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thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

CME30.EU
COVID-19 Symposium

COVID-19: A View from China

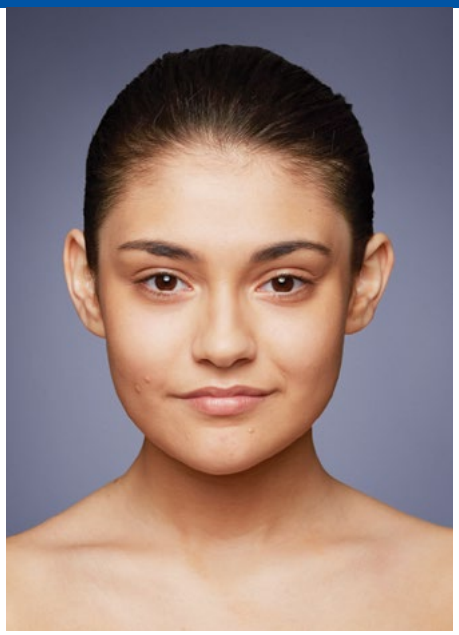
Current state of the art approaches in Hepatobiliary Imaging

COVID-19 Update on Facts and Imaging

Meeting Prof. Pierre Schembri Wismayer

Pandemics and Social Responsibility

DUAC (CLINDAMYCIN/BENZOYL PEROXIDE) IS AN EFFECTIVE TREATMENT THAT HELPS YOUR MILD TO MODERATE ACNE PATIENTS TO SEE IMPROVEMENTS FAST[1,3]



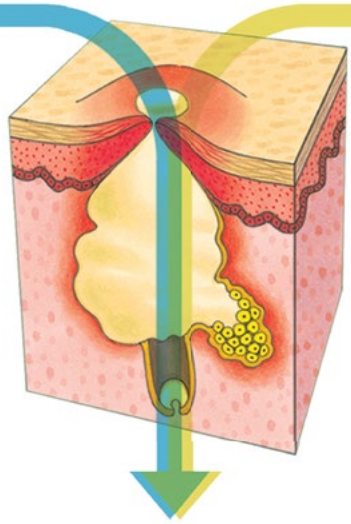
DUAC HAS A DUAL MODE OF ACTION[2]

Benzoyl Peroxide

- Keratolytic[2]
- Treats comedones[2] and inflammatory lesions[5]
- Bactericidal action against *P. acnes* strains[2]

Clindamycin

- Suppresses *P. acnes* [2]
- Anti-inflammatory action[5]



Duac:[2]
Unblocks follicles
Reduces inflammation
Kills bacteria
Reduces the potential for bacterial resistance

DUAC UNDERSTANDS WHAT'S IMPORTANT TO PATIENTS

- **Duac works fast, starting to work in just 2 weeks[3]**
- **Duac is a once daily treatment[2]**
- **Duac is generally well-tolerated[2,5]**

Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[1]

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[4]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin

• Gently pat dry

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

TIPS[4]

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

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

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

TRADE NAME: Duac Once Daily Gel 10mg/g + 50mg/g. **ACTIVE INGREDIENTS:** Clindamycin phosphate/anhydrous benzoyl peroxide. **PHARMACEUTICAL FORM:** Gel. **INDICATIONS:** Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. **POSOLOGY:** Adults and Adolescents (12 years and over): Once daily (evening) to affected area. Should not exceed more than 12 weeks. Applied in a thin film after washing gently with mild cleanser and fully drying. Was hands after application. **CONTRAINDICATIONS:** Hypersensitivity to active substances/lincomycin/excipients. **PRECAUTIONS:** Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated/broken skin. Caution in patients with a history of regional enteritis, ulcerative colitis, antibiotic-associated colitis, atopic patients, concomitant topical acne therapy. Increase in peeling and reddening will occur in most patients during first few weeks of treatment. If severe local irritancy, discontinue. Prolonged exposure to sun should be avoided. In patients with sunburn, this should be resolved before use. If significant diarrhoea/abdominal cramps occur, discontinue (symptoms may indicate antibiotic-associated colitis). May bleach hair or coloured fabrics. Patients with a recent history of systemic or topical clindaymcin and erythromycin are more likely to have pre-existing anti-microbial resistant Propionibacterium acnes and commensal flora. Cross-resistance: May occur when using antibiotic monotherapy. **PREGNANCY /FERTILITY / LACTATION:** *Pregnancy:* only after careful risk/benefit assessment. *Fertility:* no data. Lactation: should not be applied to breast area. **UNDESIRABLE EFFECTS:** Very common (≥1/10): erythema, peeling, dryness. Common (≥1/100 & <1/10): burning sensation. Refer to the SPC for full list of undesirable effects. **LOCAL PRESENTATION:** 30g gel. **MARKETING AUTHORISATION NUMBER:** MA192/02801. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline (Ireland) Ltd. Legal Category: POM. **Date of Preparation:** May 2019.

For the latest product information, please refer to the full SPC available from: gskpro.com/en-mt/products or contact us at GSK Malta (phone: +35621238131).

REPORTING ADVERSE EVENTS (AEs):

Suspected adverse events should be reported to GSK Malta through: gskpro.com/en-mt (Phone: +356212381311, Address: GSK Malta, 1 (1st floor), de la Cruz Avenue, Qormi, Malta). Malta: Cases may also be reported through medicinesauthority.gov.mt/adrportal (Malta Medicines Authority)

References: 1. Langner A *et al.* BJD 2008; **158**: 122–129. **2.** Duac 5% Summary of Product Characteristics March 2019. **3.** Langner A *et al.* JEADV 2007; **21**: 311-319. **4.** Duac 5% Patient Information Leaflet, March 2019. **5.** Lookingbill DP *et al.* JAAD 1997; **37**: 590-595.

Stiefel
a GSK company

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

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

Job no.: PM-MT-CBP-ADVR-19001 Date of preparation: November 2019

Authors

Dr Gauden Galea MD MSc(Lond) FFPH has been Director of the Division of Noncommunicable Diseases and Life-course at WHO/Europe since January 2011, and is a public health physician who has worked for WHO since 1998. He has held posts as regional adviser on noncommunicable diseases in the WHO Regional Office for the Western Pacific, and as coordinator of health promotion at WHO headquarters. He has a special interest in health promotion, the social determinants of noncommunicable diseases and the links between these diseases and the development agenda.

Dr Kelvin Cortis is a radiologist with a special interest in hepatobiliary imaging and interventional oncology. He trained in Malta and went on to subspecialise in the Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT, Palermo) and Kings College Hospital (London).

Dr Muriel Bellizzi MD MSc(Clin Pharm) DESA DEPM(ESRA) is a specialist registrar with the Department of Anaesthesia, Intensive Care and Pain Medicine. She trained in Acute and Chronic Pain at the Oxford University Hospitals in the UK and is currently part of the pain clinic team at Mater Dei Hospital.

Prof. Maurice Cauchi MD MSc PhD DPH FRCPA FRCPath was Professor of Pathology and Director of Pathology in Malta. He has published several monographs, including Health, Bioethics and the Law. For his services to the Maltese community in Australia he was made Member of the Order of Australia (AM), and given the Medalja għall-Qadi tar-Repubblika by the Maltese Government.

Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Health, Malta

Issue Guide

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DR EDWARD ZAMMIT
President, Malta College of Family Doctors

The Importance of CME

Coming from a martial arts background, I was one of the typical aficionados whose ultimate aim was to get that much coveted black belt. The belief was that once you strap that black strip of cloth around your waist, you are unbeatable and you have truly mastered your art. However, after attaining the black belt, my instructor with his patient smile and calm demeanour would look me in the eye and say, "Son, you have mastered nothing. This was just a teaser. The true path to mastery has just begun."

The medical field is even more complex. While most traditional martial arts are almost immutable, the medical field is constantly evolving, branching out and expanding at an inexorable pace. Guidelines and, even protocols can change on a daily basis. Common and supposedly standard practices become redundant in the blink of an eye.

Gone are the days when acquiring a membership or even fellowship in one of the prestigious Colleges was considered to be the end of the line. You would be pardoned for taking a short well-deserved break after joining the ranks of your esteemed peers, but calling it a day on your continuing medical education (CME) would be condemning yourself to a life of professional stagnation. CME is a lifelong continuing process extending throughout your professional life.

CME addresses various issues and requirements for the active practitioner:

1. Keeping up with latest developments.
2. Sharpening existing skills and learning new ones.
3. Career advancement.
4. Meeting licensing/certification requirements.
5. Earning and maintaining membership in professional organisations.
6. Preserving job satisfaction and preventing burnout.

A needs assessment precedes any attempt at organizing a CME programme, and based on those needs the programme is created. To ensure the success and viability of the programme, one has to plan for follow-up CME activities to reinforce learning, and feedback mechanisms for quality assurance purposes.

Every day the healthcare professional is bombarded by a constant flow of medical information, whether from email updates by professional and accredited organisations, Facebook notifications, journals, pharmaceutical companies and an ever growing number of sources.

One might be pardoned for thinking that one can get his or her daily dose of CME from the tabloids and social media platforms. So-called experts are preaching their sermons to their millions of followers, including professionals, and it is easy to fall in the trap of believing that fame confers credibility. On the other hand, discussions with learned and experienced colleagues often lead to new insights, knowledge and often, changes in practice.

Unfortunately, sources of reliable medical information have become the proverbial needle in the haystack.

This is where accreditation comes in. Accreditation ensures and certifies the suitability of medical education programmes as well as the competence of medical schools and other academic institutions in the delivery of medical education. Organisations like the World Federation of Medical Education and UEMS-EACCME evaluate agencies and their CME programmes against internationally-accepted criteria for accreditation. This in no way must appear as an imposition on institutions to conform to a single curriculum or standard. Each country, region and even local institution has its own particular set of cultural and social conditions, which will per necessity add diversity to a programme. One would expect an Australian doctor in the outback to focus a bit more on scorpion stings, while a doctor in Zimbabwe would do well to be up-to-date with his tropical diseases.

The internationally-accepted criteria provide a template for providers of medical education, and the agencies which accredit them to define institutional, national and regional standards. Not all of these standards will be relevant in every setting.

Another aspect is the medium of delivery. Conferences, Journal Clubs, workshops were and still are popular and highly effective forms of CME activity. The Internet era gave us another tool - e-learning.

E-learning is an umbrella term encompassing the use of electronic educational technology including electronic devices, digital media and computer software. Rushing to that late evening lecture after a harrowing day at work, (and probably snoring though the last half hour) tends to make one wary of CME events. Healthcare professional also have personal and family commitments which they must attend to and which inevitably take priority. On the other hand e-learning offers access to multiple streams of accredited medical educational material in the convenience of your home or clinic, at any time of day or night ... with the click of a mouse button.

In this regard, The Synapse is once again on the forefront of medical education in Malta. CME30.eu is a new portal providing online Continuing Medical Education in an easy and enjoyable format. The rationale behind CME30.eu is that every medical professional should at least undertake 30 minutes of CME every week. CME30.eu provides single educational sessions, masterclasses, as well as online courses. Users of CME30.eu will be able to keep track of their CME activities through their personal profiles and can also keep a record of 'off-line' CME activities by uploading certificates.

All activities are accredited for the purposes of CME by the Malta College of Family Doctors and Medical Association of Malta, as representatives of UEMS.

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

References:

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.
2. Gilbert DN, *et al.* Sanford guide to Antimicrobial Therapy v.3.11 – last updated March 11, 2014. Sperryville; Antimicrobial Therapy, Inc. 2014.
3. Lieberthal AS *et al.* The Diagnosis and Management of Acute Otitis Media. Pediatrics. 2013; 131; e964 Epub 2013 Feb 25.
4. Augmentin ES Summary of Product Characteristics, Nov 2017.

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

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

DR GAUDEN GALEA
WHO REPRESENTATIVE, CHINA

COVID-19 A View from China

The views expressed are those of the author alone and do not necessarily represent those of WHO.

MARCH 1, 2020 (WITH MINOR UPDATES ON MARCH 29, 2020)

Since this article was first published online, a month has passed and that is a long time for COVID-19. Malta has gone from zero to 149 cases and the number will have grown by the time this appears in print. Figure 1 sets the number of cases in Malta epidemic against those in Hong Kong SAR (China) and Singapore. The rise in the Hong Kong SAR and Singapore figures relate to a rise in imported cases, but also to some efforts to relax the stringent constraints on population movement. The curves illustrate the speed with which the epidemic can take off and emphasise how important it is for the population not to become complacent, and to strictly adhere to the public health guidance to stay at home. With the extensive preparations being made in Malta, and the cooperation of the general public, it is hoped that the line in Malta will remain flat and avoid the rapid take off. As has been shown elsewhere, a flat, long drawn out epidemic curve is associated with lower mortality and much lower costs to society.

The graph suggests that Malta's numbers are about a month behind Hong Kong SAR and Singapore. During an epidemic, its rate of spread may be estimated using the index R(t), also called the effective reproduction number. R(t) varies over time and takes into consideration the number of susceptible people in the population and the effectiveness of control measures. An R(t) above 1 means that an epidemic will continue to grow; a value near 1.5 will lead to explosive growth unless checked. Such a value has been discussed recently in the Maltese media, rightly with a call not to relax the control measures. A period of stringent constraints with intensive testing of suspects will ascertain whether R(t) has been brought below 1. For the next few months, all populations around the world will be adopting what has been called "the dance" of social constraint and relaxation, in pulsed containment efforts that seek to keep R(t) below 1 while minimising the social and economic impact.

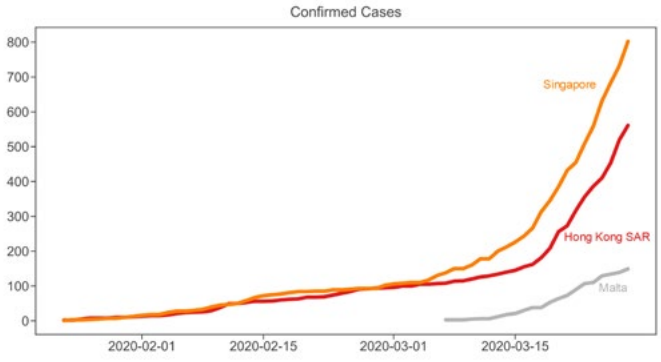

Figure 1. Confirmed cases in Malta, Hong Kong SAR (China), Singapore

THE CHINA EXPERIENCE

It is Day 89 of the COVID-19 epidemic, counting from the date of closure of the Huanan Seafood Wholesale Market in Wuhan, Hubei Province, in China. In the three months since then, the country has reported over 81 thousand cumulatively diagnosed cases and over three thousand deaths but has now achieved a state of zero local cases, a major milestone. This article summarizes the key findings of the report of the WHO-China Joint Mission on COVID-19 for the attention of the Maltese medical community as it gears itself for Malta's own outbreak.

CHINA HAS DEMONSTRATED THAT IT IS POSSIBLE TO CHANGE THE COURSE OF COVID-19 OUTBREAKS

The epidemic curve (figure 2, taken from the WHO-China Joint Mission Report) should be a much taller normal distribution based on the reproduction number ranging between 2.0-2.5 estimated from models of the transmission dynamics of the virus. Instead, the curve is blunted, flattened, skewed to the right, indicating that in the last week of January, some intervention changed the course, slowed down the spread, and initiated a plateau, then a decline. In the absence of a vaccine or therapy, China used time-honoured measures of containment and social distancing that have been part of the arsenal of public health for centuries. It is possible to emulate the success of China, but the measures call for collective action with great determination.

FIVE STEPS TO CONTAINMENT

The containment of an outbreak of COVID-19 needs five steps of increasing intensity:

1. The **universal population measures** of hand hygiene, food hygiene, respiratory etiquette, and social distancing came first in China and were aggressively promoted in social media and all traditional media. China also required mask wearing for all.
2. **Case Isolation**: The high transmissibility of the virus and the infective nature of even mild cases requires active and rigorous case finding and isolation. Case definitions should not unduly restrict eligibility for testing – within the limits of kit availability and lab capacity. Cases should be rapidly diagnosed and taken out of circulation; China initially took two weeks on average to identify a case; that has now been reduced to three days from onset.
3. **Close contact quarantine**: Close contacts of all cases should similarly be rigorously quarantined for 14 days beyond the last exposure to the case. With each infected

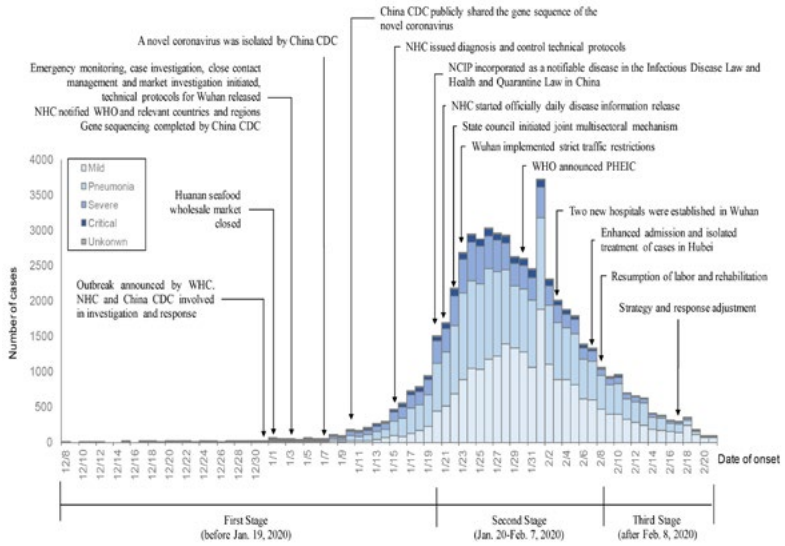

Figure 2. Epidemic curve by date of onset. **China CDC:** China Centers for Disease Control and Prevention; **WHC**: Wuhan Health Commission; **NHC:** National Health Commission; **PHEIC:** Public Health Emergency of International Concern; **NCIP:** Chinese name for the disease officially called COVID-19 by WHO.

individual leading on average to two more cases among their close contacts, rigorously enforced quarantine is the only way to effectively break the chains.

4. **Suspension of public gatherings**: China set the example during the Chinese New Year Festival (a two week period that started on 25th January this year). Temple fairs, cinemas, restaurants, and all large scale festivities were cancelled. Schools were closed (still closed at the time of writing). The traditional week of public holiday was extended.
5. **Movement restrictions**: At its extreme, these involved the complete closure of Wuhan, a city of 11 million people. In other cities lesser measures were adopted but still quite effective in restricting movement on a large scale, including the closure of express ways into certain large cities.

These five steps were not applied evenly throughout China, but a tailored approach to applying these measures was taken in different provinces, based on the prevalence of infection. In a province where there are no cases, universal precautions and public mobilisation will be appropriate, but in one where there is sustained community transmission, the more powerful of these interventions (suspension of mass gatherings and movement restrictions) will be needed. In order to **gauge the level of community transmission**, testing should be applied liberally to samples from the Influenza-like Illness surveillance system (the ILI sentinel system) but also opportunistically on suspicious cases presenting in general practice or ambulatory settings.

COPING WITH THE OUTBREAK

Even as these containment measures were proving successful, China still prepared and is preparing still for the possibility of larger numbers of cases. Lessons for Malta include:

1. President Xi Jinping and Premier Li Keqiang took personal responsibility and leadership for the response. A Joint Prevention and Control Task Force **repurposed to the whole machinery of government** and all government departments were required to make the fight against the virus their top priority.
2. **Collective action by the population** is essential. In China it is inspiring to see the thousands of health care workers and volunteers mobilised to the front line in Wuhan. It is also important to note the acceptance by the population and community grid system (a form of neighbourhood watch) to monitor and enforce quarantine. Clear guidelines are available: for landlords, for business owners, for hotel managers, and all the population, from taxi drivers to security guards are informed of their part in the battle. **Communication and risk communication** are key to keeping the population informed about their personal behaviour and about their need to adhere to the public health directives.
3. While the measures taken to contain the epidemic have been available since the Middle Ages, China's approach to them has been **highly technological**. Big data has been deployed to track cell phones and to monitor quarantine. Artificial Intelligence has been deployed in the diagnosis of CT scans. Virtual hospitals and telemedicine have been used to reduce the number of routine visits that people have to make for other reasons to hospital.
4. Given that severe and critical cases may take three to six weeks to recover or die, in a community outbreak there will be high demand for oxygen, for ventilation, and the occupancy of intensive care beds will be prolonged. The **availability of life support (beds and ITU staff) for prolonged periods** will be one of the determinants of case fatality. A recent paper estimates that the overall symptomatic case fatality risk (the probability of dying after developing symptoms) of COVID-19 in Wuhan was around 1.4% - this is lower than previous published estimates but still many times the 0.1% rate usually estimated for seasonal influenza.
5. Throughout all this, access to health care expertise is essential, and the protection of health care workers through strengthened **infection prevention and control** procedures is essential. Indeed, evidence in China suggests that many of the HCWs infected acquired the virus earlier on, when possibly the use of personal protection and universal precautions may not have been as rigorous.

RELVAR ELLIPTA

fluticasone furoate/vilanterol

24hr symptom control, without a second dose

INNOVATIVE molecules[1,2]

24hr **EFFECTIVE**[3]

SIMPLE AND INTUITIVE[4,5]

References: 1. Braithwaite I *et al.* Respir Med 2016; 119:115–121 - **2.** Bardsley G, *et al.* Respir Res 2018; 19:133 - **3.** Relvar Ellipta SmPC - **4.** Svedsater H *et al.* npj Prim Care Resp Med. 2014; 24: 14019 - **5.** Svedsater H *et al.* BMC Pulm Med. 2013; 13:72.

Relvar 92/22mcg & 184/22mcg are indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists.
- patients already adequately controlled controlled on both inhaled corticosteroid and long-acting $beta_2$-agonist.[3]

Please refer to full SmPC for detailed information.

PM-MT-FFV-PSTR-200001 Date of Preparation: March 2020

INNOVIVA

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, total lactase deficiency or glucose-galactose malabsorption should not use 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 infection, bronchitis, influenza, candidiasis 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**: GlaxoSmithKline (Ireland) Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** January 2019.

For the latest product information, please refer to the full SPC available from: gskpro.com/en-mt/products or contact us at GSK Malta (phone: +35621238131). Suspected adverse events should be reported to GSK Malta through: gskpro.com/en-mt (Phone: +356212381311, Address: GSK Malta, 1 (1st floor), de la Cruz Avenue, Qormi, Malta). Cases may also be reported through medicinesauthority.gov.mt/adrportal (Malta Medicines Authority)

DR KELVIN CORTIS

Current state of the art approaches in Hepatobiliary Imaging

HEPATOBILIARY MAGNETIC RESONANCE IMAGING

Magnetic Resonance Imaging (MRI) of the abdomen is the current gold-standard imaging modality in a wide array of pathologies that involve the upper abdominal organs. Up to a decade ago, it was very difficult to obtain good quality diagnostic images of any moving organ, including the liver. Continued technological advance has nowadays made it possible to image abdomen, and even organs with fast continuous motion such as the heart. MRI is a multiparametric exam – in that it is the only imaging modality that provides us with an array of different information; this is not only limited to 'enhancement' following administration of intravenous contrast (unlike CT). The additional information that is provided includes the intrinsic T1 and T2 signal of the tissue under study (Figure 1), sequences that show us the presence of macroscopic or intracellular fat, sequences that show us the degree of diffusion of water molecules (diffusion weighted imaging, DWI), sequences that allow quantification of specific ions or macromolecules, and sequences that show us organ or lesion stiffness.

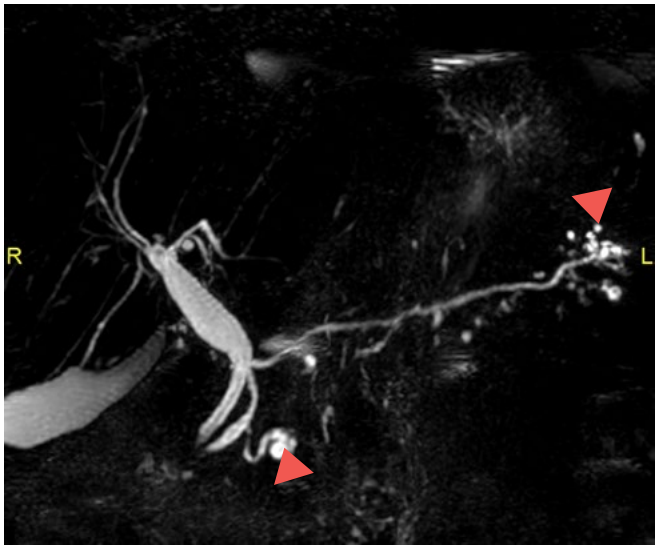

Figure 1: Magnetic resonance cholangiopancreatography (MRCP) is a special application of MRI. Images are heavily T2 weighted and fat-suppressed, this emphasises the pancreatico-biliary tree and suppresses the surrounding tissues. This MRCP shows the pancreaticobiliary tree in great detail. Note is made of multiple branch duct intraductal papillary mucinous neoplasms (IPMNs, arrowhead), precursor lesions at low risk of becoming pancreatic adenocarcinoma that need frequent monitoring by serial MRI.

Two types of contrast agents can be used for abdominal MRI - extracellular contrast agents that travel within the vascular pool to be excreted by the kidneys, and hepatobiliary contrast agents (HBAs). HBAs are also gadolinium-based (like extracellular contrast agents), however they can be used for both dynamic vascular and hepatobiliary phase imaging given that around 50% of these contrast agents are taken up by hepatocytes with subsequent biliary excretion (hepatobiliary phase, Figure 2). The fraction taken up by hepatocytes produces a notable prolonged increase in liver signal intensity with minimal or no enhancement of non-hepatocellular lesions.

DWI relies on imaging motion of water molecules. Free water molecules are in constant random motion (Brownian motion). Motion of water molecules within the cellular microenvironment is impeded by their interaction with cellular compartments, including the hydrophobic cell membrane and intracellular organelles. Restriction in the diffusion of water molecules is therefore directly proportional to the degree of cellularity of the tissue. Most malignancies are hypercellular relative to the surrounding tissue – restricting Brownian motion, and thereby diffusion (Figure 3).

CONTRAST ENHANCED ULTRASOUND (CEUS)

Contrast ultrasound relies on the use of microbubbles that are small enough to cross capillary beds (< 7μm). Such microbubbles need to be stable enough to endure cardio-pulmonary transit before ending in the systemic circulation. They also need to be stable enough to endure the low-energy ultrasound beam for the time required to reach a diagnosis. Microbubbles react to the alternating compression and rarefaction of sound waves in the ultrasound beam. They halve in size during compression and double in size during rarefaction. This results in a strong reflected signal, allowing us to visualize individual microbubbles even though the mean diameter of microbubbles is 2.5μm. The most widely available agent in Europe was approved in 2001 and consists of Sulphur Hexafluoride (SF6) stabilised in a

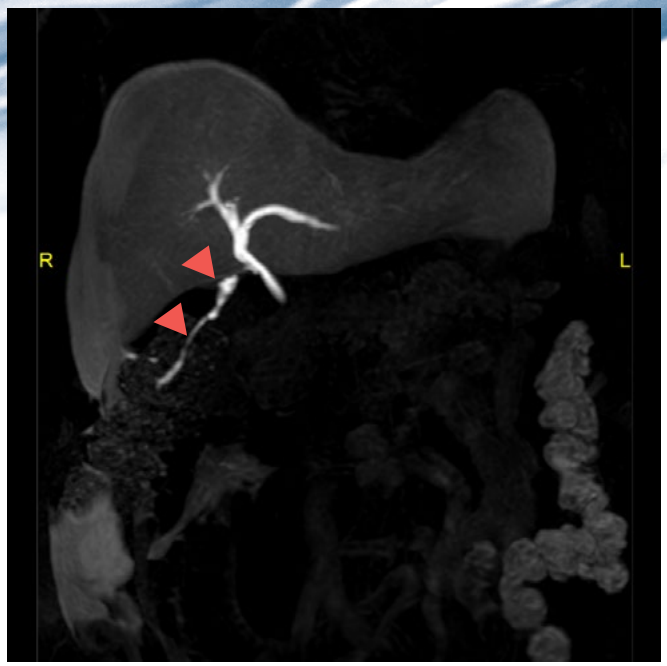

Figure 2: Patient with a persistent bile leak post-cholecystectomy. MRI using hepatobiliary contrast agents was performed in order to identify site of the leak. Leakage from the cystic duct stump is seen (arrowhead), together with layering of contrast around the liver. Patient had endoscopic stenting, with resolution of the bile leak and excellent recovery.

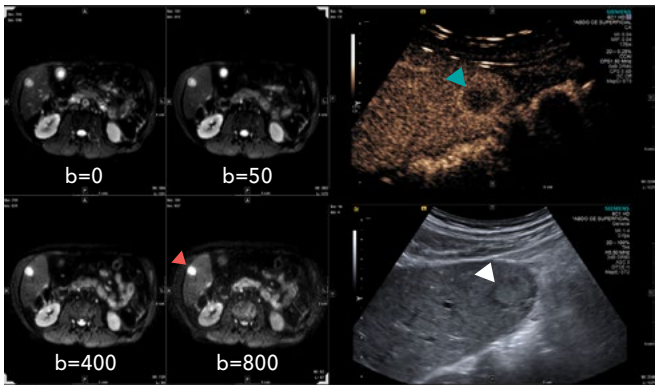

Figure 3: Solitary colorectal metastatic deposit seen on both DWI MRI (red arrowhead), contrast ultrasound (blue arrowhead), and conventional ultrasound (white arrowhead). DWI shows restricted diffusion, with the lesion being more conspicuous on the heavily diffusion weighted image (b=800) as compared to the other images (b=0, 50, 400).

phospholipid monolayer membrane. Microbubbles are excreted via the lungs, allowing safe use in patients with renal failure. CEUS is useful in a wide variety of clinical scenarios (Figures 3 and 4). Contraindications are rare, and include a recent acute coronary syndrome, clinically unstable ischaemic heart disease, known significant right-to-left shunts, severe pulmonary hypertension, uncontrolled systemic hypertension, and acute respiratory distress syndrome. Safety has not yet been established in pregnancy and lactation.

ELASTOGRAPHY

Chronic liver disease is becoming more and more common in the developed world. This is mostly due to the increased prevalence of non-alcoholic liver disease (NAFLD). Clinical, radiological, and biochemical features point to established cirrhosis, but not earlier potentially reversible fibrosis. Fibrosis is a response to chronic liver injury and is thought to be mediated by hepatic stellate cells (myofibroblasts), located in the perisinusoidal space (space of Disse). Accurate detection and intervention at the earlier stages of fibrosis has the potential to reduce morbidity and prevent end-stage disease, since early fibrosis is potentially reversible.

From a physics point of view, elastography aims to image the Young's E modulus, which measures the force (per unit area) that is needed to stretch (or compress) a material sample. All elastography techniques rely on the same basis: an external force is applied to the studied tissue and the resulting movements are then followed.

Traditionally, the presence and grading of fibrosis was achieved through image-guided percutaneous liver biopsy (PLB). This has been considered as being the gold standard for the past 50 years despite numerous advantages, including the invasive nature of a biopsy (not an ideal test to keep monitoring disease in the same patient; however risk of serious complications is low), sampling variability (especially important since the specimen obtained represents less than 1/50,000 of liver),[1] and high inter-observer variability during microscopic evaluation.[2]

Elastography can be performed using both ultrasound and MRI. In both cases shear waves are generated in tissues following the application of a directional force

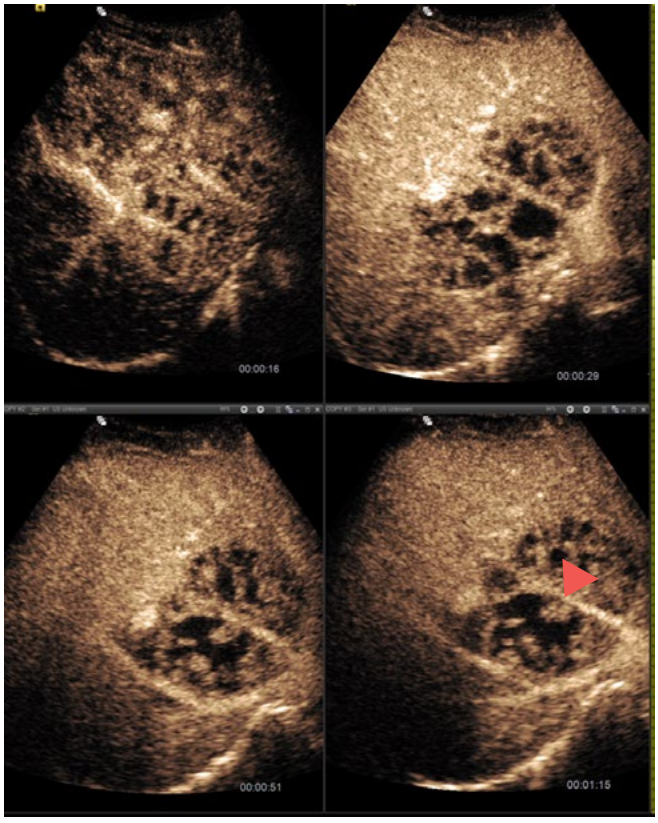

Figure 4: CEUS showing a multilocular pyogenic liver abscess straddling the middle hepatic vein (arrowhead), in a young patient with diabetic ketoacidosis. This was not visible on conventional ultrasound.

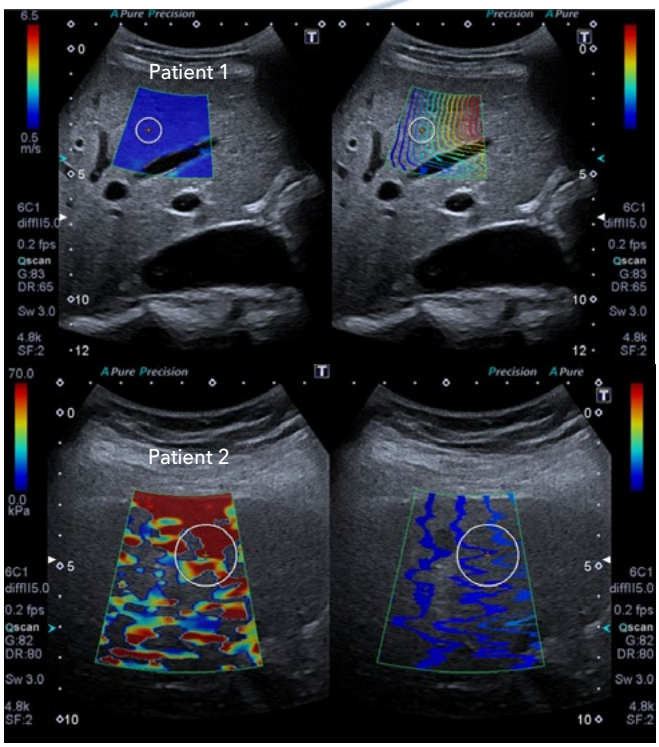

Figure 5: Two different patients who underwent 2D-SWE. Color-coded images depict tissue stiffness in both cases, with the propagation map to the right. The lines of the propagation map are parallel, confirming that the measurements taken are reliable.

Normal elasticity is seen in a young healthy female (Patient 1). Contrasting images are seen at the bottom in a mid-aged male with nonalcoholic steatohepatitis cirrhosis, with evident increased stiffness (Patient 2) and increased interval between consecutive lines of the propagation map.

which causes shear deformation. One of the most extensively studied approaches in ultrasound is 'point' shear wave elastography (SWE) via acoustic radiation force imaging (ARFI).[3] The force produced slightly displaces the tissue at the focal spot according to Hooke's law. Following this, the transducer switches into imaging mode to detect displacements of the focal spot by tracking of the ultrasound signal (called "speckle"). This identifies the displacement of tissue with sensitivity of less than a micrometer. ARFI elastography is very accurate – with areas under the curve ranging from 0.848 to 0.862 when compared to actual liver biopsies.[4]

Another ultrasound-based approach is two-dimensional (2D) SWE (Figure 5), in which the elasticity profile of a larger section of tissue is evaluated. Here shear wave arrival times (or "wavefronts") at different locations are plotted, allowing a 2D map of shear wave properties within a section of liver to be generated. Some manufacturers also display a propagation map, with contour lines to depict shear wave arrival times at different points in the tissues, in order to guide optimal sampling.

MRI elastography (MRE) is accomplished in 3 steps: generation of mechanical shear waves in tissue by an acoustic driver, imaging of these shear waves with a special MRI sequence, and processing of the wave information to generate elastograms.[5] The volume of liver parenchyma assessed with a single slice of MRE is about 250cm^3. This is much higher than point shear wave elastography (0.5–1.0cm^3), and nearly 500 times that of a liver biopsy (10–50mm^3).[6] MRE can show heterogeneous involvement of the liver in fibrosis (Figure 6), and is usually feasible in most patients (obese, bowel interposition, ascites). However, the most important advantage when compared to ultrasound-based methods lies in its high reliability in diagnosing fibrosis in significantly obese patients, a major limitation in ultrasound.

Confounding factors that might decrease the accuracy of elastography include postprandial condition (patients must be fasted for at least 3 hours prior to elastography), elevated aminotransferases to more than 5x the upper limit of normal in the context of necroinflammation (seen in acute hepatitis or acute liver failure), right heart failure, and cholestasis.

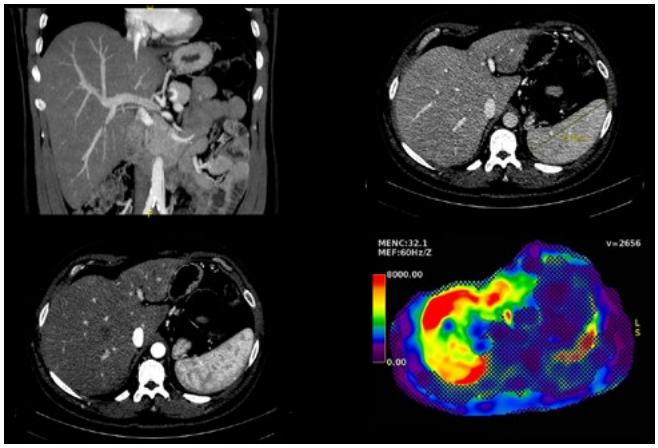

Figure 6: Conventional CT images show hepatomegaly in a patient with NAFLD. No evidence of cirrhosis on CT. MRE (bottom right image) shows patchy increased liver stiffness (seen in green, yellow, and red) compatible with established cirrhosis despite normal appearances in CT.

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Dr Ian Ellul meets **Prof. Pierre Schembri Wismayer**, eclectic researcher at the UoM's Faculty of Medicine and Surgery.

R&I: Nuts & Bolts

DO YOU BELIEVE YOUR PARENTS INFLUENCED YOU IN BECOMING A DOCTOR?

Both my parents were doctors. My father Dr Roy Schembri Wismayer used to work as pathologist and my mother is Dr Mercedes Zarb Adami. Although both parents never directly influenced us on the matter, indirectly this may have influenced me, and my sister Marika, to choose medicine. Our other three siblings chose different pathways. Although my first inclination was to become a zookeeper and then veterinary surgeon, this metamorphosized to a liking for human medicine at around 14 years of age. Maybe this stemmed from the fact that I used to see my father carry out flame photometry, and microbiology tests on agar plates in the laboratory just off our garden [duly inspected and certified by local health authorities]. This was the seventies when Malta experienced the medical strike following a disagreement between the government and the Medical Association of Malta.

IN JUNE 2019 THE EUROPEAN COMMISSION PUBLISHED THE 'PEER REVIEW – MALTESE RESEARCH AND INNOVATION SYSTEM' WHICH STATED THAT 0.55% OF MALTA'S GDP IS SPENT ON R&D, WHICH IS "ON A DOWNWARD TREND"; THIS IS "AT ODDS WITH ITS STATED OBJECTIVE OF REACHING 2% OF GDP … BY 2020." THIS MAY HOWEVER BE ATTRIBUTED TO THE FACT THAT GDP IN 2014 WAS < €8 BILLION AND IN 2019 IT WAS > €13 BILLION. WHAT ARE YOUR THOUGHTS ON THIS?

Malta lacks basic scientific literacy. The general population seems to lack even a basic understanding of e.g. what is a virus, related transmission mechanisms, stem cells, etc. The reaction of the Maltese people to the COVID-19 pandemic is an example. This certainly stems from the low investment in this area, even if one factors in the increase in GDP along the years. Our education system may be part of the problem. Since childhood we are taught to always obey our teachers and not challenge what we are taught. The result of this is amply seen at University level. Let us consider medical students as example. From experience I can say that they shine for memory recall but then they generally stall on questions relating to thinking. This is seen less in foreign medical students. I strongly believe that our students should be taught differently from childhood, with more discussion groups and more lab work in lieu of lectures. This is what we advocate in the workshops which we organize as part of Science in the City and Teen Science Café initiatives. I strongly believe that instilling a sense of creativity at a young age stimulates a culture of research.

Truth be told, in recent years Malta did invest heavily in IT in relation to research; also, MCST funding has increased considerably. Recently the UoM also started offering four annual research grants of €60,000 each. Biomedical and Life Sciences research is eligible for one such grant and participants compete through an open-call. However, funding for R&D locally is still low when compared to other countries. Politicians talk about a knowledge economy but this, in reality, is still lacking. In keeping with this, when PhD students graduate, another challenge arises. Few or no jobs are available locally. It is thus important for policy makers to forecast supply and demand and invest accordingly. It seems that when the generics companies came to Malta there wasn't enough talent locally. On the other hand, today we are seeing more PhD students graduate, however the Life Sciences Park only seems to attract small companies with limit demand for postdocs. This could well lead to a brain drain. Further to this another challenge relates to the postdoc posts at the UoM in that it only offers *temporary* contracts which preclude researchers from getting any bank loans. What I suggest is that University starts to offer a pool of postdocs on a *permanent* basis with a decent pay; however, the salary should be less than that offered by industry so that they eventually leave and free up the postdoc posts for other researchers.

YOU ARE INVOLVED THE RESEARCH PROJECT MALTAHIP WHICH HAS DEVELOPED A NOVEL HIP JOINT. THIS IS CLOSE TO BEING PATENTED. WHAT MAKES YOUR INVENTION STAND OUT?

Have you ever questioned why arthritis in the leg affects the hip and knee but not the ankle, even though the ankle supports greater weight? The reason lies in the anatomy. The hip and knee are curved from 2 axes with pressure mainly exerted on one point. On the other hand the ankle is curved on 1 axis only with pressure distributed on an entire line. This motivated us to use the anatomy of the ankle to develop the MaltaHip. This makes our hip different from other hip prostheses that are anatomically much more similar to each other, except for their composition. Our results to date are promising. MaltaHip seems to provide superior wear resistance of approx. 300%. This could well be a game changer.

Apart from myself, Prof. Ing. Joseph Buhagiar, Prof. Ing. Pierluigi Mollicone and Ing. Donald Dalli from the Faculty of Engineering, UoM are involved in this research. In our case Malta's small size is actually advantageous. The engineering department is only 150 metres from the Biomedical Sciences

Building so collaborating is easy. We first used computer modelling and then Empav Engineering Ltd, a local company, machined the first prototypes. MaltaHip has also been tested on a cadaver by local orthopaedic surgeons, Mr Ray Gatt and Mr Ryan Giordamaina. The surgeons concluded that the stability and movement were exceptional, which means that the implant may also appeal to the Eastern market who are accustomed to squatting instead of sitting down. Further testing has taken place at an accredited laboratory in Germany. The project could only have been possible with the €200,000 grant from MCST through the R&I Fusion Programme.

After the preclinical phase is concluded, and once the patent is in hand, we need to publish extensively on the matter. Afterwards comes the clinical testing. We are currently developing the business plan together with an Anglo-American company. We could approach a market leader who may or may not wish to collaborate with us because MaltaHip may translate in less overall hip sales; otherwise from a strategic point of view we could collaborate with insurance companies. Healthcare systems in countries like the US, Germany and Switzerland rely heavily on health insurances. Yet another option is to go to 2nd tier companies who may use MaltaHip to put a foot in the door of the hip replacement market.

ONE OF YOUR BRAINCHILDS INVOLVES THE USE OF HISTIOCYTES FOUND IN THE CHRYSALIS OF THE WHITE BUTTERFLY CABBAGE FOR LEUKEMIA. PRE-CLINICAL TESTING HAS BEEN PROMISING. CAN YOU EXPLAIN MORE?

In the chrysalis, the caterpillar lyses completely leaving only a few *histiocytes* which are like stem cells. These produce the entire butterfly, causing differentiation of gut, nervous system, muscle etc. So my hypothesis was that the histocytes can be used for the treatment of acute myeloid leukemia. This research has been carried out by Dr Analisse Cassar for her undergraduate thesis, masters, PhD and she is furthering this during her postdoc. We initially tested the hypothesis of differentiation therapy on 3 cell lines of acute myeloid leukemia. However, our research branched out to chronic myeloid leukemia. This seems to be working well enough so we started carrying out research on the cells extracted from the salamander leg, sea cucumber and planaria. We are also extending this research to osteosarcoma and brain tumours.

IN A SIMILAR INTERVIEW I ASKED SURGEON DR JOSEPH DEBONO ABOUT HIS THOUGHTS ON THE BARTS MEDICAL SCHOOL WHICH OPENED LAST OCTOBER IN GOZO. HE SAID THAT HE SUPPORTS HEALTHY COMPETITION, HOWEVER, ONE MEDICAL SCHOOL SHOULD NOT HAVE AN IMPROVED SERVICE AT THE EXPENSE OF THE OTHER. DO YOU SHARE HIS FEELINGS?

I agree that competition is healthy but Malta has a resource problem. One must remember that Malta has always limited the number of students who enrol in medicine for a simple reason ... our hospitals have a limited number of patients which need to be shared by all students as part of their clinical training. The fact that currently 150 students are enrolling each year in the UoM's medicine course means that there are approx. 450 clinical year students. On the other hand, Barts is aiming to have 60 students each year with each year doing clinical practice. This would hypothetically mean that training for the UoM's 450 clinical year students could be reduced because patients in our hospitals would need to be shared between 750 students.

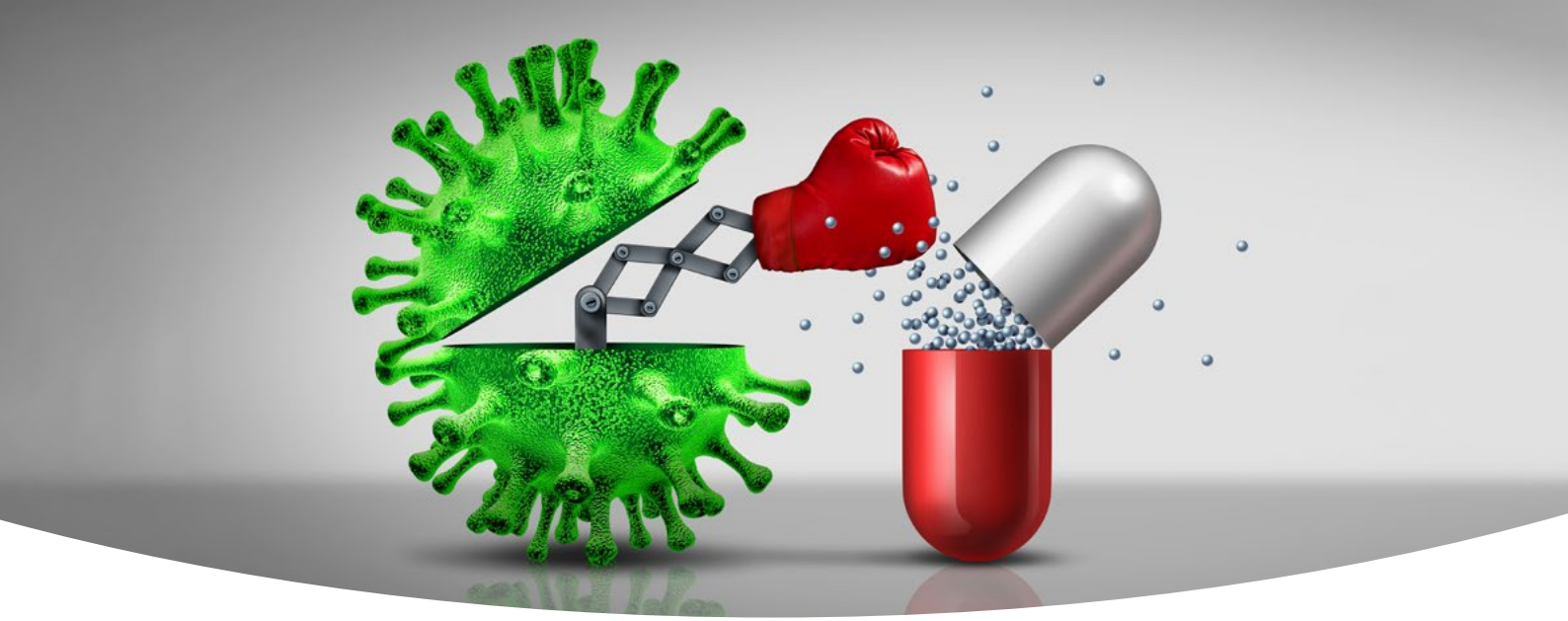
I RECENTLY INTERVIEWED PROF. SANDRO GALEA - DEAN AT THE BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH, US - WHO MADE REFERENCE TO THE 'HEALTHIEST GOLDFISH'. HE CLAIMED THAT WE SHOULD INVEST IN CREATING A WORLD WHERE WE CAN 'DIE HEALTHY' RATHER THAN SPEND MONEY IN A FUTILE EFFORT TO LIVE FOREVER WHILE IGNORING THE CORE DRIVERS OF HEALTH. HOW MUCH DO YOU THINK THE ENVIRONMENT AFFECTS THE INCIDENCE OF CANCER LOCALLY?

In my research group, we classify cancer in two groups, those which affect solely adults such as lung, pancreas and stomach, and those which affect both adults and children such as gliomas, sarcomas and leukemias. There is a clear biological difference. Those which affect solely adults are generally located on the exterior such as skin, lung and colon whilst the others are found on the inside such as bone marrow and brain. Our hypothesis is that we develop cancer as adults [on the outside of our body] through *continuous* exposure, rather than occasional exposure. On the other hand, the risk from the overall environment is greater for children. Benzene emissions from cars and pesticides have been shown to lead to paediatric cancers [on the inside] even with limited exposure.

WOULD YOU HAVE IMAGINED THIS LIFE 20 YEARS AGO?

I always wanted this life of research and lecturing. However, it is painstakingly long to build a research team that is needed to finally achieve some results. My wish is to develop a medical company with a focus on innovation. On a side note, I would also have liked to be slimmer and more healthy. Weight management is something which is on my mind … we can possibly discuss this in a future interview …

YOU READ THESYNAPSE BECAUSE ... both as a general doctor (I still function as a GP of sorts with family and friends) and as a lecturer, it is important to keep oneself up-to-date. Teaching pre-clinical sciences like anatomy and cell biology is most useful when they are informed by clinical scenarios. Just like international journals like 'Evidence-based Medicine', local journals like The Synapse help in this endeavor.



Carbapenem Resistant Enterobacteriales (CRE)

and it's clinical implications

Prof. Michael Borg
Chair, National Antibiotic Committee

This eLearning Session is aimed to increase the familiarity of healthcare professionals with CRE - a very significant hospital pathogen which is also relevant to the community setting.

LEARNING OBJECTIVES

- To increase appreciation of the new challenges posed by Carbapenem Resistant Enterobacteriales (CRE).
- To increase understanding of the modes of spread and prevention of CRE.
- To highlight the different risks between hospital and community environments.
- To highlight proper risk assessment of the accommodation requirements and management of CRE carriers in the community, especially in nursing homes.

PARTNER ORGANISATION
Malta College of Pathologists

PEER REVIEW
Malta College of Pathologists

Imaging in Prostate Cancer

Dr Warren Scicluna
Consultant Radiologist

There are a number of prostate imaging modalities available which have different roles in the diagnosis, staging and treatment of Prostate Cancer. The e-Learning session is aimed at explaining the importance of MRI of the prostate with respect to other modalities and in concordance with PSA level and digital rectal findings.

LEARNING OBJECTIVES

- To provide an overview of a number of imaging modalities available for prostate imaging.
- To guide healthcare professionals on how the decision on which imaging modality is used is made depending on the clinical question.
- To give an overview of PSA testing; including its importance, role as a screening and monitoring tool as well as red flags in PSA result values and trends which warrant referral.
- To explain the role of MRI of the prostate in the localisation, diagnosis and staging of prostate cancer as well as in the monitoring of response to treatment.

Myeloproliferative Neoplasms

Although Myeloproliferative Neoplasms are considered as very rare, they are in fact not so uncommon and several Healthcare Professionals may meet patients suffering with these conditions in their practice.

This eLearning Session is a general introduction to Myeloproliferative Neoplasms with the aim of increasing the familiarity of Healthcare Professionals with these relevant conditions.

LEARNING OBJECTIVES

- To increase the familiarity of Healthcare Professionals with Myeloproliferative Neoplasms which can present incidentally but also catastrophically.
- To highlight the clinical features and diagnosis of different Myeloproliferative Neoplasms through individual case presentations.
- To outline the principles of therapies available and used in the management of Myeloproliferative Neoplasms.
- To highlight scenarios in which patients should be referred back to their haematologist and other general aspects involved in the care of these patients such as routine vaccinations and drug interactions.

PARTNER ORGANISATION

Malta College of Pathologists
Department of Pathology, MDH
Department of Pathology, University of Malta

PEER REVIEW

Malta College of Pathologists
Department of Pathology, MDH
Department of Pathology, University of Malta

Dr Alexander Gatt
Consultant Haematologist

INDUSTRY SUPPORT

The production of this eLearning session is supported by Novartis Oncology as a service to the medical community. The content of this session is completely independent and not influenced directly or indirectly by the supporting Company.

NOVARTIS

PEER REVIEW

MARNMP - Malta Association of Radiologists and Nuclear Physicians

INDUSTRY SUPPORT

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MARNMP
Maltese Association of Radiologists and Nuclear Medicine Physicians

SAINT JAMES HOSPITAL

ACCREDITATION

All sessions have the following accreditations:

Medical Association of Malta as representative of UEMS
0.5 Credits

Malta College of Family Doctors
0.5 Credits

On completion of this module you will be awarded 1 Point. Each point is equivalent to MCFD 0.5 CPD units / 0.5 European CME Credits (ECMEC's).

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CONTINUING MEDICAL EDUCATION

SEROXAT

The Anxiolytic Antidepressant:[1,2]

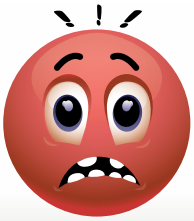
Major Depressive Disorder (MDD)[3]

Generalised Anxiety Disorder (GAD)[3]

Social Anxiety Disorder (SAD)[3]

Post -Traumatic stress Disorder (PTSD)[3]

Obsessive Compulsive Disorder (OCD)[3]



Panic Disorder[3]

Different indications require different dosage regimens. Please refer to the full SPC for more prescribing information.

SEROXAT ABRIDGED PRESCRIBING INFORMATION

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

TRADE NAME: SEROXAT. **ACTIVE INGREDIENT:** Paroxetine. **PHARMACEUTICAL FORM:** Film-coated tablets, 20mg. **INDICATIONS:** Major Depressive Episode, Obsessive Compulsive Disorder, Panic Disorder with and without agoraphobia, Social Anxiety Disorders/Social phobia, Generalised Anxiety Disorder, Post-traumatic Stress Disorder. **POSOLOGY:** Administer once daily in the morning with food. Refer to full SPC for dosing information for specific conditions. Withdrawal symptoms seen on discontinuation of Paroxetine: abrupt discontinuation should be avoided. ***Elderly:*** maximum dose should not exceed 40mg daily. ***Children and adolescents:*** Should not be used. ***Renal/hepatic impairment:*** Dose should be restricted to lower end of dosage range. **CONTRAINDICATIONS:** Hypersensitivity. Should not be used in combination with MAOIs, thioridazine or pimozide. PRECAUTIONS: Treatment should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAOI; Do not use in children and adolescents under the age of 18 years; Suicidal thoughts or clinical worsening: an improvement may not occur in the first few weeks of treatment: patients should be closely monitored; Use of paroxetine has been associated with development of akathisia: most likely to occur within first few weeks of treatment: do not increase dose in these patients; Serotonin syndrome/neuroleptic malignant syndrome may develop rarely: treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. Do not use in combination with serotonin-precursors; Use with caution in patients with a history of mania, severe renal and hepatic impairment, diabetes (there have been studies suggesting an increase in blood glucose levels may occur when paroxetine and pravastatin are co-administered) and in epilepsy; Drug should be discontinued if patients who develop seizures; There is little clinical experience of concurrent use with ECT; Use with caution in narrow angle glaucoma or history of glaucoma, patients with cardiac conditions or at risk of hyponatraemia; Caution when administered concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase risk of bleeding; Paroxetine may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen: concomitant use should be avoided; Withdrawal symptoms may occur on discontinuation of Paroxetine treatment; Paroxetine may cause symptoms of sexual dysfunction. Refer to full SPC for information on drug interactions. ***PREGNANCY/FERTILITY/LACTATION: Fertility:*** SSRIs may affect sperm quality but this is reversible following discontinuation of treatment. ***Pregnancy:*** Use in pregnancy only when strictly indicated due to potential increased risk of cardiovascular malformations during the first trimester; symptoms such as respiratory distress, cyanosis, apnoea, seizures and other complications may occur in the neonate after maternal paroxetine use in later stages of pregnancy and increased risk of persistent pulmonary hypertension of the newborn (PPHN). ***Lactation:*** Use during lactation can be considered. **UNDESIRABLE EFFECTS:** ***Very Common (≥ 1/10):*** Nausea, Sexual dysfunction; ***Common (≥ 1/100, <1/10):*** Increases in cholesterol levels, decreased appetite, somnolence, insomnia, agitation, abnormal dreams (including nightmares), dizziness, tremor, headache, impaired concentration, blurred vision, yawning, constipation, diarrhoea, vomiting, dry mouth, sweating, asthenia, body weight gain; Increased risk of bone fractures in patients receiving SSRIs and TCAs; Common withdrawal symptoms include: dizziness, sensory disturbances, sleep disturbances, anxiety, headache. Adverse events from paediatric clinical trials: Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility were observed. Refer to full SPC for the full list of adverse reactions. **LOCAL PRESENTATIONS:** 20mg Tablets (by 30 tablets). **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline (Ireland) Ltd **MARKETING AUTHORISATION NUMBERS:** MA192/02501. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** October 2019.

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)

Suspected adverse events should be reported to GSK Malta through: gskpro.com/en-mt (Phone: +356212381311, Address: GSK Malta, 1 (1st floor), de la Cruz Avenue, Qormi, Malta). Cases may also be reported through medicinesauthority.gov.mt/adrportal (Malta Medicines Authority)

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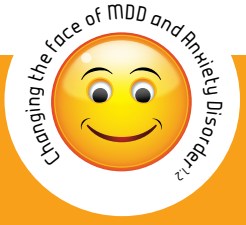

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Job No: PM-MT-PRX-ADVR-190001 Date of preparation: February 2020

PROF. MAURICE CAUCHI

Pandemics and Social Responsibility

Wars and epidemics bring the best and the worst in a population. We have witnessed actions which can be described as laudable, even heroic. At the other extreme, we have also sometimes witnessed actions best described as selfish or idiotic at best but which can be dangerous to the general public, reflecting an atavistic regress unworthy of a civilised nation.

In Malta we have been blessed with an excellent health service, with very well qualified individuals whose expert advice we are only too happy to accept. With regards to the current pandemic, Malta has been among the first to take public health measures to control its spread among the population. Such precautionary steps can be effective only if everybody obeys the directives, even when these impose a certain amount of inconvenience or sacrifice. Nobody particularly likes locking oneself at home rather than go out for a walk on the esplanade. And no misplaced sense of duty should overcome such an embargo.

One is also embarrassed to see the overreaction exhibited by some members of the general public who in an unbelievable panic starting hoarding foodstuffs and other items, worried about a general shortage of such items, however unlikely this appears to be. A war mentality seems to linger in a population which has had more than its fair share of wars, hunger, and general insufficiencies of daily requirements, but surely this is taken to ludicrous extremes. We should all be aware that there is no fundamental reason why supply should be threatened: no u-boats, no bombs, no challenge to supply. The only reason for this fear is fear itself: a most effective and disastrous way of creating an emergency.

A raft of social issues may result from the indiscriminate utilisation of services. Medicines and medical facilities are meant to deal primarily with normal conditions and are bound to become stressed in times of epidemics. Hence the need for all of us to use such services frugally and responsibly. Overuse by one section of the population is bound to result in deficiencies for others. Doctors, pharmacies, no less than shops and supermarkets, can feel the stress or become simply overcome by such demands.

At some stage, governments have the responsibility to intervene in an effort to ensure order and reduce conflict. We have already seen cases where hefty fines have been imposed on those who cannot bear restrictions like social spacing or self-segregation. Perhaps it is time to also put a limit to what services one may expect to be made available. In countries where demand for medical care has become overstretched, basic ethical issues are being raised as to how, in an emergency, to ration limited facilities, including hospital beds or ventilators, for example. Such extreme situations could put doctors at risk of having to decide on factors such as whose life is more worth saving and similar disturbing conundrums.

While we, in Malta, hope that we will not be reaching this emergency level in the foreseeable future, it is well to emphasize that the obligation to prevent it is not merely the responsibility of governments and administrators. It is also very much dependent on the practice of the general public. Already we have seen in the last decade an enormous increase in the utilisation, some might even say abuse, of medical facilities. The public must be made aware that resources are not infinite, and that judicious use of them is everybody's responsibility.

In relation to this is the question of information required by the public. A general comment is often heard, namely that the average person is often confused about the facts related as to how best to deal with a potentially deadly pandemic. This is in spite of the plethora of information given by health authorities, the news media and available online. One gets the impression that it is not so much a shortage of information that is the cause of this, but rather too much information, given through various sources, which vary in credibility if not responsibility.

Information for the general public should be brief, clear, repeated frequently, given preferably by a recognisable figure of authority in short, crisp fashion, without over emphasizing the risk to certain sections of the community while at the same time giving the impression that some members are immune.

While this is a time of stress for the whole community, we have to avoid binary distinctions which has led in some countries to isolate the old and others at increased risk while the rest of the population still congregate in a celebratory mood in places like the famous Bondi Beach in Sydney.

DR MURIEL BELLIZZI

Guidance for Oral Opioid Reduction in Primary Care

BACKGROUND

Opioids are essential in treating the severe acute pain, and pain associated with cancer and end-of-life; however, in the last 10 years, numerous studies have shown that there is little evidence of benefit for long-term opioids in patients with chronic non-cancer pain as regards pain, quality of life or functioning. Nowadays, there is better understanding of the risks, which include dependence and opioid-related mortality amongst others. For this reason, the International Association for the Study of Pain (IASP) supports the use and availability of opioids at all ages for the relief of severe pain during short-lived painful events and at the end-of-life. Healthcare professionals play an important role in minimizing overuse and overdosing as well as understanding morphine equivalent dosing in an effort to help reduce the likelihood of such potential morbidity and mortality associated with opioids.

INDICATIONS FOR OPIOID TAPERING AND/OR DISCONTINUATION

The clinician should always review the patient's progress while on opioids, including any new information about the cause of pain as well as the patient's overall health and function.[1] Discontinuing or tapering of opioid therapy may be required for many reasons. Some indications that would sound the alarm for stopping opioids are seen in Table 1.

OPIOID ANALGESIC DEPENDENCE

Indicators that suggest the possibility of dependence should be explored in those patients on long-term opioid prescription (these may not necessarily preclude the use of opioids for pain, but prolonged use needs close supervision). Such indicators for dependence may include: previous history of addiction; family history of addiction; reluctance to acknowledge psychological contributors to

Table 1: Selected indications that could warrant stopping opioids

OPIOID CESSATION INDICATIONS	
Patient request to stop opioids	Underlying painful condition resolves or stable for ≥3 months
> 120mg oral morphine equivalent per day	Side effects intolerable or impair function
Opioids not providing useful pain relief	Patient receives a definitive pain relieving intervention e.g. joint replacement for osteoarthritis
Opioid trial goals not met	Strong evidence that the patient is diverting their medication
Medical complications	Non adherence to treatment plan or indicators showing dependence behaviour
Overdose risk increased	Opioids used to regulate mood instead of regulating pain

Table 2: Assessing the risk

Patient Factors
Depression, anxiety and history of mental illness
History of alcohol and substance abuse
History of opioid or prescription drug misuse
Inability to engage in services to meet educational and psychological health needs

Prescribing Factors
High doses > 120mg morphine equivalent/day
Multiple opioids
Multiple formulations of opioids
More potent opioids
Concurrent benzodiazepines, gabapentinoids or sedatives

pain; psychiatric comorbidity; correlation of increasing pain with requests for increased opioid dose; psychological deterioration; reliance on pharmacological treatment only without any self-management such as exercise, physiotherapy and psychological support; incidence of lost prescriptions/dropped bottles/extra medications needed for trips abroad; and continued use despite side effects such as constipation and sedation.

ASSESSING THE LOW RISK VS HIGH RISK PATIENT FOR OPIOID THERAPY CESSATION

A low risk patient can easily be managed within the Primary Care sector but in the case of a high risk patient one should consider seeking specialist advice (Table 2). Consider also using an **Opioid Risk Tool**[2] which is a brief, self-report screening tool designed for use in adult patients in primary care settings. This can be done in less than one minute and has been validated for both male and female patients. This scoring system will categorise patient as low or high risk of having an abusive drug-related behaviour.[2]

MORPHINE EQUIVALENT DAILY DOSE

Morphine equivalent dosing (MED) determines a patient's cumulative intake of any opioid drug over 24 hours.

The daily dose of opioids can be calculated by:

1. Determine the daily amount of each opioid the patient takes
2. Convert each opioid to morphine equivalent dose
3. Add them together

The British Pain Society recommends a maximum of 120mg morphine equivalent dose in 24 hours. *At this dose or higher, one can assume that the pain is not opioid sensitive and they should be reduced or stopped in a cautious manner.*

DOSE CALCULATOR: CALCULATION OF MORPHINE EQUIVALENT DAILY DOSE (MED)

An easy way to calculate the total amount of morphine equivalent dose is by using an online calculator found online: *https://www.mdcalc.com/morphine-milligram-equivalents-mme-calculator*.

Opioids Aware (*https://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware*[3]) is a website resource for patients and healthcare professionals to support safe prescribing of opioid medicines for pain (Table 3). It was developed in collaboration with Public Health England, the Faculty of Pain Medicine, and the British Pain Society with representatives from the Royal College of General Practitioners, the Royal Pharmaceutical Society, and the Faculty of Addictions, Royal College of Psychiatrists.

Table 3: Opioids Aware - Five Headline Points

1. Opioids are very good analgesics for acute pain and for pain at the end-of-life but there is little evidence that they are helpful for long-term pain.
2. A small proportion of people may obtain good pain relief with opioids in the long term if the dose can be kept low and especially if their use is intermittent (however it is difficult to identify these people at the point of opioid initiation).
3. The risk of harm increases substantially at doses above an oral MED of 120mg/day, but there is no increased benefit.
4. *If a patient is using opioids but is still in pain, the opioids are not effective and should be discontinued, even if no other treatment is available.*
5. Chronic pain is very complex and if patients have refractory and disabling symptoms, particularly if they are on high opioid doses, a very detailed assessment of the many emotional influences on their pain experience is essential.

(Adapted from *https://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware*[3]).

SIX PRACTICAL CONSIDERATIONS FOR PHYSICIANS TO REDUCE HIGH DOSE OPIOIDS

1. Education: Explain the Importance of Reducing Opioids to the Patient

Identifying the side effects from opioids, especially if they are relevant to their personal life such as constipation, day-time somnolence or poor night-time sleep is essential in order for the patient to understand the risks of opioids and comply with a reduction plan.

enough already.

It's time to prevent migraine with Aimovig®.

First and only therapy of its kind, specifically designed to prevent migraine by targeting the CGRP receptor[1]

Consistent and sustained efficacy across the migraine spectrum[1-3,6]

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- Over 90% of patients completed Aimovig pivotal trials[1-3]

Simple, once every 4 weeks administration with no loading dose[1]

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erenumab

Release the grip of migraine[1-5]

References:

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AIMOVIG®
▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION:
70mg Solution for injection in pre-filled pen. Each pre-filled pen contains 70 mg (erenumab).

140mg Solution for injection in pre-filled pen. Each pre-filled pen contains 140mg (erenumab).

INDICATION:
Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

DOSAGE:
Adults: Treatment is intended for patients with at least 4 migraine days per month when initiating treatment with erenumab. The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks. Each 140 mg dose is given either as one subcutaneous injection of 140 mg or as two subcutaneous injections of 70 mg. Clinical studies have demonstrated that the majority of patients responding to therapy showed clinical benefit within 3 months.
Pediatric patients: The safety and efficacy of Aimovig in children below the age of 18 years have not yet been established. No data are available.

Special populations: ♦ *Elderly* (aged 65 years and over): Aimovig has not been studied in elderly patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age. ♦ *Renal impairment / hepatic impairment:* No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment.
Treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine. Aimovig is for subcutaneous use. Aimovig is intended for patient self administration after appropriate training. The injection can be administered into the abdomen, thigh or into the outer area of the upper arm. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard.

CONTRAINDICATIONS:
♦ Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS:
♦ Hypersensitivity reactions: Serious hypersensitivity reactions, including rash, angioedema and anaphylactic reactions have been reported with erenumab in post-marketing experience. These reactions may occur within minutes, although some may occur more than one week after treatment. In that context, patients should be warned about the symptoms associated with hypersensitivity reactions. If a serious or severe hypersensitivity reaction occurs, initiate appropriate therapy and do not continue treatment with erenumab. ♦ Patients with certain major cardiovascular diseases were excluded from clinical studies. No safety data are available in these patients. ♦ In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. ♦ In patients with latex sensitivity: The removable cap of the Aimovig pre-filled syringe/pen contains dry natural rubber latex, which may cause allergic reactions in individuals sensitive to latex.

INTERACTIONS:
No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies. No interaction with oral contraceptives (ethyl estradiol/norgestimate) or sumatriptan was observed in studies with healthy volunteers.

ADVERSE REACTIONS:
Common (≥1 to <10%): Hypersensitivity reactions including anaphylaxis, angioedema, rash, swelling/oedema and urticaria, Constipation, Pruritis, Muscle Spasms, Injection site reactions.
Please consult the Summary of Product Characteristics for a detailed listing of all adverse events before prescribing.

PREGNANCY, LACTATION AND FERTILITY:
Pregnancy: There are a limited amount of data from the use of erenumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Aimovig during pregnancy. Lactation: It is unknown whether erunumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, use of Aimovig could be considered during breast-feeding only if clinically needed. Fertility: Animal studies showed no impact on female and male fertility.

LEGAL CATEGORY: POM

PACK SIZE: 1 pre-filled pen 70mg, 140mg

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

MARKETING AUTHORISATION NUMBER:
1 pre-filled pen 70mg (EU/1/18/1293/001)
1 pre-filled pen 140mg (EU/1/18/1293/004)

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.

2020-MT-AIM-13-FEB-2020

NOVARTIS

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2. Engagement and Preparation for Dose Reduction: The Patient should be Involved in the Decision of Opioid Reduction

It is essential that the patient is involved in opioid reduction and preparation for dose reduction. This will help give them more control of the reduction plan which will ultimately result in a more successful process and ultimately cessation of these drugs.

Preparation for dose reduction may also include hospital admission or discussing with other specialities with regards to any possible deterioration to their physical and mental health co-morbidities. It is also essential that the patient's pain is monitored during the tapering process and other non-opioid options are considered. Non-opioid pharmacological agents may include paracetamol, NSAIDs as well as anti-depressants including duloxetine, amitriptyline or other TCAs, and anti-convulsants such as gabapentin and pregabalin. Non-drug related pain management strategies like mindfulness and cognitive behavioural therapy should also be considered.

The manner in which opioids are tapered is irrelevant as long as the overall daily dose continues to decrease. It is essential that all physicians caring for the same patients are informed of the opioid reduction plan so that they do not inadvertently increase the opioid doses.

3. Choice of Opioid Reduction Scheme

There are two methods for reducing opioids in patients taking immediate or sustained-release formulations[4];

1. The first choice involves initially *weaning down the immediate release* (IR) PRN doses.
   a. Frequency of IR opioids are kept constant but dose is reduced weekly (e.g. from 15mg to 10mg to 5mg);
   b. The same dose is maintained but the frequency is reduced (e.g. from QDS to TDS to BD).
2. The second option involves the *reduction of the modified release* (MR) dose by approximately 10% per week whilst keeping the same IR dose. The patient is advised against increasing the PRN doses as this would contradict the weaning process of the MR formulation. Allowing the patient to choose whether the morning or evening dose is reduced first is advisable as this will give more control. Table 4 gives an example of how to reduce morphine slow release tablets (MST).

Table 4: Tapering of morphine slow release tablets

	MORNING MST AM (MG)	EVENING MST PM (MG)
Week 1	80	80
Week 2	70	80
Week 3	70	70
Week 4	60	70
Week 5	60	60

3. Fentanyl patches are available as 12, 25, 50, 75 and 100mcg/hr patches. 12.5mcg/hr of fentanyl is equivalent to 45mg of oral morphine per day (12.5mcg/hr patches are labelled as 12mcg/hr to avoid confusion with the decimal places). The duration of each patch should last between 48 to 72 hours and therefore they are prescribed every 3 days. Fentanyl patches dose is reduced by 12.5mcg/hr every fortnight.

4. The Weaning Plan

Switching to the tablet form of opioids also helps the weaning process. Having the whole bottle available may facilitate abuse since it is tempting and easier to have a 'sip' from the bottle rather that measuring the doses. Morphine sulphate oral solution contains alcohol, therefore one has to think also of alcohol dependence; the patient may not even be aware of this.

5. Emotional Impact and Expectations:

Any associated anxiety and depression should be managed effectively. Physicians should also ensure that patients understand that the tapering process can be difficult, and that they would need additional support, including mental health specialists. Patients with untreated depression and other mental health

disorders are at increased risk for misuse or abuse of controlled medications, including addiction and overdose. Additionally, untreated depression can interfere with the resolution of pain.[5,6]

6. Withdrawal Symptoms

Opioid withdrawal symptoms can be various although in general are not life threatening. However, these symptoms may cause patients to seek opioids from other clinicians or non-medical sources. Therefore it is essential that good communication is present between the patient and the clinician and that the patient is made aware of such symptoms. Withdrawal symptoms can occasionally be unpleasant. They can be similar to flu-like symptoms including sweating, chills, headache, myalgia, arthralgia and fatigue which can start from 6 to 36 hours following the last opioid dose and diminish over 3 to 7 days, although most patient will report a feeling of malaise for several weeks particularly if they have been taking very high doses.[7] The use of muscle relaxants, antiemetics, anti-diarrhoeal agents such as loperamide and non-opioid analgesics may be considered.[8]

The **Clinical Opiate Withdrawal Scale (COWS**) is an 11-item scale that can help clinicians both in the outpatient and inpatient setting. Rating common signs and symptoms of opioid withdrawal as well as monitoring these symptoms over time will help clinicians determine the severity of opioid withdrawal.[9]

CONCLUSION

The termination of opioid therapy should not mark the end of treatment, but should continue with other modalities, either through direct care or referral to other healthcare specialists, as appropriate.[10-12] Physicians should consider referral at any stage for optimisation of non-pharmacological pain management strategies and/or education and support for opioid tapering which all ultimately aim for the same goal, that of opioid cessation.

USEFUL RESOURCES

- The Pain Toolkit by Pete Moore gives practical advice and techniques to manage pain: www.paintoolkit.org
- An excellent five minute overview of chronic pain by the Hunter Integrated Pain Service in Australia: www.youtube.com/watch?v=5KrUL8tOaQs
- Follow-up video called *Understanding Pain: Brainman stops his opioids*: https://www.youtube.com/watch?v=MI1myFQPdCE
- Managing chronic pain – supported by NHS
  Sheffield Persistent Pain - https://www.sheffieldachesandpains.com/persistent/persistent-pain
- Support for patients with pain
  British Pain Society - www.britishpainsociety.org
  Pain Concern - http://painconcern.org.uk
- Videos about chronic pain and how to manage it
  Chronic pain - www.healthtalk.org
- WHO animated videos
  Depression - www.youtube.com/watch?v=XiCrniLQGYc

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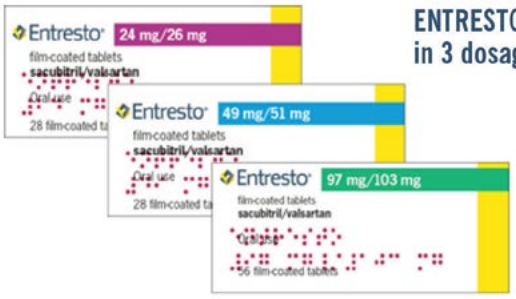

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Before your NYHA Class II patients with HFrEF leave your office, take action with ENTRESTO—and keep them on the right path.

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 co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. Undesirable effects: Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. Legal classification: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2018-MT-ENT-30-APR-2018

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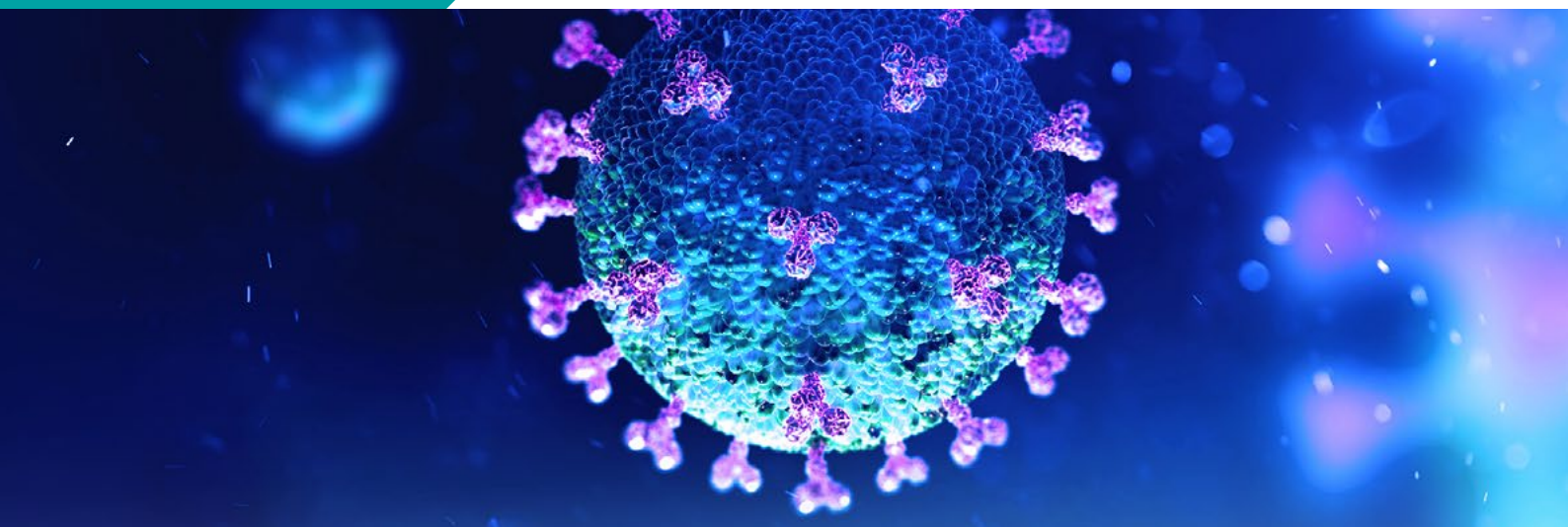
DR PIERRE VASSALLO



COVID-19
Update on Facts and Imaging

Since Dec 31, 2019, we have been bombarded by daily reports in the global news on the progress of spread of the Novel Corona Virus 2019, now known as COVID-19. A report issued by the Maltese Department of Health confirmed that COVID-19 spread to Malta on March 7, 2020.[1]

FACTS

Coronaviruses have a predilection for the respiratory tract. Numerous strains of the coronavirus exist, which can cause anything from the common cold to life-threatening respiratory infections. The disease is transmitted by a droplet mechanism (sneezing and coughing), hand contact (if hands are contaminated by sneezing or coughing) or by physical contact with an infected individual.

If COVID-19 virus remains within the upper respiratory tract, the presenting symptoms are those of the common cold (cough, sneezing and fever). If the virus involves the lower respiratory tract, it causes pneumonia, which can be severe and sometimes life-threatening particularly in elderly individuals and in those people whose immunity has been compromised by other diseases.

The main problem with controlling the disease is its incubation period of up to 14 days, during which time the individual carries the virus and can infect others but shows no symptoms. The present strategy for preventing spread is to enforce a 2-week self-quarantine (at home) on all those individuals returning from those regions with large numbers of infected cases; these include Northern Italy, China, Singapore, Japan, Iran and South Korea.

The media have undoubtedly had a major impact on the level of awareness of this disease worldwide. It is impressive to see reports from reliable sources such as the European Centre for Disease Prevention and Control, where in almost real-time, we learn of the number of cases in each country. It is rather disturbing, as of March 25, to see large countries such as Ukraine and Bhutan, have less cases than Malta.[2] However, these reports must be evaluated with caution, because the quality of the national health services in each country will impact the number of detected and reported cases. On a more critical note, it would be interesting to see how statistics for other viruses (such as the influenza virus) compare with those of COVID-19 to understand whether this is really a new scenario or just another "déjà vu".

DIAGNOSTIC CRITERIA

One of the first peer-reviewed scientific publications that reported on the signs and symptoms of Coronavirus appeared in the New England Journal of

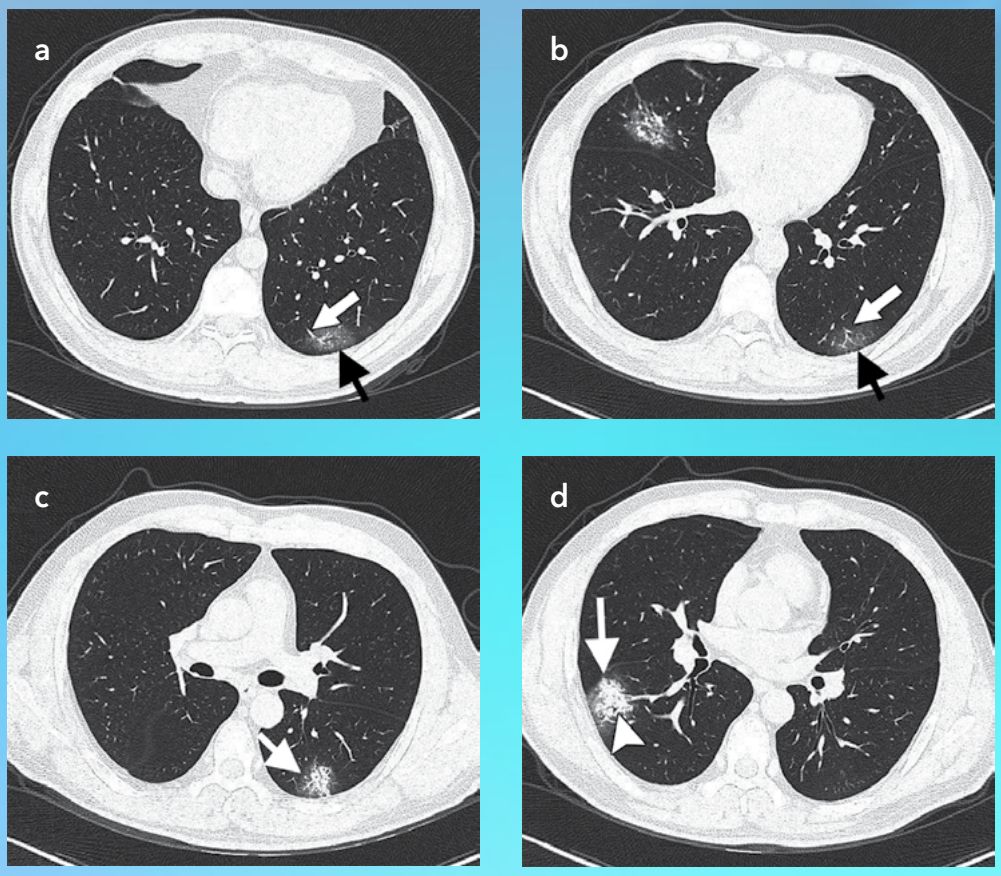


Figure 1: CT images show bilateral multifocal ground-glass opacities (GGO) (black arrows in a and b), mixed GGO (white arrow in c) and consolidation lesions (arrow in d). Traction bronchiectasis (arrowhead, d) and vascular enlargement (white arrow, a and b) are also noted.

Medicine on January 29, 2020.[3] This article reported on clinical findings in the first 425 recorded cases of COVID-19 from Wuhan, Hubei Provence, China. These were confirmed using real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) performed on swabs taken from the upper respiratory tract or from bronchial lavage samples. Initially, only symptomatic cases who had direct or indirect contact with the Wuhan Seafood Market were tested. Subsequently, test criteria were updated and a sharp rise in the number of confirmed cases was observed with a marked increase in non-linked cases.[3] Due to the limited resources for RNA testing in China resulting from the large demand, health authorities were obliged to introduce clinical and imaging findings as well as a history of exposure as criteria for diagnosing COVID-19 infection in the Hubei Provence; this further complicated statistical evaluation, making the effects of disease containment measures more difficult to assess.[4,5]

CLINICAL PRESENTATION

A report from the Chinese Centre for Disease Control has shown that most case patients were 30 to 79 years of age (87%), 1% were aged 9 years or younger, 1% were aged 10 to 19 years, and 3% were age 80 years or older.[4] In this report, most cases had been diagnosed in Hubei Province (75%) and many of those reported Wuhan-related exposures (86%).

Most cases were classified as mild (81%; i.e. nonpneumonia and mild pneumonia). However, 14% were severe (i.e. dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (i.e. respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[5]

IMAGING FINDINGS

The most valuable method for imaging COVID-19 infection is chest CT (computed tomography). Most affected patients have shown the following CT findings:

1. Ground glass opacities (GGO)
2. Mixed GGO and lung consolidation
3. Vascular enlargement and
4. Traction bronchiectasis.

Figure 1 illustrates the above CT findings in a patient who had a short-term exposure to Wuhan and was suffering from fever and cough; these clinic features are considered as mild symptoms.[6]

Lung lesions in COVID-19 infection are more likely to be bilateral, basal, multifocal and peripheral.

Two reports have shown that patients showing the following lung CT findings are more likely to already have or to progress to severe life-threatening disease:[6,7]

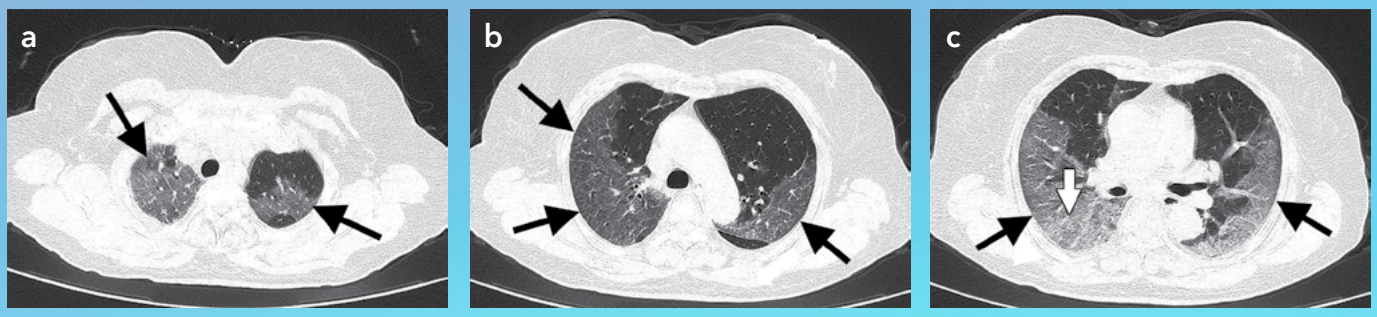


Figure 2: CT Scans through the lungs (a, b and c) show bilateral diffuse ground glass opacities (black arrows in a, b and c) and reticulation (white arrow in c).

1. Architectural distortion
2. Traction bronchiectasis
3. Lymph node enlargement and
4. Pleural effusions.

Finally, one research group indicated that diffuse lung disease is more frequent in severe cases.[6]

Figures 2 and 3 illustrate some of the above features in patients with confirmed COVID-19 infection who were suffering from severe symptoms including respiratory distress. These findings may be seen in any severe lower respiratory tract infection.

In summary, even though the above CT scan features may not be pathognomonic for COVID-19 infection, they are useful in detecting RT-PCR negative or equivocal cases and in the absence of lab resources as was experienced in China when demand outstripped the supply for testing kits. CT may also be useful in detecting subclinical infections. Based on the above report, CT is helpful for identifying those cases that have or are likely to progress to severe life-threatening disease.

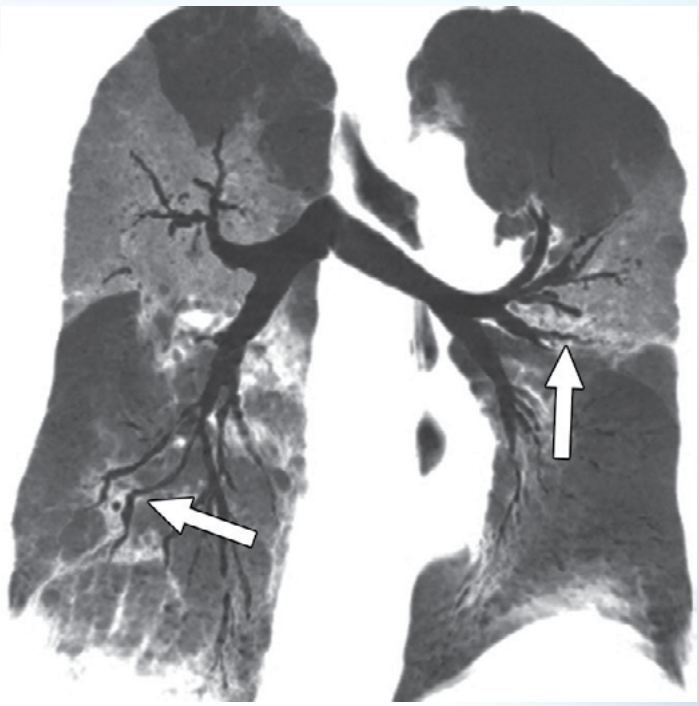


Figure 3: Coronal CT reconstruction show irregular bronchial wall with traction bronchiectasis and architectural distortion (white arrows).

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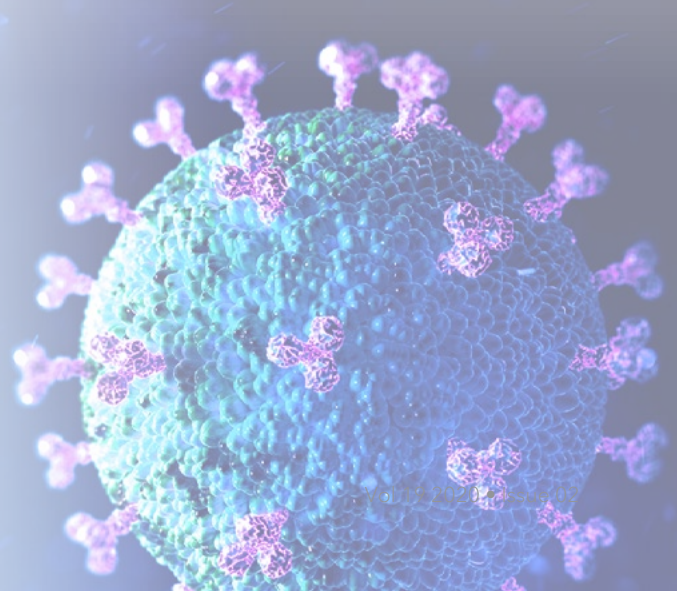

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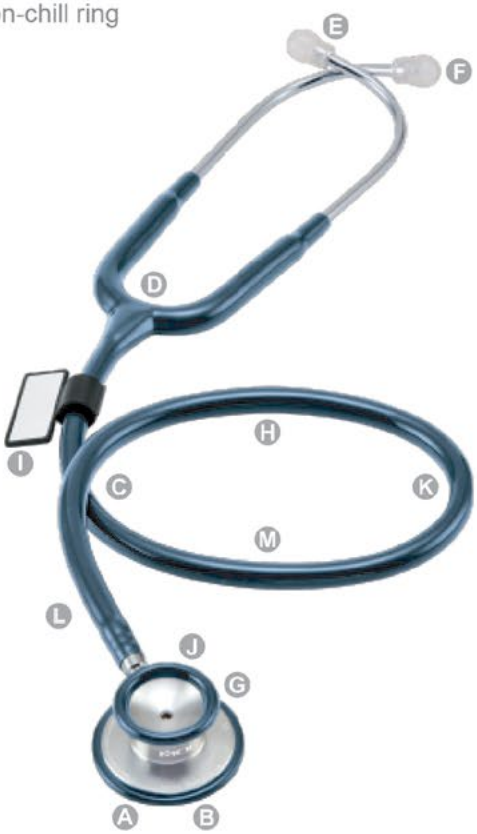

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