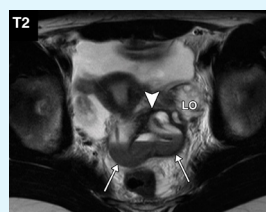


Figure 10. Tubal torsion in a teenage girl causing severe pelvic pain. This axial T2-weighted image shows haematosalpinx (arrows) and a "beak" sign (arrowhead) at the level of the torsion. The left ovary (LO) is normal.

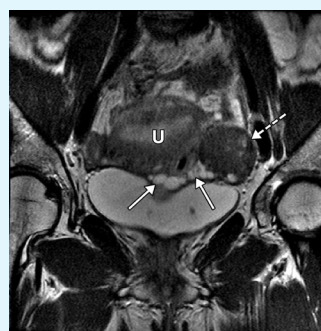


Figure 11. Endosalpingiosis in a young woman. This coronal T2-weighted image shows multiple hyperintense cystic structures (arrows) between the uterus and bladder. The low signal mass in the left ovary (dashed arrow) was confirmed on pathological analysis to be a borderline serous ovarian tumour.

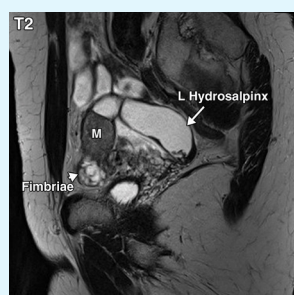


Figure 12. Primary fallopian tube carcinoma in a 62-year-old woman presenting with pelvic pain. This sagittal T2-weighted image shows a hypointense mass (M) in the distal end of the distended left fallopian tube arrow. The fimbriae can be seen just inferior to the mass.



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