THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

Volume 18, 2019 Issue 01 ISSN number 2313-8084

Normal Variants of the Lower Limbs in Children

TheSYNAPSE eLearning

CRISPR-Cas9 and its Clinical Applications

Meeting Suzanne Ford

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/0001/18

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

ABORTION, ETHICS AND TORT LAW
A RED HERRING?

EDITORIAL

I wish to start this editorial by posing a question. Should a young female patient who enters in your clinic, and whose father is known to you as suffering from Huntington's, be informed of her father's condition? As you may recall, Huntington's disease is an autosomal dominant neurodegenerative disorder, meaning that having a mutation in only one of the two copies of the *HTT* gene - the *HTT* gene provides instructions for making a protein called Huntington - is enough to cause the condition. When a person with Huntington's has children, each child has a 50% chance of inheriting the mutated gene and developing the condition.

So, returning to that young patient of yours who is of child-bearing age, would you inform her of her father's condition or confidentiality would prevail?

Well, we are currently experiencing this scenario in what can be considered as one of the first cases in the UK where judgement is expected on a relative's claim over issues of genetic responsibility. Lawyers are bringing a case against the St George's Healthcare NHS Trust, involving a woman who is suing doctors because they failed to tell her about her father's fatal hereditary disease before she had her own child. The woman discovered – after giving birth – that her father carried the gene for Huntington's disease and that her own daughter has a 50% chance of having it. The lawyers argument that if the patient knew about her father's condition she would have tested herself for the condition and if positive, she would have terminated her pregnancy. In keeping with this, her lawyers floated the idea that the definition of a patient may not just be the person who provided a genetic sample, but may be also defined as those affected by that genetic sample.

Well, should doctors share genetic test results with relatives, even without consent? How much effort clinicians need to put into tracing relatives? Well, knowledge on genetic components of diseases, including cancer, evolves with time and research; this poses a challenge on what is currently known, what becomes known, estimating the chance of developing or passing on a genetic disorder and whether such chance justifies the communication of information to relatives. One must remember that you cannot retract that information once you have given it.

The case involving the St George's Healthcare NHS Trust is unnaturally complex. The patient's father shot and killed his wife in 2007 and was convicted of manslaughter. In 2009, doctors at the St George's Hospital diagnosed him with Huntington's disease and proposed to tell his daughter about his condition in view of the fact that she was pregnant. He refused to do so and the doctors accepted his decision. In 2010 the woman gave birth and four months later she accidentally learned by one of her father's doctors that her father had Huntington's. In 2013 she tested positive for the Huntington's disease gene; her own daughter, now eight, has a 50% chance of having it.

Interestingly, in 2015 the High Court of Justice ruled against the patient's claim since such move was interpreted to undermine the doctor-patient relationship; also the court recognised that doctors might also be overly burdened if they are required to assess whether or not to make disclosures to patients' relatives. However, this decision was overturned by the Court of Appeal in 2017. The latter acknowledged the arguments of the High Court of Justice but said that these should not preclude the patient from having the opportunity to have the particular circumstances of her case heard in the High Court for a full trial. The trial is set for November 2019.

That a duty of confidence exists in relation to medical information is axiomatic. However, common sense dictates that the rule of confidentiality is not absolute. In special circumstances it may be justified to break confidentiality where the aversion of harm by the disclosure substantially outweighs the patient's claim to confidentiality. Before disclosure is made in such circumstances, an attempt should be made to persuade the patient in question to consent to disclosure; the benefit to those at risk should be so considerable as to outweigh any distress which disclosure would cause the patient.

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

Production: Outlook Coop

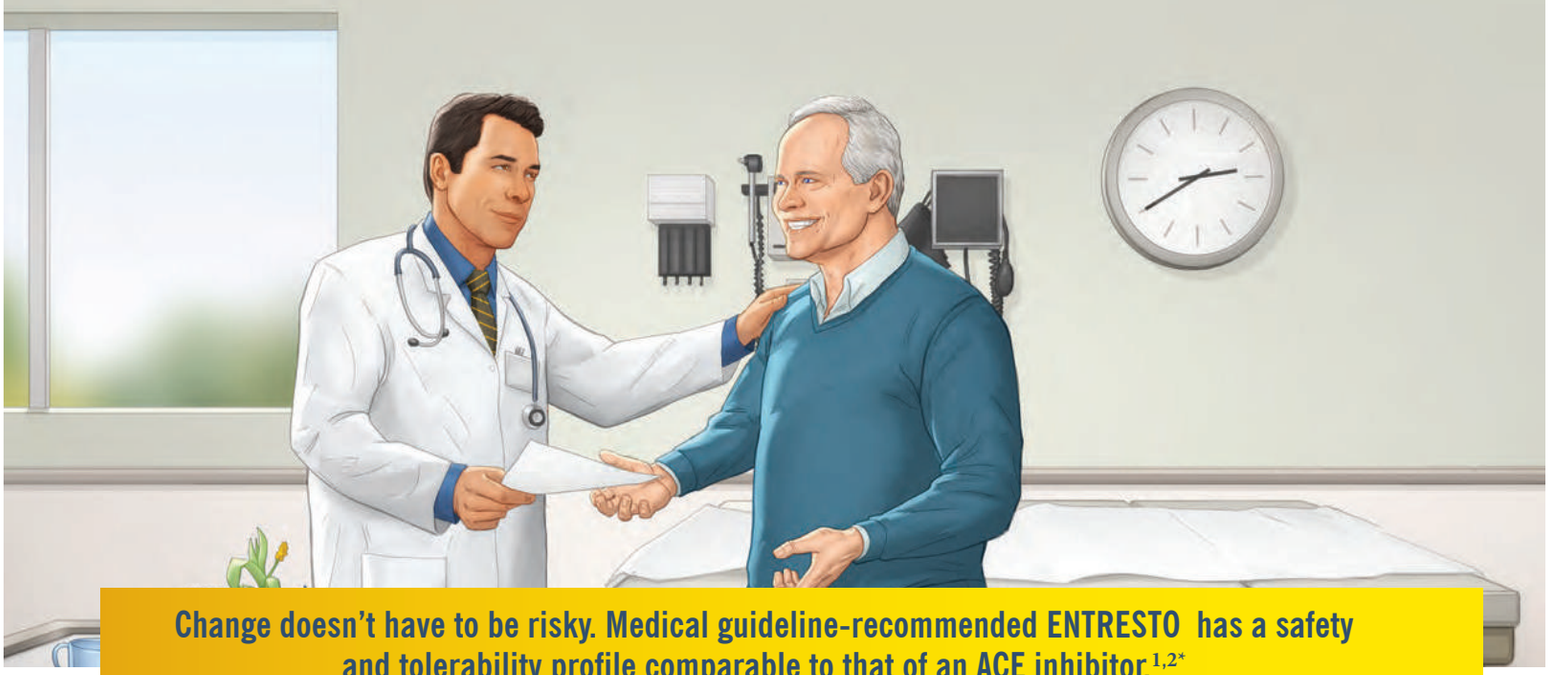
Printing: Europrint Ltd

OUR COLLABORATORS

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

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

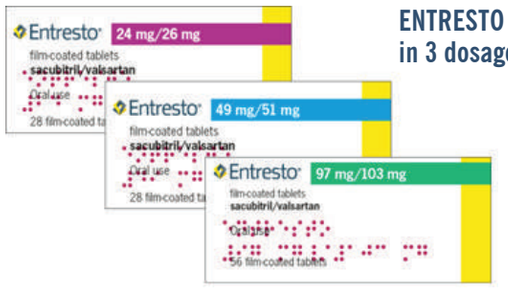
Start with confidence



Change doesn't have to be risky. Medical guideline-recommended ENTRESTO has a safety and tolerability profile comparable to that of an ACE inhibitor.[1,2*]

Start ENTRESTO today

- GO — The starting dose is 24/26 mg or 49/51 mg, twice daily, depending on the patient's current treatment and medical condition[1]
- The target dose is 97/103 mg twice daily[1]
- Stop using an ACE inhibitor for 1.5 days (36 hours) before starting ENTRESTO[1]



ENTRESTO is available in 3 dosage strengths[1]

ENTRESTO contains valsartan, and therefore should not be coadministered with another ARB-containing product.

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

References: 1. Novartis Europharm Ltd. Entresto Summary of Product Characteristics. **2.** Ponikowski P, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;18(8):891-975.

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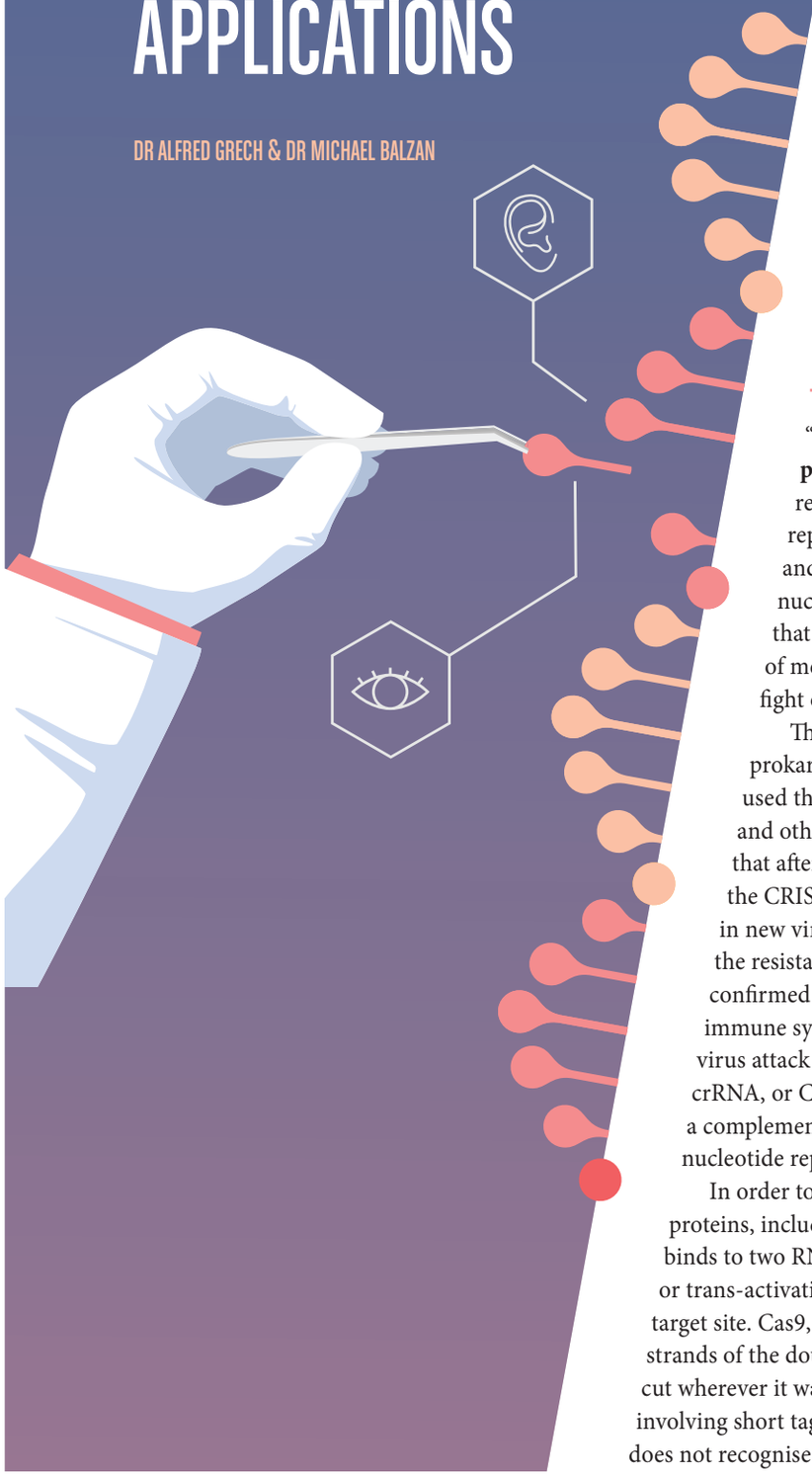
ISSUE GUIDE

TheSynapse

CRISPR-CAS9 AND ITS CLINICAL APPLICATIONS

DR ALFRED GRECH & DR MICHAEL BALZAN



ABSTRACT

CRISPR-Cas9 is a powerful and simple tool for editing genomes. It allows researchers to alter DNA sequences and gene function. Its potential applications include correcting genetic defects and treating and preventing the spread of diseases. In China, clinical human trials using CRISPR-Cas9 are now in progress.

INTRODUCTION

CRISPR (pronounced "crisper") and its therapeutic use in human cell lines is revolutionising biomedical research. In particular, this is because CRISPR makes it straightforward to edit or inactivate genes in a cell line. It also simplifies the approach of creating animal models that are then used to explore diseases. Indeed, research work, which took months or years, can now be completed in weeks.

THE KEY PLAYERS

"CRISPR" stands for "**c**lusters of **r**egularly **i**nterspaced **s**hort **p**alindromic **r**epeat". In detail, CRISPR is a bacterial DNA region made up of two specialised characteristics: (i) nucleotide repeats that are distributed throughout the CRISPR region, and (ii) spacers, bits of DNA that are interspersed among the nucleotide repeats. In general, the spacers are taken from viruses that have attacked the bacteria. Indeed, spacers are used as a bank of memories, therefore allowing bacteria to recognise viruses and fight off future attacks.

That CRISPR provides acquired resistance against viruses in prokaryotes was demonstrated over a decade ago.[1] Here, researchers used the *Streptococcus thermophilus* bacterium, found in yoghurt and other dairy products, as their model. Barrangou *et al.* showed that after a virus attacks a bacterium, new spacers are introduced into the CRISPR region. In addition, by taking out the spacers or putting in new viral DNA sequences, the researchers were able to change the resistance of the bacterium against a particular virus. It was thus confirmed that CRISPRs have a role in the regulation of the bacterial immune system. Indeed, after introducing a spacer, a subsequent virus attack causes a portion of the CRISPR to be transcribed into crRNA, or CRISPR RNA. In this case, the CRISPR template produces a complementary sequence of RNA, with each crRNA consisting of a nucleotide repeat and a spacer portion.[2]

In order to stop foreign attacks, bacteria use CRISPR RNA and Cas proteins, including Cas9. Cas9 is an enzyme that cuts foreign DNA. It first binds to two RNA molecules: the crRNA, and another one called tracrRNA, or trans-activating crRNA. Both RNAs then guide Cas9 to the cleavage target site. Cas9, using two separate domains on its structure, cuts both strands of the double helix, resulting in a double strand break.[2] Cas9 does not cut wherever it wants in the genome. Instead, there is a built-in mechanism involving short tags known as PAMs ("protospacer adjacent motifs"): if Cas9 does not recognise a PAM next to its target site, it does not cut.

GENOME EDITING TOOL

Genomic DNA holds instructions for all living things. CRISPR-Cas9 provides the means to alter these instructions. It does this through a break or a cut in the DNA therefore circumventing the repair mechanisms and introducing the alterations. It was this knowledge that fuelled the spiralling interest in CRISPR-Cas9. In principle, the revolution began in 2012 with two research papers describing how the bacterial CRISPR-Cas9 can be transformed into a simple genome-editing tool. Jinek *et al.*[3] and Gasiunas *et al.*[4] concluded that Cas9 could cut any DNA region if the nucleotide sequence of the crRNA is changed. Jinek *et al.* went further and fused crRNA and tracrRNA to create a single guide RNA (gRNA). Overall, genome editing requires the Cas9 protein and a gRNA.

Operationally, a stretch of 20 base pairs that matches the gene to be edited is designed. Subsequently, an RNA molecule that is complementary to the 20 bp stretch is constructed. Just like a pair of scissors, Cas9 and the RNA will then cut the DNA. In the end, the cell's natural repair mechanisms will work (e.g. through non-homologous end joining, or NHEJ) to introduce the changes in the genome.

CLINICAL APPLICATIONS

It was a matter of time until the bacterial CRISPR-Cas9 was used in a clinical setting.[5] So far, it has been used to ameliorate muscle function in mice with Duchenne muscular dystrophy.[6] In particular, using CRISPR, researchers deleted the defective gene, allowing the mice to produce one of the main proteins in the muscles. CRISPR is also being exploited to treat HIV,[7] since it can attack multiple regions of the viral DNA, therefore making the development of virus resistance harder. In turn, this can decrease the chance of viral escape and resistance to treatment. In the field of cancer, CRISPR is being applied to turn on and off genes implicated in the development of cancer, to inspect the protein domains involved in cancer, and also, to evaluate the drug targets.[8]

In vitro and animal models of human disease have also demonstrated that CRISPR-Cas9 can be effective in the correction of genetic defects, thus paving the way for clinical therapeutic applications in humans. Yuan *et al.*,[9] for example, investigated the role of αA-crystallin in rabbits. αA-crystallin increases cellular stress tolerance and prevents precipitation of denatured proteins.[10] It is these functions that maintain eye lens transparency and prevent cataracts.[11] Yuan *et al.* demonstrate that mutations in αA-crystallin are linked to the formation of cataracts. In detail, it was shown that a CRISPR-Cas9 mutation of αA-crystallin causes congenital cataracts, failed differentiation of lens fibres, microphthalmia, and obscurity. In light of this, further investigations should pursue the association between mutations in the αA-crystallin gene and congenital cataracts in humans.

CRISPR-Cas9 is also being used to understand cystic fibrosis, an autosomal recessive, chronic, genetic disease of the lung caused by mutations in the cystic fibrosis transmembrane regulator (CFTR). Sanz *et al.*,[12] for instance, describe an efficient method for editing three different and rare CFTR mutations, which together account for 3% of patients suffering from cystic fibrosis. In a similar method, Schwank *et al.*[13] used CRISPR-Cas9 to correct the CFTR locus through homologous recombination in intestinal stem cell organoids of patients.

In addition to cataracts and cystic fibrosis, CRISPR-Cas9 studies have also been carried out on Fanconi anaemia,[14] hearing loss,[15] haemophilia,[16] leishmaniasis[17] and malaria.[18] For example, hearing loss affects about 1 in 500 newborns. It is known that genetic deafness is often due to mutations of the inner ear genes. Using CRISPR-Cas9, the roles of these genes can be studied through the disruption of normal gene alleles via the NHEJ mechanism. In particular for genetic hearing loss, CRISPR-Cas9 can disrupt mutations through NHEJ, or repair mutations via homology-directed-repair (HDR), both of which could restore hearing. Zou *et al.*[15] have shown that genome editing is an efficient tool in the mammalian inner ear in vivo.

In situ genome editing has also resulted in successful correction of haemophilia, an X-linked genetic bleeding disorder due to a lack in coagulator factor IX (haemophilia B). In the human F9 gene, Guan *et al.*[16] identified a new mutation (Y371D) in haemophilia B. Using CRISPR-Cas9 to generate transgenic mice, they confirmed that this novel mutation results in severe haemophilia. Guan *et al.* proceeded to develop therapeutic strategies targeting this mutation.

In regard to the parasitic *Leishmania donovani* that causes leishmaniasis disease, Zhang *et al.*[17] exploited the CRISPR-Cas9 tool to specifically mutate the parasitic genome. In this case, high-throughput functional analysis can be used to understand its functional genes, thus promoting the discovery of future therapeutic strategies. In a similar approach, but for a different parasite, Hammond *et al.*[18] used CRISPR-Cas9 to target female reproduction in the malaria mosquito vector *Anopheles gambiae*. In addition, in the agricultural and food industries, CRISPR-Cas9 has been applied to vaccinate industrial cultures (e.g. for yoghurt) against viruses.[19] Phage infection of starter cultures is a widespread and significant problem in the dairy industry. The process of applying CRISPR-Cas9 is simply to select those bacterial strains that make the best yogurt, expose them to

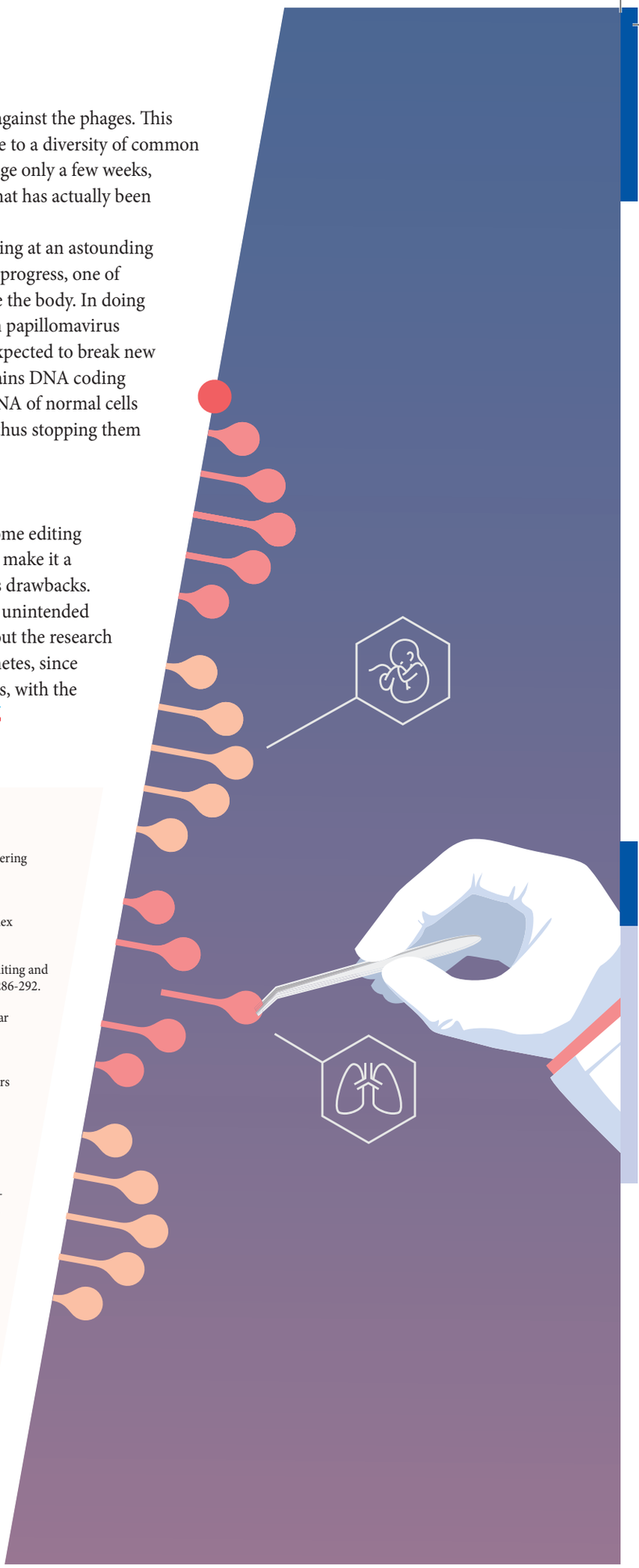
IN VITRO AND ANIMAL MODELS OF HUMAN DISEASE HAVE ALSO DEMONSTRATED THAT CRISPR-CAS9 CAN BE EFFECTIVE IN THE CORRECTION OF GENETIC DEFECTS, THUS PAVING THE WAY FOR CLINICAL THERAPEUTIC APPLICATIONS IN HUMANS

phages and screen for strains that become naturally vaccinated against the phages. This process is repeated until you end up with a strain that is immune to a diversity of common phages. In view of the fact that this entire process takes on average only a few weeks, many people have possibly unknowingly consumed a product that has actually been manufactured using CRISPR-enhanced starter cultures!

In general, the CRISPR genome editing revolution is advancing at an astounding pace. In China, for instance, 20 clinical human trials are now in progress, one of which will use CRISPR, for the first time ever, to edit cells inside the body. In doing so, the aim is to prevent cervical cancers by targeting the human papillomavirus (HPV) genes that cause the tumour to grow. This HPV trial is expected to break new ground. Instead of editing cells outside the body, a gel that contains DNA coding for CRISPR is applied to the cervix. CRISPR should leave the DNA of normal cells untouched, however, it should destroy cells infected with HPV, thus stopping them from turning cancerous.

CONCLUSION

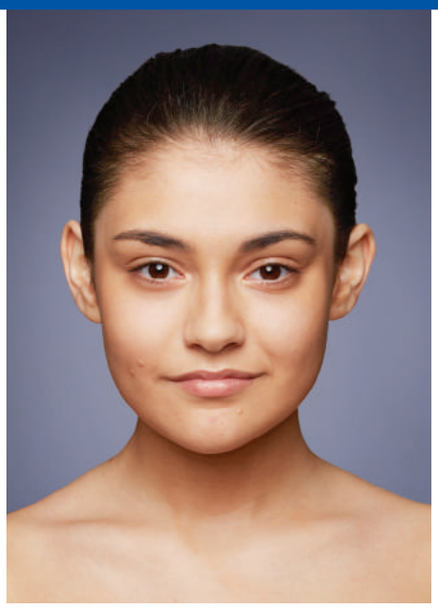
Overall, the robustness and simplicity of the CRISPR-Cas9 genome editing in human cells and model organisms such as mice and primates make it a promising tool in clinical research. However, it is not without its drawbacks. Indeed, if the DNA is cut at sites other than the intended target, unintended mutations are introduced. CRISPR has also raised questions about the research ethics of human genome editing, especially in embryos and gametes, since these can be passed on to subsequent generations. In spite of this, with the progress seen to date, it is clear that this is just the beginning.



REFERENCES

1. Barrangou R, Fremaux C, Deveau H, *et al.* CRISPR provides Acquired Resistance against Viruses in Prokaryotes. *Science* 2007;315(5819):1709-12.
2. Doudna JA, Charpentier E. Genome Editing. The New Frontier of Genome Engineering with CRISPR-Cas9. *Science* 2014;346(6213):1258096.
3. Jinek M, Chylinski K, Fonfara I, *et al.* A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science* 2012;337(6096):816-21.
4. Gasiunas G, Barrangou R, Horvath P, *et al.* Cas9-crRNA Ribonucleoprotein Complex Mediates Specific DNA Cleavage for Adaptive Immunity in Bacteria. *PNAS* 2012;109(39):E2579-86.
5. Mahmoudian-sani MR, Farnoosh G, Mahdavinezhad A, *et al.* CRISPR Genome Editing and its Medical Applications. *Biotechnology & Biotechnological Equipment 2017;* 32(2):286-292.
6. Bengtsson NE, Hall JK, Odom GL, et al. Muscle-specific CRISPR/Cas9 dystrophin gene editing ameliorates pathophysiology in a mouse model for Duchenne muscular dystrophy. *Nat Commun* 2017;8:14454.
7. Wang Z, Pan Q, Gendron P, *et al.* CRISPR/Cas9-Derived Mutations Both Inhibit HIV-1 Replication and Accelerate Viral Escape. Cell Rep 2016;15(3):481-489.
8. Yao S, He Z, Chen C. CRISPR/Cas9-Mediated Genome Editing of Epigenetic Factors for Cancer Therapy. *Hum Gene Ther* 2015;26(7):463-71.
9. Yuan L, Yao H, Xu Y, *et al.* CRISPR/Cas9-Mediated Mutation of alphaA-Crystallin Gene induces Congenital Cataracts in Rabbits. *Invest Ophthalmol Vis Sci* 2017;58(6):BIO34-BIO41.
10. Augusteyn RC. Alpha-Crystallin: A Review of its Structure and Function. *Clin Exp Optom* 2004;87(6):356-66.
11. Maulucci G, Papi M, Arcovito G, *et al.* The Thermal Structural Transition of Alpha-Crystallin inhibits the Heat Induced Self-Aggregation. *PLoS One* 2011;6(5):e18906.
12. Sanz DJ, Hollywood JA, Scallan MF, *et al.* Cas9/gRNA Targeted Excision of Cystic Fibrosis-Causing Deep-Intronic Splicing Mutations Restores Normal Splicing of CFTR mRNA. *PLoS One* 2017;12(9):e0184009.
13. Schwank G, Koo BK, Sasselli V, *et al.* Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients. *Cell Stem Cell* 2013;13(6):653-8.
14. Osborn M, Lonetree CL, Webber BR, *et al.* CRISPR/Cas9 Targeted Gene Editing and Cellular Engineering in Fanconi Anemia. *Stem Cells Dev* 2016; 25(20):1591–1603.
15. Zou B, Mittal R, Grati M, *et al.* The Application of Genome Editing in Studying Hearing Loss. *Hear Res* 2015;327:102-8.
16. Guan Y, Ma Y, Li Q, *et al.* CRISPR/Cas9-Mediated Somatic Correction of a Novel Coagulator Factor IX Gene Mutation Ameliorates Hemophilia in Mouse. *EMBO Mol Med* 2016;8(5):477-88.
17. Zhang WW, Matlashewski G. CRISPR-Cas9-Mediated Genome Editing in *Leishmania donovani*. *MBio* 2015;6(4):e00861.
18. Hammond A, Galizi R, Kyrou K, *et al.* A CRISPR-Cas9 Gene Drive System Targeting Female Reproduction in the Malaria Mosquito Vector *Anopheles gambiae*. *Nat Biotechnol* 2016;34(1):78-83.
19. Barrangou R, Horvath P. CRISPR: New Horizons in Phage Resistance and Strain Identification. Annu Rev Food Sci Technol 2012;3:143-62.

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



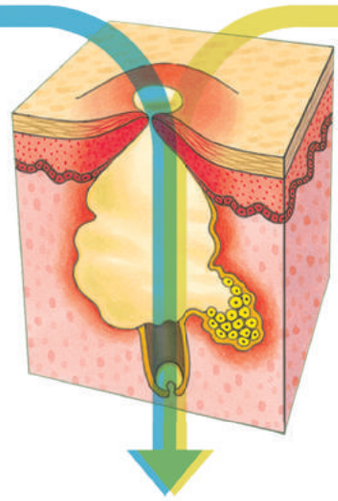
DUAC HAS A DUAL MODE OF ACTION[2]

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 commmensal flora. Cross-resistance: May occur when using antibiotic monotherapy. **PREGNANCY/FERTILITY /LACTATION:** *Pregnancy:* only after careful risk/benefit assessment. *Fertility:* no data. *Lactation*: should not be applied to breast area. **UNDESIRABLE EFFECTS:** *Very common (≥1/10)*: erythema, peeling, dryness. *Common (≥1/100 & <1/10)*: burning sensation. *Refer to the SPC for full list of undesirable effects.* **LOCAL PRESENTATION:** 30g gel. **MARKETING AUTHORISATION NUMBER:** MA300/01401. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline UK Ltd. **Legal Category:** POM. **Date of Preparation:** September 2017.

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

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) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

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

References: 1. Langner A *et al.* BJD 2008; **158**: 122-129. **2.** Duac 5% Summary of Product Characteristics, January 2015. **3.** Langner A *et al.* JEADV 2007; **21**: 311-319. **4.** Duac 5% Patient Information Leaflet, October 2014. **5.** Lookingbill DP *et al.* JAAD 1997; **37**: 590-595.

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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.: MLT_GIB/CBP/0001/17 Date of preparation: November 2017

NORMAL VARIANTS OF THE LOWER LIMBS IN CHILDREN

MS MARTINA GALEA WISMAYER
MR THOMAS AZZOPARDI

ABSTRACT Normal lower limb variants in children are a frequent cause of referral to orthopaedic specialists and often a cause of parental concern. Physiological variants of growth may improve or resolve spontaneously and thus, do not need any surgical intervention. A thorough history and examination, as well as an understanding of the natural progression of angular and rotational variants will assist general practitioners to reassure parents and to identify any pathological conditions which require specialist management.

KEYWORDS Normal variants, development, lower limbs, children, musculoskeletal

Musculoskeletal symptoms in children are a common presentation in primary care.[1,2] Parents are often concerned about the appearance of their child's legs or their gait and general practitioners might have some difficulty in reassuring them. A number of referrals to orthopaedic clinics can be classified as physiological variants of growth[2] which do not need any operative intervention.[3] The aim of this review is to aid clinicians in identifying these normal variants and any abnormal characteristics which are indicative of an underlying pathological condition.

A. NORMAL PHYSIOLOGICAL VARIANTS

The most common variants of the lower limbs can be categorized into angular deformities, rotational deformities and flexible pes planovalgus.

1. ANGULAR DEFORMITIES

Genu varum ('bow legs') and genu valgum ('knock knees'), the most frequently encountered angular deformities, refer to the tibiofemoral angle in the coronal plane, which can be evaluated by measuring the intercondylar and intermalleolar distances (Fig 1). Physiological variants tend to be symmetrical and painless. Normally, up to the age of 18 months and as the child begins to walk, genu varum (mean 15 degrees) can be noted. The normal tibial torsion frequently seen in this age group further exacerbates this manifestation and therefore, referral for genu varum is most common in the 10-14 month age group. As the child grows, the knees tend to go into a valgus position (mean 12 degrees) which, after 7 years of age, gradually corrects itself to the normal 7-8 degrees of valgus seen in adults.[4] Consequently, referral for genu valgum generally occurs at 3-4 years of age. One must keep in mind that the normal physiological genu valgum may be exacerbated by flatfeet, ligamentous laxity and obesity.[5] Alarm symptoms include pain, asymmetry, progression, unilaterality or association with other deformities e.g. short stature. Genu varum over the age of 2 years is a red flag and requires specialist referral to exclude an underlying pathological condition such as Rickets or Blount's disease.

Presentations for painless genu varum also peak in adolescents participating in high impact sports such as football or rugby. The reason for this is suspected to be the result of high sporting demands on the developing skeleton.[2] There is currently no concrete guidance which can be given to these individuals; however, if associated with pain, further investigations are necessary to exclude any co- existing pathology e.g. meniscal tears.

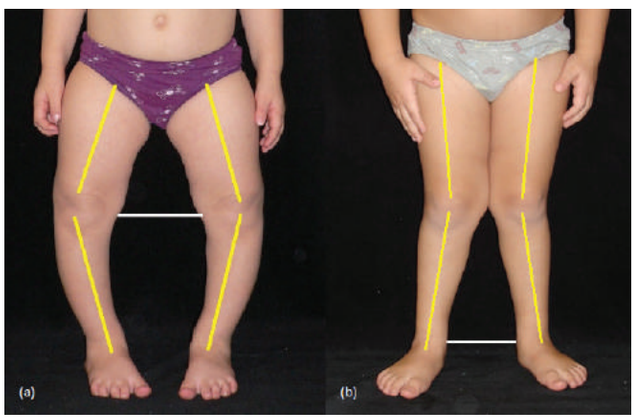


Fig 1 a. Genu varum- white line represents the intercondylar distance.[6]
b. Genu valgum- white line represents the intermalleolar distance.[7]

2. ROTATIONAL DEFORMITIES

The most common presentation for rotational deformities is an in- or out-toeing gait. Although foot position is the most noticeable symptom, the hips and tibias also contribute to the rotational profile of a child. Despite being a common concern, only 0.1% of these deformities persist and are severe enough to require operative intervention.[8]

2.1 In-toeing Gait

The commonest causes of an in-toeing gait are the following:

i. *Internal Tibial Torsion*

Internal tibial torsion is the most frequent cause for in- toeing between 1-3 years of age. It is often bilateral and resolves spontaneously by the age of 6 years. It is also thought to be the result of intrauterine positioning.[8,9] Parents present with concerns of a clumsy gait and frequent falls, and examination when prone reveals an increased thigh foot angle (Fig. 2).[8] Normal thigh foot angles vary from a mean of 5 degrees internal rotation in infants to 10 degrees external rotation from the age of 8 years.[9] Pathological or physiological genu varum may be present and 33% of cases, are associated with metatarsus adductus.[8] Most cases are treated conservatively but if functional problems with severe deformity persist beyond the age of 6-8 years, operative intervention may be considered.[9]

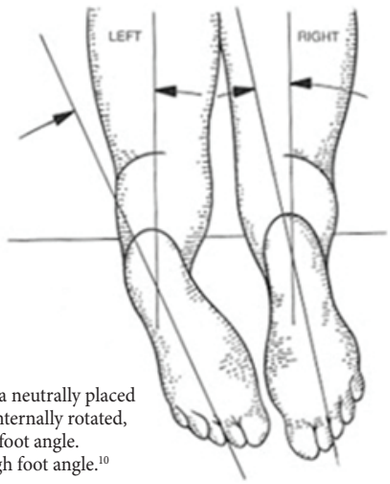


Fig. 2. Thigh foot angle. With a neutrally placed patella, the foot on the left is internally rotated, therefore increasing the thigh foot angle. The right leg has a normal thigh foot angle.[10]

ii. *Increased Femoral Anteversion*

Femoral anteversion refers to the angle created between the femoral neck axis and the transcondylar axis of the knee[2] (Fig. 3). At birth, 30-40 degrees of femoral anteversion is normally present, which gradually decreases with growth to the normal 16 degrees in adults. Generally children with increased femoral anteversion present at 4-6 years of age, with an in-toeing gait, frequent falls and an eggbeater pattern when running.[2, 11] They sit most comfortably in a 'W' position[2, 11] (Fig. 4). It is often bilateral (a unilateral abnormality should be of concern), hereditary and is twice as common in girls. It is associated with other packaging disorders e.g. internal tibial torsion, and usually resolves spontaneously by the age of 10 years. Examination reveals increased hip internal rotation to >70degrees and decreased external rotation to <20degrees when prone (normal internal rotation is 20-60 degrees and external rotation is 30-60 degrees).[11] 80% of cases are treated conservatively and parents can be reassured that there is no increased future risk of hip/knee osteoarthritis or impaired function.[2] Orthotic devices/physiotherapy do not alter its progression.[2, 11] If <10 degrees of external rotation is observed in the older child[11] or if persistent into teenage years with resultant cosmetic concerns, a corrective osteotomy may be offered.[2]

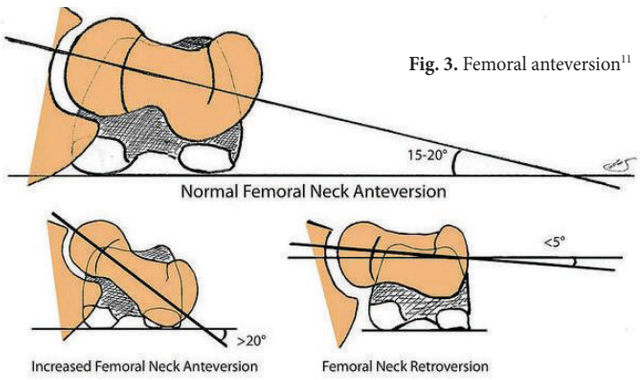


Fig. 3. Femoral anteversion[11]

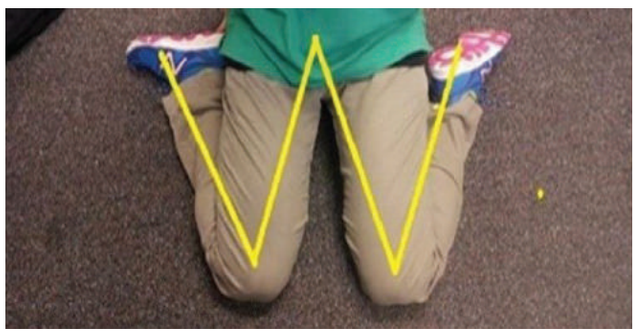


Fig. 4. 'W' position in a child with increased femoral anteversion[12]

Metatarsus adductus ('banana foot') is one of the most frequently encountered congenital foot defects,[8] characterized by a curved lateral foot border secondary to an adducted forefoot (at the tarsometatarsal joints) and a normally aligned hindfoot (Fig. 5a). It is unilateral in 50% of cases and may be seen in cases of oligohydramnios, first and late pregnancies and twin pregnancies. In 95% of cases, it resolves spontaneously by the age of 4 years. Examination reveals a heel bisector line which passes beyond the 2nd webspace (Fig. 5b) and a crease in the medial border may be seen in the rigid variant. The latter is associated with developmental dysplasia of the hip[2] and

merits specialist referral for close monitoring. Non-operative management usually involves regular passive stretching by the parents, casting of the foot to maintain a proper alignment[10] or use of reverse last shoes. Up to 14% may progress in severity requiring operative intervention after 4 years of age.[2]

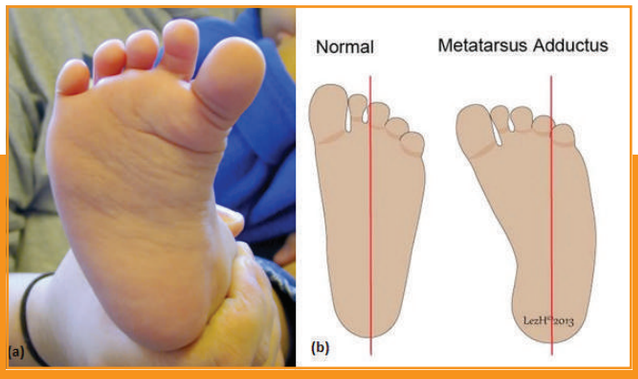


Fig. 5 a. Metatarsus adductus with the characteristic curved lateral border.[13] b. Heel bisector line in a normal foot and in a foot with metatarsus adductus.[14]

2.2 Out-toeing Gait

Up to 2 years of age, an out- toeing gait may be noticed.[8] Above this age group, out- toeing may be due to external tibial torsion or less commonly femoral retroversion, especially in obese children. If unilateral and in older children, Perthes' disease or slipped capital femoral epiphysis should be excluded.[2] Unlike internal tibial torsion, external tibial torsion worsens with skeletal maturity as the leg normally externally rotates with growth and may therefore result in long-term disability. It is more commonly seen in adolescent girls with anterior knee pain or patellar instability due to patellofemoral malalignment. Although first line treatment is conservative, tibial or femoral derotational osteotomies may be necessary.[15]

3. FLEXIBLE PES PLANOVALGUS (FLEXIBLE FLATFOOT)

90% of musculoskeletal presentations in children concern flat feet. All neonates and toddlers have flat feet due to a fat pad beneath the medial longitudinal arch of the foot, lack of neuromuscular control and ligamentous laxity.[2] It usually resolves spontaneously by 4-8 years.[16] Although asymptomatic, presentation is often due to parental concern about the appearance of the foot or the fear of pain or long-term disability. It is commonly associated with obesity and hyperlaxity and is usually familial.[2] Examination reveals a valgus hindfoot with a flattened medial longitudinal arch which reconstitutes when standing on tiptoes or hallux dorsiflexion[16] (Fig. 6). No treatment is required for flexible flatfeet and parents can be reassured that the arch will develop with growth.[16] Insoles are commonly used however Cochrane reviews have shown that they are ineffective and cause unnecessary pain and discomfort.[2]

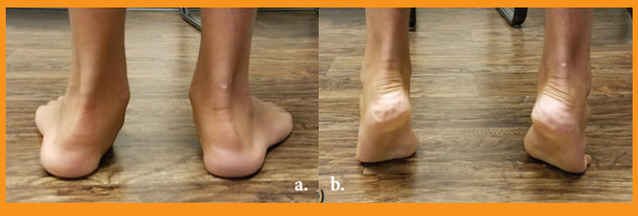


Fig. 6. Flexible pes planovalgus. a. Flattened medial longitudinal arch with a valgus hindfoot. b. Medial arch reconstitutes when standing on tip toes.[16]

B. ASSESSMENT AND EXAMINATION

A detailed history and examination is essential (Box 1). Occasionally malalignment of the lower limbs may be a symptom of an underlying condition e.g. neuromuscular disorders including cerebral palsy.[2]

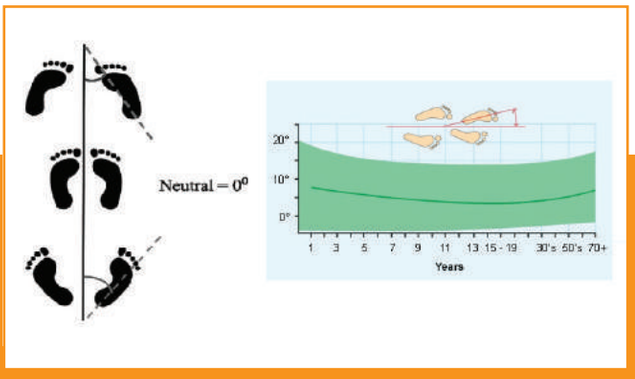


Fig. 7. Foot progression angle. Normal values are -5 degrees to +20 degrees, in-toeing > -5 degrees, out-toeing >20 degrees.[17,18]

BOX 01

IMPORTANT POINTS IN THE HISTORY AIMED AT DIFFERENTIATING BETWEEN NORMAL AND PATHOLOGICAL CONDITIONS

- Reason for presentation?
  Parental anxiety vs. symptomatic child
- Progression of Condition
- Gestational History & Method of Delivery including presentation
- Delayed Milestones
  Is the child walking?
  At what age did he/she start walking?

N.B. Conditions in children < 5 years (< 2 years in genu varum) with asymptomatic, bilateral, symmetrical features are usually normal variants.If a child >5 years (> 2 years in genu varum) presents withpainful, unilateral and asymmetrical features, specialist referral is warranted.

EXAMINATION

- Height
- Weight

While Standing

- Coronal Alignment: Genu Varum or Valgum
- Measure
  1. *Intercondylar distance:* the distance in cm between the knees with the ankles together
     Normal is < 6cm
  2. *Intermalleolar distance:* the distance in cm between the medial malleoli with the knees held together
     Normal is < 8cm

- Arches of the Foot
  Does the medial arch reconstitute when standing on tip toes in cases of flat foot?

While Walking

- Foot Progression Angle (The angle of the foot while walking forward; *Fig. 7)*
  In-toing or out-toeing gait

While Running

- 'Eggbeater pattern' in increased femoral anteversion
  Is the deformity exacerbated?

While Sitting on the Floor

- 'W' position in increased femoral anteversion

When Prone on the Couch

- Thigh foot angle for tibial torsion
- Lateral curvature of the foot and the heel isector line for metatarsus adductus
  Normally the line bisects the 2nd webspace
- Range of hip internal and external rotation for increased femoral anteversion

When Supine on the Couch

- Assess the hips, knees, ankles and feet
- Reassess the coronal alignment without the effects of gravity

TAKE HOME message

BOX 02

REFER TO A SPECIALIST IN THE FOLLOWING CASES:

- Genu Valgum < 2 years of age and Genu Varum > 2 years of age
- Painful Genu Varum in adolescents
- Asymmetrical, unilateral or progressively worsening deformities
- Knee, hip or thigh pain in school children due to risk of Perthes' disease
- Knee, hip or thigh pain in adolescent children, especially if obese, due to risk of Slipped Capital Femoral Epiphysis
- Rigid Metatarsus Adductus
- Internal tibial torsion over 6-8 years of age or a thigh-foot angle >15 degrees
- Rigid flat foot

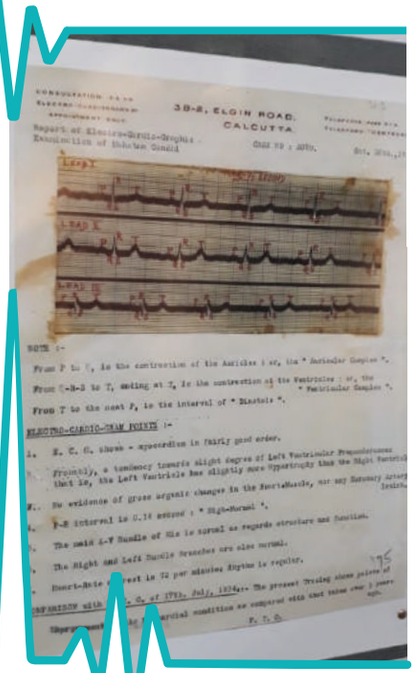
REFERENCES

1. Brooks PM. The burden of musculoskeletal disease—a global perspective | SpringerLink. Clinical Rheumatology 2006;25(6):778-781.
2. Yeo A, James K, Ramachandran M. Normal lower limb variants in children. BMJ 2015;7(350):h:3394.
3. Staheli LT, Corbett M, Wyss C et al. Lower-extremity rotational problems in children. Normal values to guide management. J Bone Joint Surg Am 1985;67(1):39-47.
4. Sabharwal S, Zhao C, Edgar M. Lower limb alignment in children: reference values based on a full-length standing radiograph. J Pediatr Orthop 2008;28(7):740-6.
5. Heath CH, Staheli, LT. Normal limits of knee angle in white children--genu varum and genu valgum. J Pediatr Orthop 1993;13(2):259-62.
6. Toddler's feet : Developmental problems (Foot Factoids). http://foottalk.blogspot.com/2006/01/toddlers-feet-developmental-problems.html.
7. Leg and Knee Knots. http://alborzotc.com/.
8. Staheli LT. Rotational problems in children. Instr Course Lect 1994;43:199-209.
9. Shirley E. Internal Tibial Torsion. https://www.orthobullets.com/pediatrics/4060/internal-tibial-torsion.
10. Souder C. Metatarsus Adductus. https://www.orthobullets.com/pediatrics/4061/metatarsus-adductus.
11. Souder C. Femoral Anteversion. https://www.orthobullets.com/pediatrics/4059/femoral-anteversion?expandLeftMenu=true.
12. The "W" sitting position in young children. Kid's Island Nursery: February 2016.
13. Podopediatrics - Metatarsus Adductus Flashcards. https://www.memorangapp.com/flashcards/114351/Podopediatrics+-+Metatarsus+Adductus/.
14. Orthokids Metatarsus Adductus. http://www.orthokids.com.au/conditions-treated/foot-ankle/metatarsus-adductus.
15. Stahl D. External Tibial Torsion. https://www.orthobullets.com/pediatrics/4121/external-tibial-torsion.
16. Siegall E. Flexible Pes Planovalgus (Flexible Flatfoot). https://www.orthobullets.com/pediatrics/4069/flexible-pes-planovalgus-flexible-flatfoot.
17. Carr JB, Yang S, Lather LA. Pediatric Pes Planus: A State-of-the-Art Review. Pediatrics 2016;137(3):e20151230.
18. Torsion of the lower limb in children. http://bestpractice.bmj.com/topics/en-us/748/images-and-videos.

LISTEN TO
MAHATMA GANDHI'S 'HEARTBEATS' AT THE NATIONAL GANDHI MUSEUM

In 2019 different programmes will be showcased at the National Gandhi Museum in New Delhi to commemorate the 150th birth anniversary of the Gandhi, born in 1869. Visitors will get a chance to listen to the recreated heart beats of Mahatma Gandhi after collecting his ECG (electrocardiography) readings.

During his youth, Gandhi gave up on his dream to become a doctor as his father and elder brother were opposed to dissection of dead bodies. However, Gandhi managed to get training in basic nursing and he also worked as compounder at the Saint Aidan's Mission Hospital run by Dr Lancelot Parker Booth in South Africa.



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Knowing that the pastor enjoyed his drink, a hotel owner offered him a case of cherry brandy for Christmas in exchange for a free ad in the church newsletter.

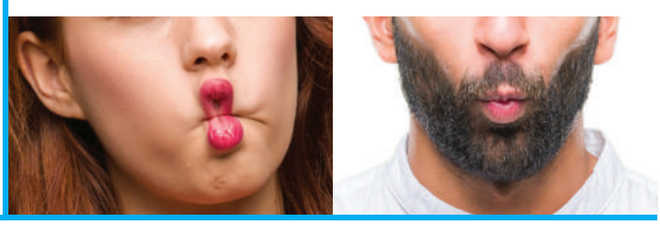
The pastor agreed and as promised, ran this in the next issue:

"THE PASTOR WOULD LIKE TO THANK PATRICK SMITH FOR HIS KIND GIFT OF A CRATE OF FRUIT AND FOR THE SPIRIT IN WHICH IT WAS GIVEN."

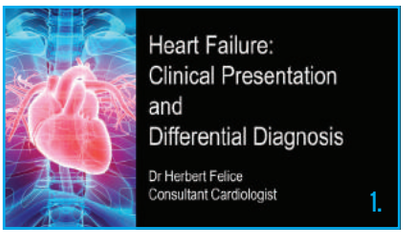
ADVERSE EFFECTS

According to a new report published in the US, adverse effects occurred in **over 2,000 women** who used Botox across the world last year…

NONE OF WHOM SEEMED SURPRISED!



MASTERCLASS *in Heart Failure*



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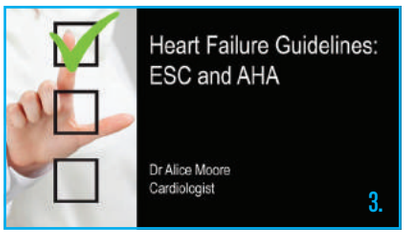

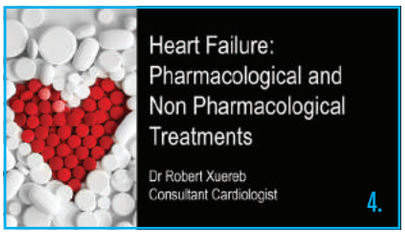

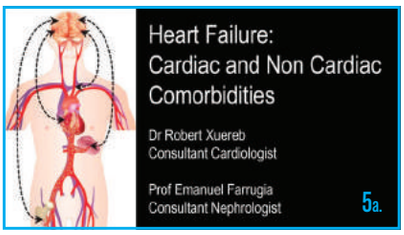

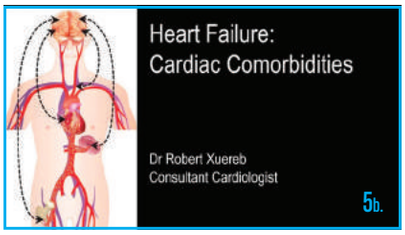

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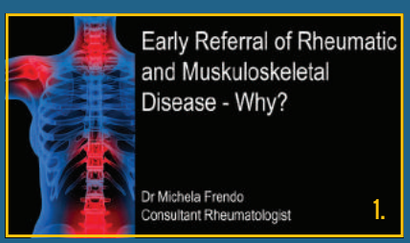

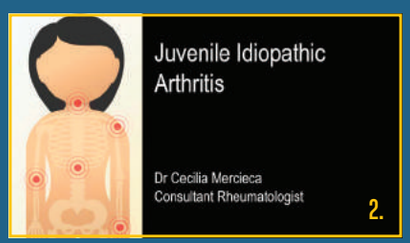

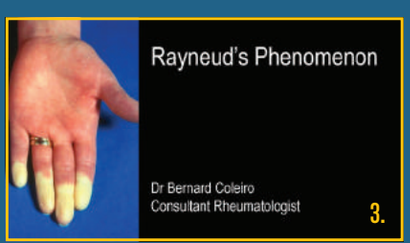

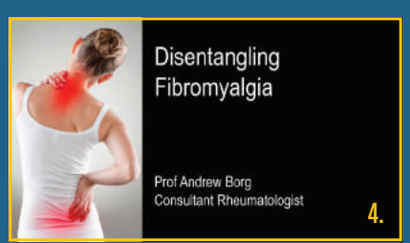

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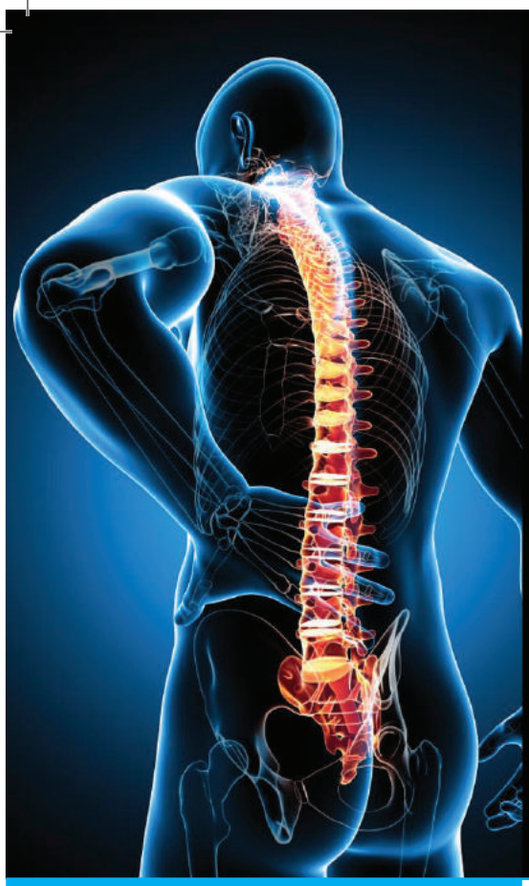

Management of Acute Pain

Dr Carmel Abela
Consultant Anaesthetist

DR CARMEL ABELA

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

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

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

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

LEARNING OBJECTIVES

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

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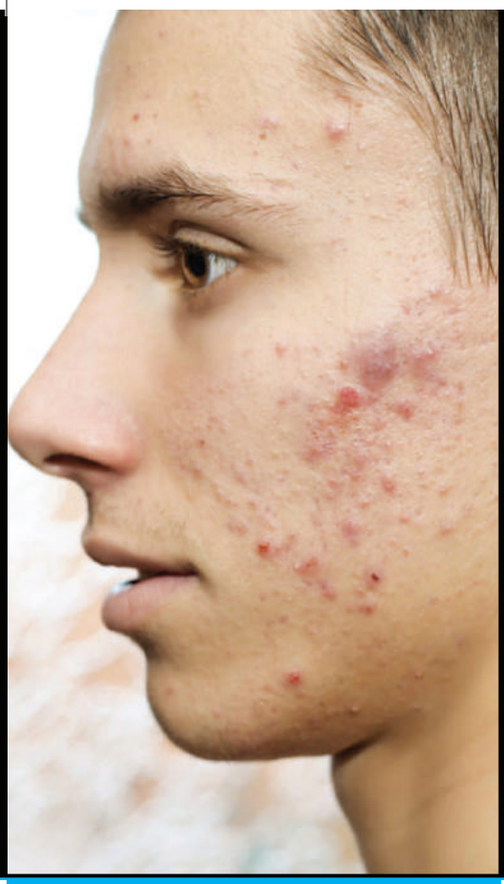

Management of Acne

Dr Godfrey Baldacchino
Dermatologist

DR GODFREY BALDACCHINO

Dr Godfrey Baldacchino is a resident Specialist at the Dermatology Department in Boffa Hospital. He graduated as a Medical Doctor from the University of Malta in 1993 and has worked in dermatology since 1995 as a Medical Officer, Senior Health Officer and Higher Specialist Trainee.

Dr Baldacchino obtained MRCP in 2008 followed by MRCP (Dermatology) in 2011. In 2016 Dr Baldacchino spent 6 months training in Brighton and Sussex University Hospital in the UK and has been a Resident Specialist since 2017.

In this e-learning session Dr Godfrey Baldacchino describes the presentation and possible causes of acne. Dr Baldacchino also discusses the various treatment options available for the management of acne, how the decision on which treatment is chosen is made and offers advice that healthcare professionals should give to patients suffering from acne or when receiving acne treatment.

LEARNING OBJECTIVES

- To improve understanding of acne by healthcare professionals
- To guide treatment optimization and the avoidance of management pitfalls

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Actifed* oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders [1-7]

Actifed* DM COUGH LINCTUS

- relieves dry cough and nasal congestion [3,6]

Actifed* SYRUP AND TABLETS

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Actifed* EXPECTORANT

- clears chesty cough and nasal congestion [4,7]

DOSAGE		
LIQUIDS	children aged 2 to 5 years [2-4]	2.5ml every 4-6hrs as required
	children aged 6 to 11 years [2-4]	5ml every 4-6hrs as required
	adults (including the elderly) and children aged 12 years and over [5-7]	10ml every 4-6hrs as required
TABLETS	adults (including the elderly) and children aged 12 years and over [1]	1 tablet every 4-6hrs as required

OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** ACTIFED. **ACTIVE INGREDIENT:** *Actifed DM Cough Linctus:* Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Syrup:* Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Expectorant:* Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Guaiphenesin 100mg; *Actifed Tablets:* Each tablet contains Pseudoephedrine Hydrochloride 60mg; Triprolidine Hydrochloride 2.5mg. **PHARMACEUTICAL FORM:** Oral Solution and Tablets. **INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of: Actifed DM Linctus: a nasal decongestant, an anti-histamine and an antitussive; Actifed Syrup: a nasal decongestant, and an anti-histamine; Actifed Expectorant: a nasal decongestant, an anti-histamine and an expectorant; Actifed Tablets: a nasal decongestant, and an anti-histamine. **DOSAGE:** *please refer to full SPC. Actifed DM Cough Linctus, Actifed Syrup and Actifed Expectorant* are authorised for use without the need of a medical prescription in Adults and Children over 12 years. In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor. **CONTRAINDICATIONS:** Previous intolerance to any of the active substances; use of MAOI's in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure. **PRECAUTIONS:** May cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment. **INTERACTIONS:** Sympathomimetics; MAOI's. **ADVERSE EVENTS:** Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement. **PREGNANCY AND LACTATION:** Administration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child. **PRESENTATION:** *DM Cough Linctus, Expectorant, Syrup:* Amber glass bottle x 100ml; Tablets: Pack x 24 tablets. Marketing Authorisation Holder: Glaxo Wellcome UK Limited, **Marketing Authorisation Number:** MA 167/00101-7 **Legal category:** POM – Actifed Tablets, POM – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years, OTC – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years. **For further information and full prescribing information contact GlaxoSmithKline (Malta)** Ltd: Tel. 21238131. **Date of preparation:** January 2015

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

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

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

References: 1. Actifed Tablets SPC (Apr 2014); 2. Actifed Syrup SPC (Mar 2015); 3. Actifed DM Cough Linctus SPC (Jan 2015); 4. Actifed Expectorant SPC (Jan 2015); 5. Actifed Syrup SPC OTC (Mar 2015); 6. Actifed DM Cough Linctus SPC OTC (Jan 2015); 7. Actifed Expectorant SPC OTC (Jan 2015)

Job No: MLT_GIB/PDH/0005/16 Date of preparation: February 2016

EDITOR'S PICK FOR BOOKWORMS

LIVING WITH TERMINAL PANCREATIC ILLNESS

IN "*KIMI NO SUIZOU WO TABETAI*"

DR MICHELLE MUSCAT

NOVEL

Writer: Yoru Sumino
Original Publisher: Futabasha
Publication Date: June 2015

LIVE-ACTION MOVIE

Producer: Akira Kobe
Director: Sho Tsukikawa
Original Release Date: July 2017

ANIMATED MOVIE

Producer: Keiji Mita
Writer: Shinichirou Ushijima
Original Release Date: Sept 2018

The protagonist Sakura Yamauchi has a terminal pancreatic condition yet retains a positive outlook towards life with a bubbly personality. Sakura keeps a daily diary called 'Living with Dying' about her coexistence with the disease. The male, initially unnamed protagonist, Haruki Shiga, on the other hand is her polar opposite, he is reserved and has little interest in others. Sakura has come to terms with her incurable disease and shares this secret only with her family and only this one classmate, Haruki, who accidently picks up her diary 'Living with Dying' when they happened to meet in hospital. Later on she joins the library team with Haruki which is from where they start getting along with one another, albeit with very different modes of expression. Sakura is as cheerful as Haruki is oblivious. Their words and gestures vary greatly, but in the end they established an important bond that is the focal point of the story.

Through their excursions and everyday life there are small grim reminders of the truth of Sakura's condition. When they go for a trip he catches a glimpse in Sakura's bag of a sheer multitude of medications, she is also suddenly hospitalized later in the story. Her cruel reality surfaces from time to time, when the mood changes as she asks Haruki what he would do if she were to tell him that she really does not want to die, a question to which at the time he had no answer. Sakura shows no signs of denial of her condition although at one point Haruki asks her if she is really going to die.

Although it is established from the very beginning that Sakura is indeed going to die, it is made clear throughout the tale that we all are. The poignant conclusion lies in how the story unfolds to her actual cause of death and the messages she leaves behind to those she cherished in life. The climax of the story is reached when at the end they read the words '*Kimi no Suizou wo Tabetai*' which literally means 'I Want to Eat Your Pancreas'.

This metaphorical implication stems from an old superstition told by Sakura to Haruki earlier in the story which narrates that if a person has a diseased organ then one should eat that organ. At that point Haruki had changed, cradled a desire for her to get better, take a leaf out of her book and see her soul live on. The plot twist is that paradoxically her pancreatic disease was not what indeed kills her in the end.

The story is both a coming of age tale for Haruki who learns to see the world from different perspectives to his own and a tear jerking story of a girl living fully cognizant that her life expectancy is significantly reduced.

This tragic romantic drama obtained various awards and is acclaimed by many. It also spanned various adaptations having the original novel, a manga, live action movie and animated movie to its name. It recognizes that life is fleeting and one has to cherish and make the most of the small moments since sooner than you think and for reasons you may not have expected, it may be too late.

Sakura's cheerful nature and enmeshed coping mechanisms, priorities, outlook, suffering and hope provide the reader or viewer with fresh perspectives.

Although this movie is not tackled from a purely medical perspective, a lot has been written in the medical field on hope and alleviation of suffering in terminal illness.[1-6] Sakura's free-spirited character shows that in the end, illness can sometimes be, in some ways, what you make of it.

REFERENCES

1. Schuyler D. How to live with a terminal illness. The primary care companion for CNS disorders. Prim Care Companion CNS Disord 2014;16(1).
2. Drews MF. The evolution of hope in patients with terminal illness. Nursing 2017;47(1):13-4.
3. Rousseau P. The Cost of Hope in Terminal Illness. J S C Med Assoc 2015;111(4):134-6.
4. Villacieros M, Bermejo JC, Hassoun H. Validation of the Scale of Hope in Terminal Illness for relatives brief version (SHTI-b). Validity and reliability analysis. An Sist Sanit Navar 2017;40(3):391-400.
5. Bell C, Nielsen MK, Neergaard MA, et al. Remaining Lifetime After Recognition of Terminal Illness Depends on Diagnosis: A Nationwide Population-Based Cohort Study. Journal of pain and symptom management. J Pain Symptom Manage 2017;53(1) :116-23.
6. Bates AT, Kearney JA. Understanding death with limited experience in life: dying children's and adolescents' understanding of their own terminal illness and death. Curr Opin Support Palliat Care 2015;9(1):40-5.

WITH ULTIBRO® BREEZHALER® EXACERBATION PREVENTION IS IN YOUR HANDS[1]

ULTIBRO® BREEZHALER® is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)[2]

FLAME STUDY RESULTS[1]

"...[ULTIBRO® BREEZHALER®] showed not only non-inferiority, but also... consistent superiority to [Seretide®* Accuhaler®] for all outcomes related to exacerbations, lung function† and health status**."[1‡§]

The FLAME study is a 52-week head-to-head trial comparing ULTIBRO® BREEZHALER® with Seretide® Accuhaler® (LABA/ICS) in 3362 exacerbating[2] COPD patients.[1] The primary endpoint was to demonstrate that ULTIBRO® BREEZHALER® was at least non-inferior to Seretide® Accuhaler® in reduction of all exacerbations. Superiority over Seretide® Accuhaler® was a pre-defined secondary endpoint.[1]

*Fluticasone/salmeterol 500/50 mg BID. †Lung function trough FEV$_1$ (P<0.001).[1] **Health-related quality of life, SGRQ-C (P<0.01).[1] ‡Patients had at least one moderate or severe exacerbation in the previous 12 months.[1] §Annual rate reduction of all exacerbations (mild/moderate/severe): ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 11% (RR 0.89, P=0.003). Annual rate reduction of moderate or severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 17% (RR 0.83, P<0.001). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 13% (RR 0.87, P=0.23).[1] Seretide® Accuhaler® is a registered trademark by GSK.

BID, twice daily; COPD, chronic obstructive pulmonary disease.

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Ultibro Breezhaler inhalation powder, hard capsules

▼ **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. Refer to section 4.8 of the SmPC for how to report adverse reactions.**

PRESENTATION: 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. Refer to section 4.8 of the SmPC for how to report adverse reactions. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available Method of administration For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. The inhaler provided with each new prescription should be used.Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long-acting beta-adrenergic agonists or long-acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. ***Asthma:*** Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long-acting beta2-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma. Not for acute use. Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium. Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. ***Paradoxical bronchospasm:*** Administration of Ultibro Breezhaler may result in paradoxical bronchospasm which can be life-threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. *Narrow-angle glaucoma:* No data are available in patients with narrow-angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop.*Urinary retention:* No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. ***Excipients:*** This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two active substances. Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Therefore, Ultibro Breezhaler should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. The co-administration of Ultibro Breezhaler with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetics(alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or nonpotassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P-gp), raises the systemic exposure of indacaterol up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual active substances. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, dyspepsia, dental caries, bladder obstruction and urinary retention, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest pain, hypersensitivity, diabetes mellitus and hyperglycaemia. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, paradoxical bronchospasm, dysphonia, epistaxis, gastroenteritis, tachycardia, palpitations, insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:**POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003, EU/1/13/862/007 **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: +35621222872

2018-MT-ULT-23-JUL-2018b

References

1. Wedzicha JA, *et al.* Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34.
2. Novartis Europharm Ltd. Ultibro Breezhaler Summary of product characteristics.

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HOW BIG IS THE DIABETES TYPE 2 PROBLEM?

PROF. ALBERT CILIA-VINCENTI

The US Centers for Disease Control and Prevention recently claimed that more than 1 in 3 American adults have blood sugar levels that are too high.[1] They included prediabetics in their statement.

In 2016, the University of California, Los Angeles (UCLA), reported that 55% of Californian adults are either prediabetic or have undiagnosed type 2 diabetes (Figure 1).[2] Prediabetes is not a nit-picking philosophical concept. Diabetic pathologies develop during prediabetes[3] and, by the time type 2 diabetes manifests itself, patients may already have kidney impairment,[4,5] vision loss,[6-8] neuropathy,[9] atherosclerosis[10-12] and cancer.[13-15] Excessive food and drink intake, particularly the high glycaemic ones, spike blood sugar levels which also accelerate ageing by shortening telomeres.[16,17]

The goalposts for safe blood glucose levels have been changing. Levels considered dangerous now were thought to be safe decades ago. Current recommendation is for blood sugar to be kept at the low end of the normal reference range.[18-21] However, a significant section of the medical community may have failed to wake up to the life-shortening impact of prediabetes.

One diagnostic problem is that prediabetes and early stage diabetes may be missed by the standard fasting blood glucose in the presence of hyperinsulinaemia. As long as there is reasonable insulin sensitivity and hyperinsulinaemia, a fasting blood glucose may appear to be in a safe range, which is conventionally considered to be under 5.6 mmol/L, although some claim the safe upper limit ought to be 4.7mmol/L.

Hyperinsulinaemia contributes to disease states (e.g. hypertension, blood hypercoagulability and increased cancer risk) even before fasting blood glucose rises to what conventional medicine regards as prediabetic levels, namely, 5.6 – 6.9 mmol/L. For the above reasons, and in this scenario, the fasting blood glucose test should perhaps now be considered dangerously obsolete.

The haemoglobin A1c (HbA1c) blood test provides a better picture of glycaemic control than fasting blood glucose,[22] but is probably underutilised in identifying prediabetes. The safe upper limit for HbA1c is considered 5.5%, but lower ranges have been shown to be healthier.[23] HbA1c between 5.6% and 6.4% is diagnostic for prediabetes.[24]

EXCESSIVE FOOD AND DRINK INTAKE, PARTICULARLY THE HIGH GLYCAEMIC ONES, SPIKE BLOOD SUGAR LEVELS WHICH ALSO ACCELERATE AGEING BY SHORTENING TELOMERES

Metformin ought to be prescribed when the HbA1c is between 5.6% and 6.4% for prevention of type 2 diabetes,[25] together with advice on calorie restriction and, in particular, the high glycaemic ones. Metformin enhances insulin sensitivity and functions via several mechanisms to improve glycaemic control.[26-30] It has proven ability to delay or prevent type 2 diabetes.[31-33] Yet recent US surveys reveal it is prescribed to only 3.7% to 8.1% of prediabetics.[33-35]

Perhaps the term prediabetes is a misnomer because even modestly elevated glucose levels inflict microvascular damage resembling the long-term complications of type 2 diabetes.[36,37] Excess glucose is converted to triglycerides that are stored as fat (subcutaneous and abdominal) and which may result in fatty liver disease (may progress to cirrhosis and hepatocellular carcinoma). Excess glucose is inflammatory to many tissues, including arteries (atherosclerosis).[38-40] High "normal" blood sugar levels are increasingly recognised as posing an increased risk of degenerative disorders.[4-15,20,41-49]

Fasting blood glucose values in the upper "normal" range (above 4.7mmol/L) appear to be an important independent predictor of cardiovascular death in nondiabetic, apparently healthy, middle-aged men.[18] After-meal glucose levels are an even stronger predictor of disease risk.[50-52]

About 70% of prediabetics will develop type 2 diabetes in their lifetime.[53,54] It is misleading to think that prediabetes relates to a period where no diabetic damage is caused. Coronary heart disease risk is similar between prediabetics and type 2 diabetics.[47]

> EARLY DETECTION OF PREDIABETES MEANS A **GREATER LIKELIHOOD OF REVERSING IT** BEFORE IT PROGRESSES TO TYPE 2 DIABETES

Early detection of prediabetes means a greater likelihood of reversing it before it progresses to type 2 diabetes. Glucose-lowering approaches should be initiated when HbA1c exceeds 5.5% and not delayed till it reaches 6.5%.

In the area of laboratory predictive testing for cardiovascular risk, we have probably underestimated the importance of the prediabetic state (as defined by HbA1c levels above). For around 60 years we accepted the hype around cholesterol, dietary saturated fats, heart attacks and now, statins. In spite of the huge global expense on cholesterol testing and statins, atherosclerotic-related morbidity and mortality remains number one in industrialised countries.

The clinical significance of the various blood lipoproteins is still confused. We now know that there are at least two main types of LDL cholesterol, a small, dense atherogenic particle and a larger lighter one thought to be harmless. The different LDL particles are too expensive to be measured routinely. We therefore don't know whether a high LDL is due to an elevated "harmless" or "bad" LDL sub-fraction. Adding "non-HDL cholesterol" to routine testing is even more confusing. The combination of a raised fasting triglycerides level and a low HDL level is a surrogate marker for raised "bad" LDL (see previous features in the *The Synapse Journal* on the Cholesterol Controversy). What raises fasting triglycerides levels and lowers HDL are high glycaemic carbohydrates and alcohol, rather than saturated fats.

> MALTA HAS ALMOST **THREE TIMES THE HEART DISEASE MORTALITY** OF FRANCE ... **OBESITY AND BLOOD GLUCOSE LEVELS** MIGHT BE THE MAIN PROBLEM, RATHER THAN CHOLESTEROL

Glucose may be a more important damaging inflammatory agent than saturated fats. The French have the lowest heart disease mortality in Europe (and second lowest worldwide). Malta has almost three times the heart disease mortality of France. The reason is not Maltese consumption of dairy produce and meats being three times that in France. Obesity and blood glucose levels might be the main problem, rather than cholesterol. Perhaps about half our adult population is prediabetic or already diabetic, like California. Who knows?

The term "prediabetes" may render a false sense of normality. Perhaps the progression stages of type 2 diabetes could more realistically be renamed, "early diabetes", "established diabetes" and "end-stage (insulin-dependent) diabetes". A false sense of normality is also fostered by laboratories in Malta stating a "normal range" for HbA1c of up to 6.5%, when it should be up to 5.5%.

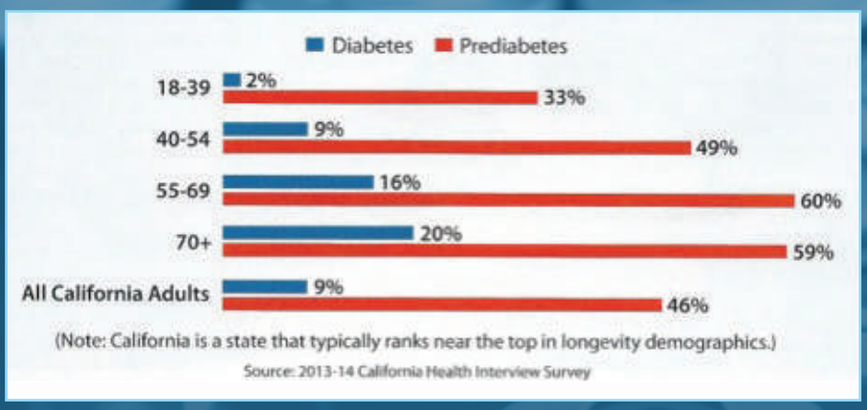

Figure 1: Diabetes cases by age group. A UCLA study found that 55% of adults in California have either diabetes or prediabetes.[2]

REFERENCES

1. https//www.cdc.gov/features/diabetesfactsheet/.
2. Babey SH, Wolstein J, Diamant AL et al. Prediabetes in California: Nearly Half of California Adults on Path to Diabetes. Policy Brief UCLA Cent Health Policy Res. 2016 (Pb2016-1): 1-8.
3. Tabak AG, Herder C, Rathmann W et al. Prediabetes: a high-risk state for diabetes development. Lancet 2012; 379 (9833): 2279-90.
4. Plantinga LC, Crews DC, Coresh J et al. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol. 2010; 5 (4): 673-82.
5. Hoehner CM, Greenlund KJ, Rith-Najarian S et al. Association of the insulin resistance syndrome and microalbuminuria among nondiabetic native Americans. The Inter-Tribal Heart Project. J Am Soc Nephrol. 2002; 13(6): 1626-34.
6. Gabir MM, Hanson RL, Dabelea D et al. Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organisation criteria for diagnosis of diabetes. Diabetes Care 2000; 23 (8): 1113-8.
7. Algvere P, Elendic S, Luft R et al. Retinal microangiography and pigment epithelial lesions in subjects with normal, borderline, and decreased oral glucose tolerance. Br J Ophthalmol. 1985; 69 (6): 416-9.
8. Tapp RJ, Tikellis G, Wong TY et al. Longitudinal association of glucose metabolism with retinopathy: results from the Australian Diabetes Obesity and Lifestyle (AusDiab) study. Diabetes Care 2008; 31 (7): 1349-54.
9. Sumner CJ, Sheth S, Griffin JW et al. The spectrum of neuropathy in diabetes and impaired glucose tolerance. Neurology 2003; 60 (1): 108-11.
10. Redgrave JN, Lovett JK, Syed AB et al. Histological features of symptomatic carotid plaques in patients with impaired glucose tolerance and diabetes (oxford plaque study): Cerbrovasc Dis. 2008; 26(1): 79-86.
11. Kurihara O, Takano M, Yamamoto M et al. Impact of prediabetic status on coronary artherscleros: a multivessel angioscopic study. Diabetes Care 2013; 36(3): 729-33.
12. Kramer D, Raji A, Plutzky J. Prediabetes mellitus and its links to atherosclerosis. Curr Diab Rep. 2003; 3 (1): 11-8.
13. Huang Y, Cai X, Qiu M. et al. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia. 2014; 57 (11): 2261-9.
14. Salinas-Martinez AM, Flores-Cortes LI, Cardona-Chavarria JM et al. Prediabetes, diabetes and risk of breast cancer: a case-control study. Arch Med Res. 2014; 45 (5): 432-8.
15. Onitilo AA, Stankowski RV, Berg RL et al. Breast cancer incidence before and after diagnosis of type 2 diabetes mellitus in women: increased risk in the prediabetes phase. Eur J Cancer Prev. 2014; 23 (2): 76-83.
16. Leung CW, Laraia BA, Needham BL et al. Soda and cell aging: associations between sugar-sweetened beverage consumption and leukocyte telomere length in healthy adults from the national health and Nutrition Examination Surveys. Am J Public Health 2014; 104 (12): 2425-31.
17. Adaikalakoteswari A, Balasubrmanyam M, Ravikumar R et al. Association of telomere shortening with impaired glucose tolerance and diabetic macroangiopathy. Atherosclerosis 2007; 195 (1): 83-9.
18. Bjornholt JV, Erikssen G, aaser E et al. Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. Diabetes Care 1999; 22 (1): 45-9.
19. Selvin E, Coresh J, Golden SH et al. Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med 2005; 165 (16): 1910-6.
20. Levitan EB, Song Y, Ford ES et al. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Atch Intern Med 2004; 164 (19): 2147-55.
21. Held C, Gerstein HC, Yusul S et al. Glucose levels predict hospilisation for congestive heart failure in patients at high cardiovascular risk. Circulation 2007; 115 (11): 1371-5.
22. Selvin E, Steffes MW, Zhu H et al. Glycated haemoglobin, diabetes and cardiovascular risk in nondiabetic adults. N Engl J Med 2010; 362 (9): 800-11.
23. Matsushita K, Blecker S, Pazin-Filho A et al. The association of haemoglobin A1c with incident heart failure among people without diabetes: the atherosclerosis risk in communities study. Diabetes 2010; 59 (8): 2020-6.
24. Prediabetes, *Web*MD, 2018.
25. Standards of Medical Care in Diabetes – 2014. Daibetes Care 2014; 37 (supplement 1): S14-S80.
26. Giannarelli R, Aragona M, Coppelli A et al. Reducing insulin resistance with metformin: the evidence today. Diabetes Metab 2003; 29 (4 Pt 2): 6s28-35.
27. Malin SK, Gerber R, Chipkin SR et al. Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. Diabetes Care 2012; 35 (1): 131-6.
28. Hundal RS, Krssak M, Dufour S et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000; 49 (12): 2063-9.
29. Caton PW, Nayuni NK, KiewishJ et al. Metformin suppresses hepatic gluconeogenesis through induction of SIRT1 and GCNS. J Endocrinol 2010; 205 (1): 97-106.
30. Hostalek U, Gwilt M, Hildermann S. Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. Drugs 2015; 75 (10): 1071-94.
31. Lily M, Godwin M. Treating prediabetes with metformin: systematic review and meta-analysis. Can Fam Physician. 2009; 55 (4): 363-9.
32. Salpeter SR, Buckley NS, Kahn JA et al. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med 2008; 12 (2): 149-57.e2.
33. Moin T, Li J, Duru OK et al. Metformin prescription for insured adults with prediabetes from 2010 to 2012: a retrospective cohort study. Ann Intern Med 2015; 162 (8): 542-8.
34. Sterling DL, Onor I, Sarpong D et al. Prescribing Patterns of Metformin in High-risk Patients with Prediabetes. J La Stae Med Soc 2015; 167 (6): 257-62.
35. Goldberg T, Kroehl ME, Suddarth KH et al. Variations in Metformin Prescribing for Type 2 Diabetes. J Am Board Fam Med 2015; 28 (6): 777-84.
36. Milman S, Crandall JP. Mechanisms of vascular complications in prediabetes. Med Clin North Am 2011; 95 (2): 309-25, vii.
37. Sprague RS, Ellsworth ML. Vascular disease in prediabetes: new insights derived from systems biology. Mo Med 2010; 107 (4): 265-9.
38. Ebenbichler CF, Kirchmair R, Egger C et al. Postprandial state and atherosclerosis. Curr Opin Lipidol 1995; 6 (5): 286-90.
39. Jacobson TA, Miller M, Schaefer EJ. Hypertriglyceridemia and cardiovascular risk reduction. Clin Ther 2007; 29 (5): 763-77.
40. Welin I, Erikson H, Larsson B et al. Triglycerides, a major coronary risk factor in elderly men. A study of men born in 1913. Eur Heart J 1991; 121 (6): 700-4.
41. Stattin P, Bjor O, Ferrari P et al. Prospective study of hyperglycemia and cancer risk. Diabetes Care 2007; 30 (3): 561-7.
42. Muti P, Quattrin T, Grant BJ et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002; 11 (11): 1361-8.
43. Cust AE, Kaaks R, Friedenreich C et al. Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 207; 14 (3): 755-67.
44. Schoen RE, Tangen CM, Kuller LH et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999; 91 (13): 1147-54.
45. Couthinho M, Gerstein HC, Wang Y et al. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 indiciduals followed for 12.4 years. Diabetes Care 1999; 22 (2): 233-40.
46. Lambin N, Cuvelier E, Gonon X et al. Abstract 2372: Hemoglobin A1c Levls are Associated with Severity and Prognosis of Systolic Chronic Heart Failure in Non Diabetic Patients. Circulation 2006; 114 (Suppl 18): II_486-II_7.
47. Li Q, Chen AH, Song XD et al. Analysis of glucose levels and the risk for coronary heart disease in elderly patients in Guangzhou Haizhu district. Nan Fung Yi Ke Da Xue Xue Bao 2010; 30 (6): 1275-8.
48. Pereg D, Elis A, Neuman Y et al. Cardiovascular risk in patients with fasting blood glucose levels within normal range Am J Cardiol 2010; 106 (11): 1602-5.
49. Bitra YR, Rapaka D Akula A. Prediabetes and Alzheimer's Disease. Indian J Pharm Sci 2015; 77 (5): 511-4.
50. Moebus S, Gores L, Losch Cet al. Impact of time since last calories intake on blood glucose levels. Eur J Epidemiol 2011; 26 (9): 719-28.
51. Onat A, Can G, CicekG et al. Fasting, on-fasting glucose and HDL dysfunction in risk of pre-diabetes, diabetes, and coronary disease in non-diabetic adults. Acta Diabetol 2013; 50 (4): 519-28.
52. Sacks DB. A1c versus glucose testing: a comparison. Diabetes Care 2011; 34 (2): 518-23.
53. Nathan DM, Davidson MB, DeFronzo RA et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Daibetes Care 2007; 30 (3): 753-9.
54. Eikenberg JD, Davy BM. Prediabetes: a prevelant and treatable, but often unrecognized, clinical condition. J Acad Nutr Diet 2013: 113 (2): 213-8.

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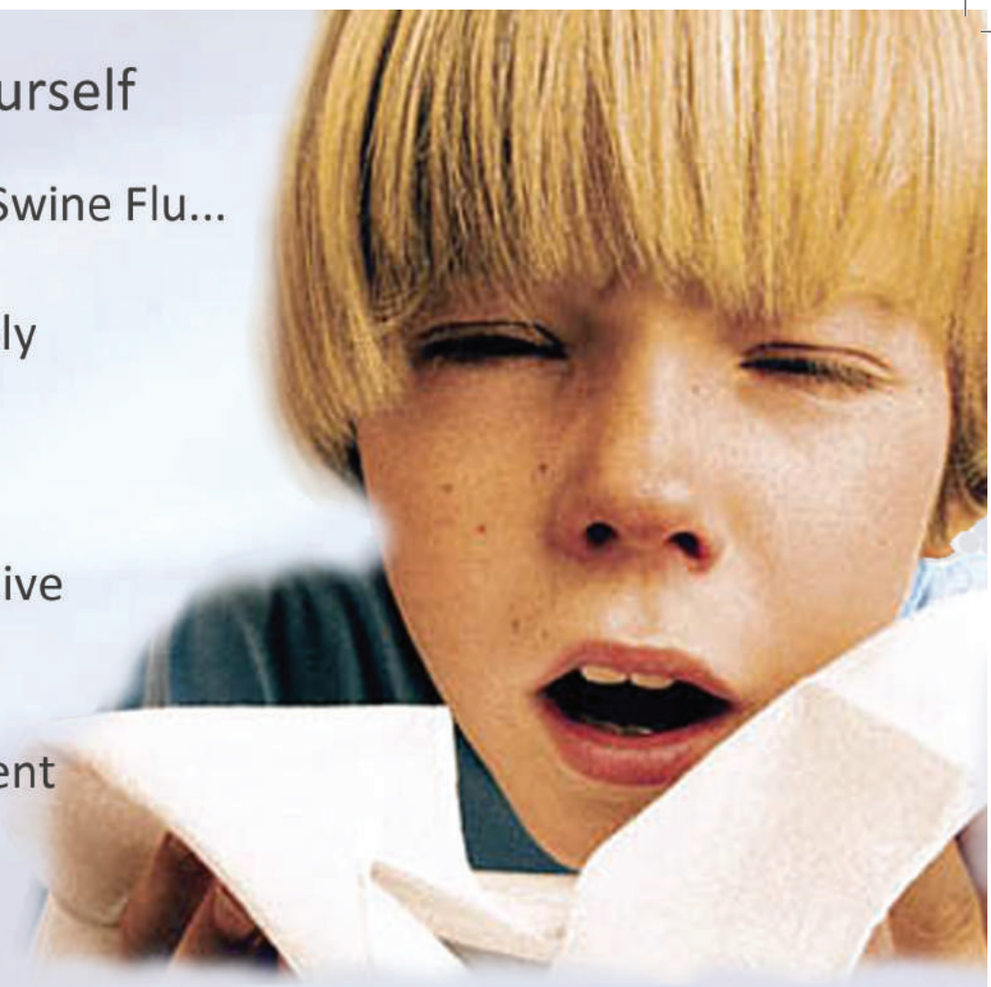

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FOCUS ON RARE DISEASES

The National Society for Phenylketonuria

Suzanne Ford

Dr Michelle Muscat interviews SUZANNE FORD, the Society Dietitian at The National Society for Phenylketonuria [NSPKU], in the UK.

Phenylketonuria (PKU) is an autosomal recessive condition. The amino acid phenylalanine is usually metabolized to tyrosine by the enzyme phenylalanine hydroxylase [PAH] also requiring a cofactor named tetrahydrobiopterin. In phenylketonuria, phenylalanine is not metabolized to tyrosine. Phenylalanine is an essential aromatic amino acid. High phenylalanine levels in patients with PKU can result in neurotoxicity. The mainstay of treatment is protein restriction in the diet.

HOW DID YOU BECOME INVOLVED WITH THE NSPKU?

I work as a dietitian in the NHS, supporting adults with PKU and have done this since 2009; I knew the NSPKU provided other services and support. I had already spoken at the society's conference and stood in for the society dietitian at another event, so when the post became vacant I was pleased to have this great opportunity.

CAN YOU TELL ME MORE ABOUT THE ORIGINS OF THE SOCIETY?

The NSPKU was founded in 1973 by Brian and Sylvia Smith who put an announcement out on national radio to appeal for interest in meeting other families affected by the disorder – they also wrote to dietitians and other families that they had addresses for. There was a preliminary meeting in a community centre in November in 1973 and then the first General Meeting in April 1974 in Blackpool. In 1975 a Medical Advisory Panel had been added and in 1983 the society employed its first dietitian, and had an internet presence by 1996.

DO YOU BELIEVE THE AWARENESS OF PHENYLKETONURIA HAS CHANGED ALONG THE YEARS?

The families who live with PKU have always been instrumental in calmly explaining what PKU is to others who need to know. In the UK, recently families and people living with PKU have surpassed themselves by writing to MPs and alerting them to the life challenges this disorder brings to those affected. These MPs have held debates in parliament – filmed on parliamentlive.tv; also, MPs tried the "PKU Diet-for-a-Day" challenge, which they publicised on social media. The diet challenge, restricting the diet to ≤10g of protein in one whole day, happened on International PKU Awareness Day - on 28 June 2018 - and was the subject MPs were most tweeting about on that day.

WHAT WAS YOUR MOST REWARDING ACHIEVEMENT?

I was pleased to appear on the BBC news channel to explain PKU and the way that the pharmacological treatment sapropterin (also called BH_4, tetrahydrobiopterin, trade name Kuvan®) could change lives for responders who have PKU. Tetrahydrobiopterin is an enzyme chaperone for the defective enzyme in PKU – PAH - and thus it can remove the significant burden of dietary treatment in responders. The BBC news item was following the report of a successful high court case for a small boy with PKU who is autistic and is now allowed to have BH_4 funded by NHS England.

A recent team effort that NSPKU volunteers and I undertook has been the analysis of the biggest PKU experiences survey done so far in the world; the survey was completed online by people living with PKU in the UK. We have now published the survey results in two papers in *Molecular Genetics and Metabolism Reports*. The widespread nature of difficulties was still a surprise to me and the experiences of women was shocking. Women felt frightened by messages about the dangers of unplanned pregnancies (phenylalanine is teratogenic); the burden of pregnancy is high, and the difficulty of self-care and PKU treatment management in combination with motherhood is a significant challenge.

CAN YOU DISCUSS THE EVENTS WHICH YOU ORGANISE AND HOW DO YOU SECURE FUNDING? HOW IS THE ASSOCIATION INVOLVED IN RESEARCH?

The NSPKU has an annual weekend conference for families, day-long educational events, health care professional meetings and training sessions. We rely on our community for fundraising: people running ultra-marathons, holding

book sales and fundraising "extravaganzas" as well as regular donations from funerals, bake sales, prize raffles, collection tubs and many other efforts, events and endeavours.

Each year the NPSKU sponsors research – we have a grant fund offering two grants up to £10,000 annually, which are awarded following assessment by our Medical Advisory Panel.

CAN YOU EXPLAIN FURTHER ABOUT POSSIBLE MEDICAL ADVANCEMENTS ON THE HORIZON YOU ARE PERSONALLY EXCITED ABOUT?

The drug treatment for PKU which is potentially nearest to being available in England is the above-mentioned BH_4 – however, we estimate only 30% of people with PKU in the UK will respond to BH_4. Pegvaliase (currently available in the US), is an enzyme substitution therapy for PKU which is injectable, and is only suitable for adults due to immunology effects.

The most exciting treatment in my opinion is a genetically engineered probiotic treatment which has successfully been through mice trials. The bacteria *Lactobacillus reuteri* was given a phenylalanine lyase gene from another bacteria, *Anabaena variabilis.* PKU mice had reduced blood phenylalanine levels after 3-4 days of treatment with the genetically modified probiotic. This seems like it would be a potentially effective treatment. The enzyme Phenylalanine lyase does the same job as the PAH which is impaired in PKU.

WHAT DO YOU ENVISAGE IN THE FUTURE FOR THE NSPKU?

The key achievement for us will be when everyone living with PKU in the UK is receiving PKU treatment to the standards outlined in the European Guidelines for Diagnosis and Management of PKU (published in brief in *The Lancet Diabetes and Endocrinology* and also in full in the *Orphanet Journal of Rare Diseases*, both in 2017). One of the many recommendations includes metabolic specialist input for people with PKU who have, in the past, been discharged from metabolic clinics, or have discontinued diet; we should be supporting them to re-access treatment. However, we don't necessarily know where these "lost to follow-up" patients are in the UK, it's possible they are in the community experiencing adverse clinical outcomes of untreated PKU. There are many challenges ahead.

More information may be found on the website: www.nspku.org/

NSPKU takes food for Phenylalanine analysis each year - Avocado after Phenylalanine Analysis

I WILL READ THE SYNAPSE JOURNAL BECAUSE...

This is the first time I encountered this publication… having gone through it, I must say that it's a concise, relevant and informative read!

In very challenging winter conditions, Andrew Tasker and friends ascend Ben Nevis, Britain's highest peak, raising £3.5k for NSPKU, Andrew has a 4 year old son with PKU

DR PIERRE VASSALLO

ULTRASOUND ASSESSMENT
OF RIGHT UPPER QUADRANT ABDOMINAL PAIN

• PART I •

Right Upper Quadrant (RUQ) abdominal pain is one of the most common presenting complaints to any clinic or emergency department. Acute cholecystitis is the most frequent cause, however more than a third of cases are due to other conditions.

Due to the numerous possible aetiologies of RUQ abdominal pain, a rapid test for identifying the cause and guiding further detailed investigation is required. Abdominal ultrasound (US) is the imaging modality of choice as a first investigation;[1] it is readily available, rapid, cost-effective, and safe since it involves no ionising radiation or potentially nephrotoxic intravenous contrast agent. Abdominal US also assesses multiple upper abdominal organ systems that could be the source of the patient's pain. It readily distinguishes other causes of pain including hepatic, pancreatic, adrenal, renal, vascular, intestinal and thoracic causes. Biliary and hepatic causes of RUQ pain will be discussed in this article. Discussion of other causes will appear in a follow-up article.

Figure 1 below shows the recommended algorithm for investigating RUQ abdominal pain.[2]

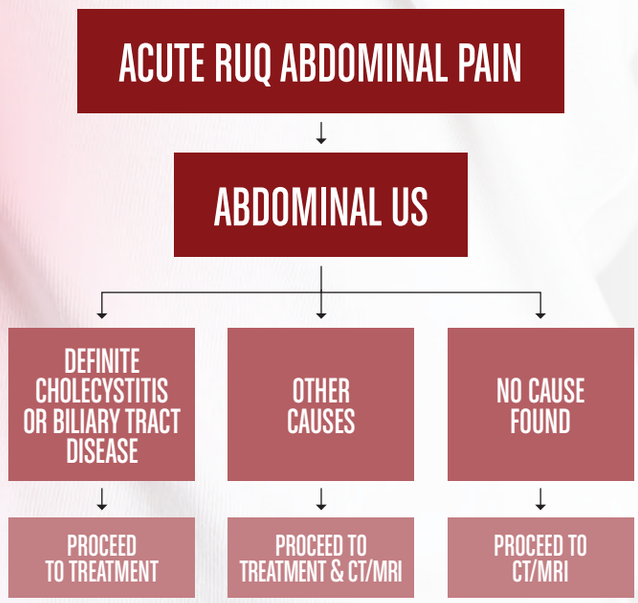

Figure 1. Diagnostic imaging algorithm for RUQ pain.

Acute cholecystitis presents with RUQ abdominal pain that may radiate to the right shoulder and may be accompanied by nausea, vomiting, and fever. Tenderness under the right costal margin sometimes with a positive Murphy's sign (accentuation of pain during inspiration) are the classical presenting signs, however they are not pathognomonic. Confirmation of clinically suspected cholecystitis, assessment of its severity and exclusion of alternative causes with US are needed.

Ninety to 95% of cases of acute cholecystitis are due to gall stones (calculous cholecystitis). On US, gall stones may be seen (Figure 2a) to obstruct the gall bladder neck or cystic duct. A positive sonographic Murphy's sign, whereby pain is accentuated during inspiration while the examining probe applies pressure on the gall bladder, helps to confirm the diagnosis. Gall bladder wall thickening (Figure 2b), sludge in the gall bladder and fluid outside the gall bladder are all features of acute cholecystitis. Gas bubbles in the gall bladder wall seen on ultrasound are indicative of gangrenous cholecystitis and represent a surgical emergency.

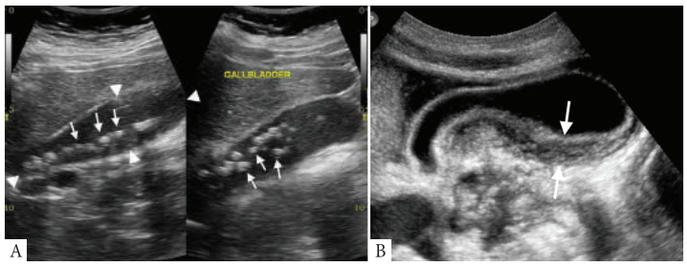

Figure 2a. Longitudinal US scan of the gall bladder containing numerous calculi (arrows). **b.** Longitudinal US scan of the gall bladder showing thickening of the posterior wall (arrows).

Hepatic causes of RUQ abdominal pain usually relate to any pathological process that distends the liver capsule; these processes may include hepatitis, hepatic enlargement due to steatosis, liver abscesses and liver neoplasms with or without intra-tumoural haemorrhage.

Hepatitis refers to any form of inflammation of the liver, which may be due to viral infection, medications, drugs, toxins, alcohol or autoimmune disease. It leads to enlargement of the liver, which presents on ultrasound as a cranio-caudal diameter of the liver over 15.5cm at the mid-clavicular line. An anterior liver margin extending below the lower pole of the right kidney is also indicative of an enlarged liver. A heterogeneous hypoechoic parenchymal texture in an enlarged liver (Figure 3a) is suggestive of hepatitis. Hyperechoic thickening around the main portal structures (Figure 3b) may be evident in acute hepatitis and is due to oedema (and consequently hypoechogenicity) of the background liver parenchyma. Numerous thickened portal triads distributed throughout the oedematous liver have been referred to a "starry night appearance" (Figure 3c). Finally, acute hepatitis may result in reactive oedema of the gall bladder wall (Figure 3d) with gall bladder wall thickening in the absence of stones or sludge. Computed tomography (CT) and magnetic resonance imaging (MR) may be used in equivocal cases and may show hepatomegaly, periportal oedema and periportal lymphadenopathy (Figure 3e).

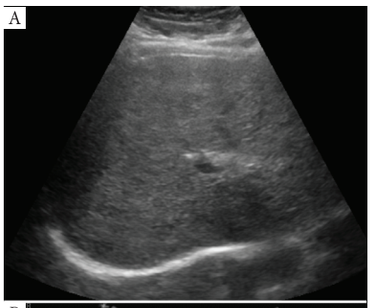

Figure 3a. Transverse US scan of the liver: Heterogeneous hyperechoic liver texture is due to acute hepatitis.

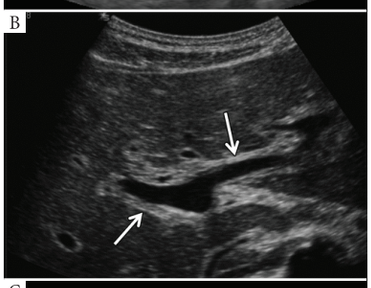

Figure 3b. US scan through the porta hepatis: Hyperechoic thickening around portal structures due to acute hepatitis.

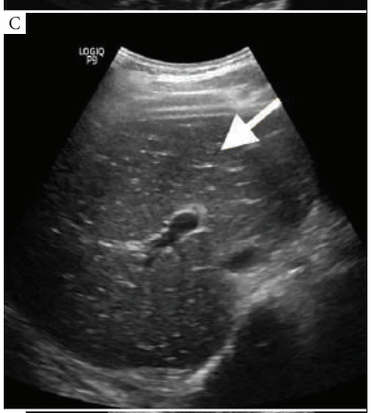

Figure 3c. Transverse US scan through the liver: "Starry sky" appearance due to background liver parenchymal hypoechogenicity resulting in hyperechoic thickening around the portal triads.

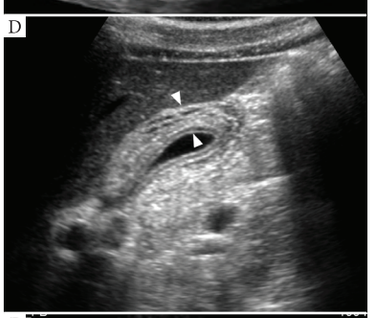

Figure 3d. Longitudinal US scan through the gall bladder: Gall bladder wall thickening secondary to acute hepatitis.

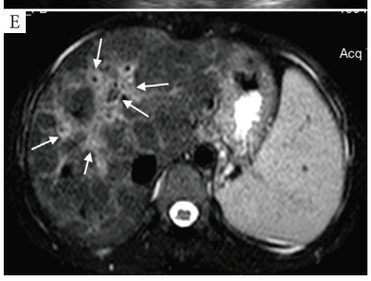

Figure 3e. Transverse T2-weighted MR scan of the liver showing periportal oedema (arrows).

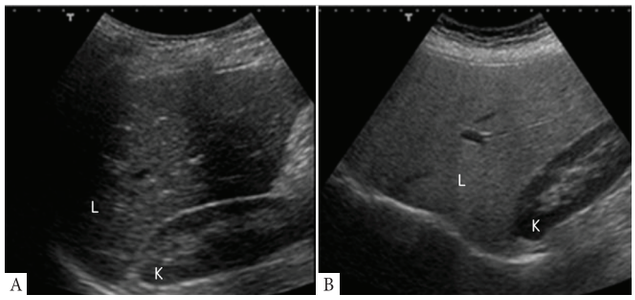

Figure 4. Sagittal US scans through the liver (L) and right kidney (K): note that in the normal case. **a.** echogenicity of liver and renal parenchyma are similar, while in a fatty liver, **b.** the liver parenchyma is hyperechoic.

Steatosis hepatis (or fatty liver) refers to an increased level of intracellular fat within hepatocytes. It may present in two forms: focal or diffuse. Both forms appear to have the same aetiology; they are more common in diabetic and obese patients, in cases of alcohol abuse or overeating and in association with drug use (exogenous steroids, amiodarone, methotrexate and chemotherapeutic agents). The steatotic portion of the liver will exhibit increased echogenicity on ultrasound, low density on CT and increased signal on T1-weighted MR images. Detection of the altered texture may be facilitated by comparison with the renal parenchyma on ultrasound (fatty liver has higher echogenicity) (Figure 4) and the spleen on CT and MR (fatty liver has lower density on CT and higher signal on T1-weighted images). MR imaging using various fat suppression techniques and intravenous contrast injection is highly useful in confirming the diagnosis.

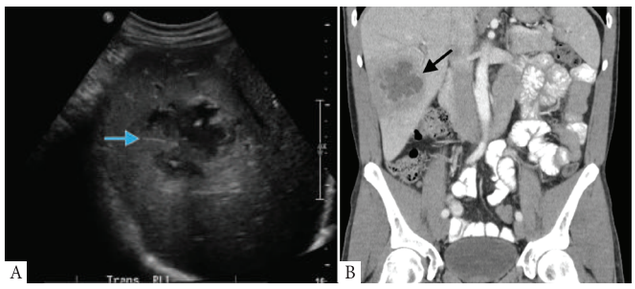

Figure 5a. Transverse US scan through the liver: The liver abscess (arrow) shows partly ill-defined margins with anechoic (fluid-containing) areas. **b.** Coronal CT Image showing a liver abscess (arrow) with the typical "cluster sign". Also note surrounding low density that represents oedematous liver parenchyma.

Hepatic abscesses are uncommon, but they do present with RUQ abdominal pain. Infection may enter through the portal vein (from e.g. diverticulitis, appendicitis), the hepatic artery (e.g. endocarditis or septicaemia) or the biliary tree (e.g. ascending cholangitis); in these cases, multiple hepatic abscesses may be present. Rarely infection may enter the liver from the right lung or through penetrating injury. Hepatic abscesses present with RUQ abdominal pain and fever. Blood cultures are only positive in 50% of cases. Infections may be pyogenic, fungal or mixed, sometimes parasitic (entamoeba or echinococcus). Liver abscesses are more common in immuno-deficient states. US depicts liver abscesses as hypoechoic thick-walled lesions with indistinct margins and thick septa (Figure 5a); hyperechoic areas within the lesions correlate with debris and gas. Colour Doppler US shows peripheral vascularity of the lesion. In some cases, further imaging is required to distinguish these lesions from necrotic tumours. CT depicts abscesses as hypodense with thick irregular contrast-enhancing rims; the appearance of a cluster of ring-enhancing lesions has been called the cluster sign and is strongly suggestive of an abscess (Figure 5b).

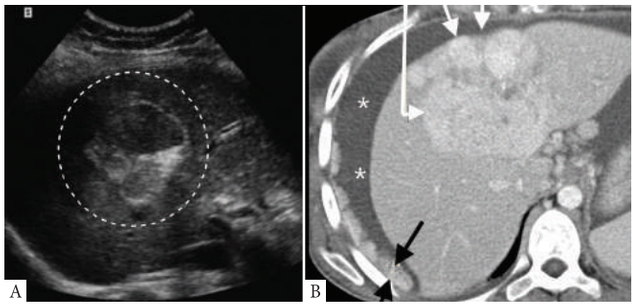

Figure 6a. Transverse US scan through the liver: the hepatocellular adenoma (circle) has ventral isoechoic components and dorsal hyperechoic areas, the latter representing intra-tumoural haemorrhage. **b.** Transverse contrast-enhanced CT scan through the liver: The enhancing hepatocellular carcinoma (white arrows) is in a subcapsular location. There is peritoneal fluid (*) and peritoneal metastases are present, both indicating capsular leak.

Hepatic tumours may present with RUQ abdominal pain. Since pain is mainly the result of capsular distension, small tumours rarely cause pain. Rapidly-growing tumours or smaller tumours with secondary intra-tumoural haemorrhage may present with pain. Hepatocellular adenomas ("hepatic adenomas"), hepatocellular carcinomas, large haemangiomas, peliosis and metastases may all develop intra-tumoural haemorrhage; this is rare in focal nodular hyperplasia. Pain is particularly evident if the expanding lesion has a subcapsular location. Hepatic adenomas are normally hyperechoic because they contain fat; secondary haemorrhage would appear as hypoechoic or anechoic areas within the lesion (Figure 6a) and peritoneal free fluid may be present if the liver capsule leaks. Hepatocellular carcinomas may have clear or ill-defined margins and may vary from hyper- to hypoechoic depending on their fat content; these differences parallel the aggressiveness (low to high) of the tumour. Haemorrhage into a hepatocellular carcinoma will appear similar to haemorrhage in any other tumour; these lesions are best assessed with CT or MR that help distinguish haemorrhage from viable tumour tissue (Figure 6b). Eighty percent of hepatocellular carcinomas develop in cirrhotic livers.

Other conditions that result in RUQ abdominal pain will be discussed in a follow-up article that will appear in the next issue of *The Synapse Journal*.

BIBLIOGRAPHY

- American College of Radiology. ACR Appropriateness Criteria: right upper quadrant pain. https://acsearch.acr.org/docs/69474/Narrative/. Published 1996. Updated 2013. Last review date: 2013. Accessed January 26, 2018.
- Joshi G, Crawford KA, Hanna TN et al. US of Right Upper Quadrant Pain in the Emergency Department: Diagnosing beyond Gallbladder and Biliary Disease. Radiographics 2018;38(3):766-793.

SEROXAT

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