Make Me More Compliant: The Oral Contraceptive Pill Has nutritional science been misinterpreted? Oncogene addiction might be the Achilles heel in cancer Cardiopulmonary Resuscitation

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Contraindications: Seebri Breezhaler is contraindicated in patients with known hypersensitivity to glycopyrronium bromide or any of the excipients. Seebri Breezhaler should not be used in patients with active bronchospasm or with a suspicion of a life-threatening bronchospasm. Seebri Breezhaler is not recommended for use in patients with severe (Grade 4) chronic obstructive pulmonary disease (COPD) as monotherapy.

Interactions: Seebri Breezhaler may potentiate the effects of other drugs that cause bronchodilation, including oral sympathomimetic amines, ipratropium, and long-acting beta2-agonists. Seebri Breezhaler is not recommended for use in patients with COPD who are receiving inhaled corticosteroids or long-acting beta2-agonists.

Adverse Reactions: Seebri Breezhaler is not associated with a higher incidence of upper respiratory tract infections compared to placebo. Seebri Breezhaler may be associated with increased oral candidiasis.

Legal Category: POM

Pack sizes: Single pack containing 361 hard capsules, together with one inhaler.

Marketing Authorisation Holder: Novartis Pharmaceuticals Limited, Wembley Road, Horsham, West Sussex, RH12 3SR, United Kingdom.

Marketing Authorisation Number: Seebri Breezhaler 44 microgram inhalation powder, hard capsules 1/1/2012/158/007/2012

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Service Inc., Representative Office Malta, P.O. Box 6, Marsa, M200 100, Malta. Tel: +356 22982371, 22982372

2014-MR-588-1-08-2014

Seebri Breezhaler 44 micrograms inhalation powder, hard capsules

This medical product is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 6.2 of the SmPC for how to report adverse reactions.

Presentation: Each capsule contains 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium. The delivered dose (361 dose) that leaves the mouthpiece of the inhaler is equivalent to 44 micrograms of glycopyrronium.

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Ebola virus disease or Ebola hemorrhagic fever is a disease of humans and other primates caused by one of the five species of the Genus Ebola virus i.e. Bundibugyo, Zaire, Reston, Sudan and Tai Forest. The Pteropodidae family of fruit bats are considered to be the natural reservoir of the Ebola virus. In layman’s terms, the virus interferes with the endothelial cells lining the interior surface of blood vessels and coagulation. As the blood vessel walls become damaged and the platelets are unable to coagulate, patients succumb to hypovolemic shock.

The index case of the Ebola virus disease was the headmaster of the local school of Yambuku, a Congolese village near Ebola River. This headmaster had toured along the Ebola river in August 1976, after which he became ill and died shortly after. Family members, as well as 11 of the 17 staff members of the small Yambuku hospital, run by Flemish nuns, also fell ill and died shortly after. The outbreak was eventually contained by quarantining local villagers in their communities, sterilizing medical equipment and providing protective clothing to medical personnel.

Today, almost 40 years after the initial emergence, it has come to haunt us again. Last March the WHO reported a major Ebola outbreak in Guinea, followed by Liberia, Nigeria and Sierra Leone. Since then, people from around the globe have died from this disease. The reason is not that the disease has gone pandemic but because of the numerous people, originating from various countries, who work in the affected areas. The two principal categories of people who have been affected are missionaries and WHO workers.

Interestingly, during the past 40 years, we have experienced Ebola in various countries. Ebola imported human cases have been reported in Switzerland, South Africa and Nigeria, and Ebola virus disease outbreaks have been reported in Congo and Sudan. On the other hand, Italy and the US have reported Ebola Reston outbreaks in imported monkeys from Philippines, whilst China and the Philippines have reported Ebola Reston outbreaks in imported monkeys or domestic pigs. Fortunately, the Reston strain appears less capable of causing disease in humans than the other four Ebola species.

Obviously the recent outbreak has placed irregular immigration in the limelight, in view of the fact that Malta and Italy (most notably, Lampedusa) are considered to be Europe’s southern gatekeepers for irregular immigrants. In fact, Malta currently hosts asylum seekers from the four implicated African countries, i.e. Guinea, Liberia, Nigeria and Sierra Leone. Obviously health authorities are doing their checks and crosses but one must also appreciate the fact that it is logistically impossible to monitor the entire 250km coast of Malta and Gozo between dusk and dawn on a daily basis. Co-operation between European and non-European countries is thus of utmost importance to effectively rise up to these challenges through a concerted effort.
Once-daily ULTIBRO BREEZHALER is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).¹

References

Author(s)

Professor Albert Cilia-Vincenti MD FRCPath is a private consultant pathologist in Malta, a scientific delegate to the European Medicines Agency (London), and Chairman of the Academy of Nutritional Medicine (London). He is a former pathology services director to the British and Maltese health services, and a former teacher of London and Malta Universities. He trained at London's Royal Marsden, Royal Free, St George's, Charing Cross and The Middlesex hospitals.

Dr Nikolai P Pace MD PhD is a lecturer and researcher at the Faculty of Medicine and Surgery, University of Malta. His research focuses on the genomics of type 2 diabetes and obesity.

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

Dr Karl Cutajar MD Dip. Health Studies is a Basic Specialty Trainee 2 in Obstetrics & Gynaecology at MDH and a casual lecturer with the UOM. He graduated in 2010 from the UOM and is currently undergoing further post-graduate studies.

Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health (specifically at Paola Health Centre) for these last 24 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees. The co-author of the article is Dr Sandra Baldacchino.

Dr Carl Tua MD is a second year Foundation trainee at Mater Dei Hospital. The articles are based on assignments done during his ongoing Masters in Internal Medicine with the University of Edinburgh.

Dr Carl Tua MD

06 Make Me More Compliant: The Oral Contraceptive Pill

08 A 21st Century Medical Revolution? Has Nutritional Science Been Misinterpreted? – An Introduction

10 Oncogene Addiction Might Be The Achilles Heel in Cancer – Part II

12 MMSA Corner & Career Opportunities

14 Cardiopulmonary Resuscitation: The History and Evidence Behind Modern Management

16 Inflammation and Insulin Resistance: Evolution, Pathology and Therapy

18 Meeting Josie Cachia

19 Quiz Section

20 Ultrasound-Guided Thyroid Fine Needle Aspiration

TheSynapse
In the 1930s, the structure of steroids was discovered, together with the notion that high dose oestrogens, progesterones and androgens inhibited ovulation. Naturally, this has led to the development of oral hormonal contraceptives. This can be considered to be one of the epochal events of the 20th century since their direct and indirect effects on hormonal and metabolic pathways have shaped a new era of pharmacological control.

This research opened the doors to experimentation and development into an ideal oral contraceptive pill (OCP). The 1950s showed the introduction and marketing of the first combined OCP, Enovid 10mg (Searle) (9.85 mg norethynodrel and 150 µg mestranol) for menstrual disorders. Following further stage 4 trials, the dose was decreased from a 10mg to a 2.5mg dose.

Further studies and understanding of the steroid cycle and products led to the discovery of new progestogens and estrogens. This in turn led to the development of newer generation combined contraceptive pills.

The evolution of the oral contraceptive pill ranged from changes in formulation, dosing, phases of action and active ingredient. The 1980s showed the introduction of the triphasic pills, whilst the 1990s showed the introduction of lower dose ethinylestradiol oral contraceptives focusing mainly on reduction of adverse side effects and enhancing tolerability to the combined oral contraceptive. In view of the decreased dosage and the 21/7 day regimes, this led to an increase in episodes of spotting or intracyclic bleeding leading to some women to shy away from the oral contraceptive or be less compliant, resulting in an increased number of unintended pregnancies.

The subsequent important milestone in the combined oral contraceptive pill development is the introduction of the 24/4 and 26/2 regimes. The shortening of the hormone-free interval resulted in further suppression of follicles and a decrease in spotting intervals, thus leading to better compliance which in turn translated in a decrease of unintended pregnancies.

The various studies which have been conducted during the five years following the introduction of COCPs such as 3mg drospereonone and 0.02mg ethinylestradiol, 2.5mg nomegestrol and 1.5mg estradiol, and quadriphasic COCPs having a 24/4 regime have evidenced better compliance and tolerability. Benefits of a shorter hormone-free interval are that women do not experience hormonal withdrawal symptoms as intensely as women using 21/7 regimens. It has been demonstrated that women with a history of pre-menstrual dysphoric disorder experienced less premenstrual symptoms such as mood swings, water retention, bloating, headaches, acne and weight gain while taking a regimen of ethinyl-estradiol and droperinone/nomegestrol for a minimum of 24 out of 28 days. These benefits may translate to better user compliance and ultimately could reduce unintended pregnancy as shown in figure 1.

In 2008, an ovulation inhibition study researched the effects of “missed pills” by replacement of the first three pills with a placebo after a completed cycle. It compared a 24-day with a 21-day regimen of 3mg drospirenone/0.02mg ethinyl estradiol. Results showed a suppression of ovarian activity, resulting in decreased hormonal fluctuations. This was substantially more pronounced in the regimen of 24 days of active tablets followed by 4 days of inactive tablets than the regimen of 21 days of active tablets followed by 7 days of inactive tablets. This means that the 24/4 regime is less prone to fluctuations especially if the patient misses a tablet.

Debate regarding the oral contraceptive pill still remains open with new regimes improving on the existing, in a struggle to create the “perfect” contraceptive with good tolerability and compliance with the least side-effects.
Is there a Pill that lets me feel like this every day?

YAZ® combines 20 µg ethinylestradiol and 3 mg drospirenone in a new 24/4 regimen. This means:

- drospirenone has a 30 hour half life, which extends its activity into the placebo interval
- provides significantly better contraceptive efficacy in real life as compared to 21/7 OC regimens
- 3 additional days of EE/drsp with antimineralocorticoid and antiandrogenic activity

References:

YAZ®, 0.02 mg/3 mg film-coated tablets (ethinylestradiol/ drospirenone) Prescribing Information

Dr Schekman claims such journals artificially restrict the number of accepted papers, which is more conducive to selling subscriptions than publishing the best research. He also argues that science is being distorted by the tyranny of the “impact factor” – researchers who publish in high impact journals can expect promotion, pay rises and professional accolades. Those who do not can expect obscurity or even the sack, a sort of Darwinian system known as “publish or perish”.

Many worry that the pressure to publish flashy research in glitzy journals encourages hype, and rewards being first over being thorough. Most scientists would be reluctant to speak up, fearing damaging their careers by rocking the boat, but one of Dr Schekman’s perks is that you no longer have to worry about such things.

In 2005, John Ioannidis, an epidemiologist who was then at Ioannina University in Greece, claimed that most published research findings are false, and exposed the ways (most notably the over-interpretation of statistical significance in studies with small sample sizes) how scientific findings can end up becoming irreproducible, that is, wrong.

Dr Ioannidis has moved to America and is launching (together with Steven Goodman) the Meta-Research Innovation Centre (known as METRICS) at Stanford. They plan to create a “journal watch” to monitor scientific publishers’ work – their mission statement is: “identifying and minimising persistent threats to medical research quality”.

Irreproducibility is one such threat. METRICS will make recommendations about how future work might be improved – for the study of reproducibility should, like any branch of science, be based on evidence of what works and what does not.

METRICS will also look into wasted effort. It has been claimed that around 85% of the world’s medical research spending is squandered on studies that are flawed in design, redundant, never published or poorly reported.

Dr Ioannidis’ pet offender is publication bias. Not all studies get published – the ones that do tend to be those that have significant results, leaving a skewed impression of the evidence.

How does all this medical research quality debate affect nutritional science which, as we increasingly realise, has important consequences for our understanding of epigenetics? There are now claims that decades-long nutritional medicine beliefs may be incorrect, having been based on poorly conducted clinical studies.

Some of the topics to be addressed in future articles, in an attempt to elucidate the claims that we’re on the brink of a 21st century medical revolution, will include:

- Has the epidemic of diabetes type 2, metabolic syndrome and obesity been caused by a combination of adulterated vegetable oils and the high carbohydrate/low fat diet advice?
- Can diabetes type 2 be reversed by nutritional modifications alone?
- Are omega-6 fatty acids healthier than omega-3? Are omega-6 fatty acids the anti-inflammatory ones, rather than omega-3?
- Has marine-derived omega-3 fatty acids any cardiovascular benefits, and does an excess intake of these lead to long-term harmful effects?
- Are saturated dietary fat and blood LDL-cholesterol related to atherosclerosis and its complications?
- Can omega-6 fatty acids improve arterial wall compliance and reverse atherosclerotic plaque?
- Do omega-6 fatty acids increase oxygen-binding capacity of cell and mitochondrial membranes? Is chronic reactive cellular hypoxia an important risk factor for cancer initiation and promotion, and do omega-6 fatty acids decrease this risk?
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This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on how to report adverse reactions.

Please refer to the full Summary of Product Characteristics before prescribing

Trade Name: RELVAR ELLIPTA. Active Ingredients: 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifluorate). Pharmaceutical Forms: 92 micrograms/22 micrograms or 184-micrograms/22 micrograms inhalation powder, pre-dispensed.

Indications: The 92 micrograms/22 micrograms dose for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate; and use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate; and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate; and adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate; and adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV1<70% predicted and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta 2-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a dose to mid interval of inhaled corticosteroid in combination with a long-acting beta2-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.

For COPD: One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. Contraindications: Hypersensitivity to the active ingredient or excipients. Precautions for Use: Delphi: Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and presenting in patients with COPD. Drug Interactions: Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). Fertility, Pregnancy and Lactation: Pregnancy: No adequate data available. Lactation: Insufficient information available. Fertility: There is no data in humans. Animal studies indicate no effect on fertility. Effect on Ability to Drive or Use Machines: No or negligible influence. Undesirable Effects: Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). Overdose: There is no specific antidote. Treatment of overdose should consist of general supportive measures. Local Presentations: Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed. Legal Category: POM. Marketing Authorisation Holder: Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom. Marketing Authorisation Numbers: EU/1/13/006/001. Date of Preparation: December 2013.

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 GlaussSmithKline (Malta) Ltd (Tel: +356 21238131).

Reporting adverse events (AUEs): Malta & Gibraltar: 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, ORM 2458, Malta (Tel: +356 21238131).

Malta: alternatively, any suspected AEs and medication error can also be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicationauthority.gov.mt/report 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 position@medicationsauthority.gov.mt.

Gibraltar: 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.medicines.gi.gov.gi/adrs.html.

Molecular Mechanisms of Oncogene Addiction

Various hypotheses have been put forward to account for the molecular mechanism of oncogene addiction, with the main ones being synthetic lethality and oncogenic shock. A favoured hypothesis is that of synthetic lethality. Two genes are said to be synthetically lethal if mutation of one of the genes is compatible with cell survival but mutation in both genes results in cell death. It has been suggested that in a cancer cell, the activating oncogene is in a synthetic lethal relationship with a gene that is inactivated in the cancer cell. Accordingly, eliminating the oncogene would lead to cancer cell death, while sparing normal cells. Using this fact to their advantage, Puyol et al. unveiled a therapeutic strategy for non-small cell lung carcinoma after discovering that a synthetic lethal interaction exists between K-Ras oncogenes and Cdk4.

One other favourite mechanism that has also been put forward to explain oncogene addiction is referred to as ‘oncogenic shock’. Here, Sharma et al. proposed that the acute inactivation of the oncogene protein (oncoprotein), results in a ‘differential decay rates of various prosurvival and proapoptotic signals’ associated with the oncoprotein (figure 1). Indeed, they suggested that the prosurvival signals (green arrows) are transient and dissipate relatively quickly upon oncogene inactivation, whereas the proapoptotic signals (red arrows) linger for a longer period of time thus committing the tumour cell to apoptotic death.

Consistent with this model, Sharma et al. observed that when lung cancer cells are treated with gefitinib, which, like erlotinib, is an epidermal growth factor receptor (EGFR) inhibitor, they are more efficiently killed than when they are treated with the prosurvival receptor ligand, EGF.

Figure 1. Relationship between oncogene addiction and oncogenic shock. In an oncogene addicted cancer cell, the prosurvival signals (green arrows) predominate over the proapoptotic signals (red arrows) and result in the survival of the cancer cell. Following acute oncoprotein inactivation, prosurvival signals dissipate rather quickly relative to the proapoptotic signals which are prolonged. Thus the lingering proapoptotic signals cause the cells to irreversibly undergo apoptosis (Source: Sharma and Settleman, 2007).

Integrating New Approaches into the Clinical Setting in Order to Characterise the State of Oncogene Addiction

Identifying the particular state of oncogene addiction in specific types of human cancer can be conducive to treating patients with appropriate molecular agents. Presently, there is no way to fully assess the total signalling pathways, inside and outside normal or cancer cells, that control their proliferation, differentiation and apoptosis. However, advances are being made in profiling patterns of gene expression, genomics, epigenomics, proteomics, network theory, systems biology and computer modelling. These advances will eventually help in identifying the Achilles’ heel in specific types (and their subtypes) of human cancer. Integrating all these techniques would then lead to tailor-make optimal therapy by developing agents that target the critical oncogene. Also they would become useful in ‘oncogenic escape’ states.

Cancers can ‘escape’ from a particular state of oncogene addiction. This results due to mutations in other genes and pathways, probably because of the genomic instability of cancers. Moreover, many research papers, such as that by Giuriato and Felsher, even suggest that upon sustained oncogene inactivation, some cancers relapse and are thus no longer dependent on the oncogene to which they were previously addicted to. This explains why using single molecular targeted agents may not achieve long-lasting remissions or cures and one needs to opt for combination therapies in such situations. But again combination therapies should be rationally designed using the integrative approaches mentioned above.

Currently, choosing the best molecular targeted agent, alone or in combination, for a specific patient with cancer is largely empirical. But this scenario is rapidly changing, as the oncologist can now choose from a rapidly developing list of diverse molecular targeted agents. This coupled with several research mechanistic studies and techniques to profile the molecular networks in human cancer and their subtypes, should exploit the concept of oncogene addiction and be conducive to more rational, effective and tailor-made therapies for cancer.

Conclusion

Cancer is multifaceted, involving many interactions between different genes, pathways and signalling cascades. This makes the detection of a single marker molecule, and thus the determination of oncogene addiction, rather complex. Besides, it has also been reported by Tonon that genetic abnormalities in cancers tend to gather around specific pathways, giving way to the concept of ‘network addiction’, rather than oncogene addiction. Therefore, the development of new integrative strategies for defining these oncogene addiction networks together with the use of molecular target agents, might, in the near future, make it possible to achieve more effective, tailor-made therapies for the treatment of human cancer.
Last August, 8 students from the MMSA made the long journey to Taipei, Taiwan to represent Malta in the International Federation of Medical Students Association (IFMSA) 63rd General Assembly August Meeting.

The Maltese delegates attended various workshops which focused on topics such as medical education, disaster risk management and mental health. These informal learning settings provide the perfect opportunity for students to discuss ideas and important topics and learn about global issues.

The Maltese delegates also acted as moderators in all sessions, including human rights and peace, reproductive health, medical education, public health and exchanges. These sessions give students vital information and skills in the respective fields, which they can then take back home and share with other students within the association.

The theme this year was ‘Sustainability in the New Era’ and there were a number of seminars focusing on this topic. Expert speakers from all over the world discussed global topics, relevant to participants not only as student activists but also as future healthcare workers. Also, fortunate to be in a country with such a unique culture, students were also given the opportunity to learn and practice different kinds of Chinese Medicine including acupuncture and moxibustion.

Two Maltese projects were presented at the activities fair, where all countries are given a chance to display their national projects so that other may adopt them. Furthermore, the delegation had the honour of representing all Maltese medical students during the plenary sessions which took place throughout the meeting.

The General Assembly was also a special one for the Maltese delegation because 2 members of our association contested for positions on the IFMSA Team of Officials. It was also a momentous one because the MMSA announced their candidature to host the General assembly in Malta in March 2016. Their bid will be presented in the next March Meeting in Turkey, and should we be elected, 1000 IFMSA members will be coming to our beautiful island in 2016 to take part in these productive and inspirational sessions, all organised by our medical students.

These General Assemblies, hosted internationally, are the perfect showcase of students who are active and interested in making a positive change, through education and advocacy for what they believe in.
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Resuscitation following cardiac arrest involves a life-saving set of skills which are practised by healthcare workers and trained laypersons throughout the world. Various associations and groups, such as the European Resuscitation Council (ERC) and the American Heart Association have training programmes on resuscitation techniques using standardized algorithms. There are different protocols for different situations, using various pieces of equipment and with a range of complexity, however the key aspects of modern resuscitation remain the same; these are summarized by the ERC guidelines as the “Chain of Survival”:

- Early recognition and call for help
- Early Cardiopulmonary resuscitation (CPR)
- Early defibrillation
- Post-resuscitation care

This article focuses on the history and development of the evidence behind some of the key aspects of modern resuscitation: airway maintenance and breathing, circulation and chest compressions, and defibrillation.

**AIRWAY AND BREATHING**

In the Book of 2 Kings, in the Old Testament the prophet Elisha restores life to a boy using a technique including placing his mouth in the mouth of the boy. There are other historical references to mouth-to-mouth including one by Napoleon’s battle surgeon and William Tossach, a British surgeon who successfully used mouth-to-mouth ventilation on a coal miner in 1744. However it was only in 1958 that Safar and McMahon provided the first evidence for the efficacy of mouth-to-mouth and mouth-to-airway ventilation by experimenting on anaesthetized and curarized adults. Their description of how to maintain an airway and provide mouth-to-mouth is similar to what one would find in a modern resuscitation textbook:

“The mouth-to-airway method, as well as the mouth-to-mouth method, permits a breath-to-breath evaluation and control of the efficacy of ventilation, since the rescuer can observe the patient’s chest at all times and can listen to the expiratory gas flow while at the same time he has both hands free for extending the head and supporting the jaw, thus maintaining a patent upper airway.”

In that year Safar also published other articles comparing airway patency in various positions, described the use of an artificial oropharyngeal airway, and compared mouth-to-mouth to other modes of ventilation such as the chest-pressure arm-lift methods. By the end of the 1960’s the head-tilt chin-lift, the jaw-thrust maneuver and mouth-to-mouth ventilation had become established, and have remained fundamental aspects to the management of airway and breathing during emergency situations.

Despite the proliferation of various instruments for definitive management of the airway, the optimal management of the airway during cardiac arrest is still unproven, with conflicting evidence for the use of tracheal intubation, supraglottic devices and bag-mask ventilation. One of the reasons that definitive airways have not always resulted in better outcomes in observational studies may be because placement of a definitive airway during CPR requires considerable experience, and may result in interrupted chest compressions and misplacement. Observational studies indicate that patients tend to be over-ventilated since this results in decreased circulation due to decreased venous return; in fact, animal experiments show that hyperventilation greatly reduced absolute survival.

In Seattle a randomized study comparing CPR by chest compressions alone with CPR by chest compressions plus mouth-to-mouth ventilation found no statistically significant difference in outcomes. This is probably due to interruptions to chest compressions from over-emphasis on ventilation. In another study, in Ontario, adding a program of advanced life support including endotracheal intubation and intravenous drugs did not improve the survival rate. These studies seem to indicate that, while ventilation is important, uninterrupted chest compressions are fundamental to CPR outcome.

**CIRCULATION AND CHEST COMPRESSIONS**

Friedrich Maass in 1891 was the first person to successfully use external cardiac massage to revive a 9-year-old boy who, during an operation for cleft palate, required extra applications of chloroform which resulted in him becoming cyanotic and pulseless. At this point Maass applied direct compressions in the region of the heart, and after 30 minutes of compressions the cyanosis disappeared and a pulse was felt. Unfortunately his discovery lay dormant, and open-chest cardiac massage,
first performed successfully in 1901 for anesthetic induced arrest, remained the dominant technique, possibly only in theatre conditions and requiring technical expertise. It was 60 years later that closed-chest cardiac massage was rediscovered when researchers experimenting with defibrillation in animals noted by chance that forceful placement of electrodes over the chest resulted in an increase in blood pressure. Following further research, they published their findings, excitedly writing about the use of closed-chest cardiac massage:

"Immediate resuscitative measures can now be initiated to give not only mouth-to-nose artificial respiration but also adequate cardiac massage without thoracotomy ... Anyone, anywhere, can now initiate cardiac resuscitative procedures. All that is needed are two hands."¹⁴

There is clear evidence that good quality chest compressions are essential for resuscitation. As discussed earlier, trials have shown that compression-only CPR did not result in worse outcomes when compared to compression and ventilation CPR. In 2006, a study showed that longer pre-shock pauses and shallow chest compressions are associated with defibrillation failure.¹⁵ Yet despite this, several large studies of in and out-of-hospital cardiac arrests have shown that chest compressions are not being adequately delivered. One study showed that chest compressions were not given 48% of the time without spontaneous circulation.¹⁶-¹⁷ This significant amount of inadequately applied manual chest compressions has led to the suggestion that mechanically applied CPR using automated machines may be superior. However a systematic review in 2012 showed that there is no evidence to show that they improve survival¹⁸ and a recent randomized control trial comparing mechanical CPR with defibrillation during ongoing compressions with manual CPR and standard defibrillation among adults with out-of-hospital cardiac arrest showed no significant difference in 4-hour survival.¹⁹ In a review of the history and future directions of CPR, Cooper et al. suggest that if, despite optimizing closed chest compressions overall survival does not improve, then open cardiac massage should be reexamined as technique, particularly when closed chest CPR fails to resuscitate patients within a short time-frame.²⁰

**DEFIBRILLATION**

The experiments of the Danish veterinarian P. C. Abildgaard who described killing chickens with a shock to the head, and then reviving them with a second shock to the chest are often described as the first scientific description of defibrillation; however it is likely that given the Leyden jars used at the time to generate the shock, the current generated would have been too small to result in defibrillation.²¹ There are several reports that may be considered to be the first descriptions of successful defibrillation in humans. In 1787 the Royal Humane Society published the case of Sophia Greenhill, a three-year-old girl who was pronounced dead after a fall, but was revived by the application of electrical shocks administered by her neighbor. However many years would have to pass for the scientific basis of defibrillation to be understood.²²

In the late 1880s the British physiologist John McWilliam wrote the classic description of ventricular fibrillation, and suggested its importance in humans:

"Instead of a coordinated contraction leading to a definite narrowing of the ventricular cavity, there occurs an irregular and complicated arrhythmic oscillation of the ventricular walls."²³

The next breakthrough was by Prevost and Battelli who described inducing fibrillation in the hearts of dogs using electrodes placed in the mouth and small intestine of the dog, but more significantly, they described how a second shock delivered to a fibrillating heart, may defibrillate the ventricles.²⁴ This work was largely forgotten until 20 years later when these experiments were independently replicated. Nonetheless defibrillation was still considered only for the theatre environment with the chest wall open, as transthoracic defibrillation was considered too dangerous due to the voltage and current required. It was research done by the USSR Academy of Medical Sciences, in particular Naum Gurvich that allowed defibrillation to be carried out using significantly less energy, by using a DC shock and biphasic waveform; features that quickly became adopted around the world.²⁵ Using this technology Paul Zoll described the first successful closed-chest human defibrillation in 1955.²⁶

With increased usage of defibrillation it quickly became clear that time is of essence. Data suggests that each passing minute of untreated ventricular fibrillation reduces the likelihood of survival by 7-10%, and the introduction of Automatic External Defibrillators (AED) with rapid response times have been shown to significantly improve outcome,²⁷-²⁸ with one study reporting an incredible 74% hospital discharge rate if a shock was delivered within 3 minutes.²⁹ Despite this, performing chest compressions for 1.5 to 3 minutes before defibrillation actually results in improved survival.³⁰

**CONCLUSION**

From the earliest origins of CPR thousands of years ago, to modern-day CPR carried out by bystanders using AEDs in our hospital situations, CPR has undergone countless advancements and reinventions. Yet despite its important role in modern medicine, the ethical and logistical difficulties in carrying out scientific trials means that high level evidence is not always available, and guidelines often rely on observational data and expert consensus. The future of CPR will depend on furthering novel techniques, but perhaps more importantly it will depend on becoming a widespread set of skills practised by the general public and not just healthcare workers, which together with increased availability of public AEDs has shown to improve outcomes. As W.B. Knouwenhoven et al. wrote in the landmark article in 1960:

"Anyone, anywhere, can now initiate cardiac resuscitative procedures. All that is needed are two hands."³¹
Chronic low-level subclinical inflammation is an established risk factor in the development of insulin resistance, endothelial damage and atherosclerosis. The obesity-associated insulin resistance in adipose, liver and muscle tissue is promoted by a switch in macrophage activation driven by transcription factors that play crucial roles in innate immunity. This review discusses the evolutionary link between body defense mechanisms and insulin resistance.

Inflammation has an established role in the development of cardio-metabolic disease. The pathogenesis of atheromas, endothelial dysfunction and vascular thrombosis that progress to numerous adverse clinical events are considered inflammatory responses to vascular injury.1 Inflammation is also strongly implicated in the pathogenesis of insulin resistance, type 2 diabetes and obesity. In these conditions, a chronic low-grade subclinical inflammatory response is characterized by the absence of the traditional hallmarks of the acute inflammatory response – pain, redness, swelling and fever – that is often a short-lived adaptive response to tissue injury or infection. Caloric excess and metabolic surplus trigger a chronic inflammatory response that involves many of the same mediators and signaling pathways as in the classical acute inflammatory reaction. In the long term, however, this chronic inflammatory response is detrimental and leads to profound metabolic complications.

The ability to mount an effective immune response to pathogens, heal tissue damage and fight infection (pathogensensing), as well as the ability to store energy to withstand starvation (nutrient-sensing) is critical for the survival of all multicellular organisms. Metabolic and immune pathways are highly conserved, closely interlinked and interdependent, with many hormones, cytokines, transcription factors and bioactive lipids functioning in both the metabolic and immune roles.2 The close interplay between metabolism and immunity is vital for the maintenance of good health – with both overnutrition and malnutrition effecting immune function. Overnutrition and caloric excess lead to immune activation and susceptibility to inflammatory disease (T2DM, atherosclerosis, fatty liver) while malnutrition leads to immunosuppression. As famine and disease pandemics have been constant threats to human health for thousands of years, it is hypothesized that they favored the evolutionary selection of strong immune responses and caloric thriftiness.3 The combination of these traits has led to the evolution of a physiology that is highly efficient in processing and storing energy and at mounting a powerful, and at times over-sensitive, immune response.

The interrelationship between immunity and metabolic pathways has robust evolutionary underpinnings. In lower organisms, the functions of adipose tissue, hematopoietic tissue and the liver are incorporated into one structure – known as the fat body in Drosophila.4 The fat body coordinates metabolic and survival responses. Possibly, the shared developmental heritage of liver, adipose and hematopoietic tissue underlies the overlapping biological roles of these organs and the use of common regulatory and signaling molecules.5 In this context, evolutionary theory suggests that nutrients act on pathogen-sensing systems to trigger metabolically-induced inflammatory responses.

The architectural organization of the liver and adipose tissue in mammals is similar. In both, the active metabolic cell (hepatocyte and adipocyte) is in close structural proximity to immune system cells (Kupfer cells, macrophages, lymphocytes and dendritic cells) and to the circulation. The histological organization of the liver and adipose tissue allows continuous and dynamic interactions between metabolic and immune responses through soluble mediators that act on distant organs, including muscle and cells of the endocrine pancreas.6 The integration of metabolism and immunity is advantageous in adverse situations, where stress and inflammatory responses to injury or infection block major anabolic pathways (such as the insulin/insulin-like growth factor (IGF) signaling) to divert energy from biosynthesis.7 None of these pathways has however evolved or adapted to situations of continuous calorie surplus. Caloric excess and metabolic overload disrupt the delicate balance between inflammatory and metabolic signaling and lead to detrimental effects on health.

Elevated levels of proinflammatory cytokines and acute phase reactants characterize the chronic inflammation that is part of the pathophysiology in obesity and metabolic syndrome. Experimental, epidemiological and clinical evidence causally links inflammation and inflammatory regulatory networks to the development of insulin resistance, obesity and their downstream consequences.8 The first clear link between obesity, diabetes and chronic inflammation was proposed by Hotamisligil et al in 1993, who showed that tumor necrosis factor alpha (TNFa) is overexpressed in adipose tissue of obese mice.9 TNFa is a proinflammatory cytokine that regulates many cellular pathways. Obese mice lacking in TNFa have improved insulin sensitivity and glucose homeostasis.10,11 TNFa is also overexpressed in muscle and adipose tissue of obese humans, and exogenous administration of TNFa leads
to insulin resistance. Furthermore, TNFα antagonists used in the management of rheumatoid arthritis have been shown to reduce insulin resistance. Numerous other cytokines and inflammatory mediators are overexpressed in human and animal models of obesity. In particular, interleukin 6 (IL6), macrophage migration inhibitory factor (MIF) and interleukin-1β (IL1β) are associated with insulin resistance. As inflammatory mediators exert their effects through complex interrelated pathways, a measure of the relative contribution of each mediator, is, at best, only an estimate.

**THE ROLE OF ADIPOSE TISSUE IN THE INFLAMMATORY RESPONSE**

Adipose tissue is largely responsible for the initiation, maintenance and progression of the inflammatory response in obesity. Besides functioning as an energy storage depot, adipose tissue secretes peptide hormones, cytokines and chemokines that act in an endocrine or paracrine fashion. Adipocytes secrete adipokines, such as adiponectin and leptin that increase insulin sensitivity as well as resistin and retinol-binding protein 4 (RBP4) that increase insulin resistance. Adipose tissue is infiltrated with bone marrow-derived macrophages, with the density of these adipose tissue macrophages (ATMs) dependent on the degree of obesity. The number of ATMs has been shown to correlate with the degree of insulin resistance.

In insulin-resistant skeletal muscle and adipose tissue, inflammatory cytokines TNFα, IL6 and IL-1β exert paracrine effects to activate inflammatory pathways. These cytokines lead to activation of Jun N-terminal kinases (JNK), inhibitors of κ B kinase β (IκKβ) and other serine kinases. The active kinases in turn activate transcription factor targets (c-Fos/c-Jun) and nuclear factor κB (NF-κB) that stimulate transcription of inflammatory pathway genes. These activated serine kinases also interact with insulin receptor and insulin receptor substrate proteins (IRS) to interfere with the normal post-receptor insulin-signaling cascade, leading to insulin resistance. Further evidence for this cytokine-mediated insulin resistance came from experiments where knockout of JNK and IκKβ prevents insulin resistance in cell or mouse models of disease. Besides the local paracrine effect, IL6, TNFα and IL1β also exert endocrine effects as these tissue cytokines leak into the circulation to exert insulin resistance in distant tissues. Adipose tissue macrophages exhibit different phenotypes according to the degree of adiposity. ATMs in lean non-obese individuals are anti-inflammatory (M2 macrophages); as opposed to ATMs in obese individuals that express pro-inflammatory genes (M1 classicaly-activated macrophages). In non-obese, insulin-sensitive conditions, adipocytes secrete factors that trigger alternative activation of macrophages. These secrete anti-inflammatory mediators. The obesity-induced changes in adipocyte gene expression triggers release of proinflammatory cytokines (TNFα, MCP-1) that lead to recruitment and activation of macrophages. The activated M1 macrophages produce and secrete copious quantities of proinflammatory mediators, including IL6, TNFα, IL1β and resistin that sustain an insulin-resistant state in adipocytes and establish a positive feedback loop that further enhances insulin resistance and inflammation. M1 macrophages (CD11c+) account for the majority of ATM content in obese individuals, and ablation of these cells has been shown to ameliorate the obesity/high-fat diet-triggered inflammation and insulin resistance.

**FATTY ACIDS AND M1 MACROPHAGE ACTIVATION**

Saturated fatty acids have strong proinflammatory effects, while polyunsaturated fatty acids are neutral and omega-3 fatty acids are anti-inflammatory. The effects of saturated fatty acids are mediated through Toll-like receptor 4 (TLR4). Toll-like receptors are key mediators in innate immunity that serve in the detection of pathogen-associated molecular patterns (PAMPs) prior to the initiation of an adaptive immune response. TLR4 has high affinity for the lipopolysaccharide component of gram-negative bacterial cell walls and normally functions in stimulating M1 macrophage activation in response to pathogens. Macrophage TLR4 expression is increased in obesity and its ablation impairs the saturated fatty acid-induced activation of inflammatory pathways in adipocytes, skeletal muscle and macrophages. Studies have demonstrated that TLR4 knockout animal models are protected from high-fat diet-induced weight gain and insulin resistance. Activation of TLR4 induces the expression of potent proinflammatory genes that encode cytokines (TNFα, IL1β), chemokines (MCP-1), type 1 interferons and inducible nitric oxide synthase (iNOS). This response leads to enhanced cell motility, phagocytosis, antigen presentation and intracellular killing.

**ANTI-INFLAMMATORY THERAPY AND INSULIN RESISTANCE**

Given the crucial role of inflammation in the pathogenesis of insulin resistance and type 2 diabetes, a number of studies have investigated anti-inflammatory pharmacologic interventions as potential therapies in insulin resistance. Human trials with etanercept (a recombinant antibody that blocks TNFα activity) have failed to improve insulin resistance in subjects with metabolic syndrome. This could possibly be due to the discrepancy in TNFα levels between the circulation and adipose tissue. TNFα mainly exerts its biological actions in a paracrine effect. Large molecule TNFα antagonists do not penetrate interstitial space effectively to neutralize the paracrine action of this cytokine, despite inhibiting circulating TNFα action.

Anakinra, a recombinant non-glycosylated form of interleukin-1 receptor antagonist (III-RA), has been shown to improve insulin sensitivity and beta cell function in T2DM patients. High dose salicylate has also been shown to improve insulin sensitivity in T2DM via inhibition of IκKβ. Anti-inflammatory agents that act selectively on pathways that drive insulin resistance offer a promising therapeutic potential for T2DM.
Hi original intention had been to become a doctor. “At the time when I was studying at university, one had to possess very particular requisites in order to proceed to study medicine. Because this was not part of my aspirations, I put aside my primary intention of becoming a medical doctor and instead proceeded to study pharmacy, graduating in 1994.” A Sliema boy through and through, one of his first locums was in fact in a pharmacy located in Sliema which he remembers fondly. “It is one of those early memories which have remained with me. Unfortunately the pharmacy is now defunct.” His post-university working experience included also hospital shifts at the St Luke’s pharmacy doing the odd 24-hour-long stints, and this for a whole three years. “Those long hours served their purpose well - that initial training in the pharmaceutical field was very important but it was also very demanding and caused me considerable inconvenience in view of another kind of training which I pursued at the time with great intensity.” In reality, Josie’s life-long passion was and remains the game of water polo. As a Sliema boy he was for many years an active player with the Sliema team in first division, apart from also playing with the national team and in second division with Marsascala. “We lived very close to the Sliema front and in my days, every boy spent his summers in and out of the water. It was the ideal way of expending energy and of filling those long lazy months of school recess. I joined the team in the early 80s and effectively capped every Sliema boy’s dream of becoming a key player with the very same team of which I was an ardent fan.” Eventually he proceeded to become one of the team’s leading players, serving as a goalkeeper and winning a good handful of awards such as a bronze medal at the European Championships and the Player of the Year title for 2009. Today he is still involved with the team, albeit from the sideline after having retired from the active career at age 39. “I have very mixed feelings about my retirement from water polo playing. I could not have been more fortunate in having spent so many successful years playing for a team I love and winning a total of 10 leagues. I retired precisely when it was time to move on and make space for younger players. I was not forced to retire because of injury, which was a very fortunate thing; it was just the right time to stop. Today I am still involved in the Sliema club committee as team manager. But it is very strange not to be inside a team as an active player, where it’s more fun and a much more dynamic experience. Water polo, seen from the outside, seems to be a totally different ball game.” On the other side of the coin, Josie is today a pharmaceutical representative and has been in this profession since 1999. “One of the reasons which motivated me to stop
working as a community pharmacist and move into the field of pharmaceutical representation was the fact that being tied down to shop hours meant that I was losing out a lot on water polo training. I had to compromise heavily between working weekends and playing games/training hours, and therefore becoming a medical representative seemed to solve that problem effectively.”

Asked about his experience of meeting medical professionals on a daily basis, Josie stresses that this is the kind of job where he has to constantly try to encourage doctors and specialists or consultants to find time to meet him. “Doctors are typically time-starved professionals and notwithstanding this, they manage to find time for representatives such as myself. My work is not just about promoting products, but rather about reporting back to doctors with new information on product trials as well as sharing new data which pharmaceutical companies disseminate to us representatives.” Josie explains how doctors play an important role in pharmacovigilance since adverse reactions are not necessarily always identified through trials but can be reported to representatives by individual doctors. “We are on the front line dealing with the front liners - it is the doctors who can gauge how products interact, can help draw risk assessment analysis, and allow us to report back to the mother company on issues which reflect on product efficacy or otherwise.”

“This leads to the eternal tug of war between generic and branded products. Whilst doctors may be pressurised by the public to prescribe the lower costing generic medicinals, it is good to remember that it is the big companies which produce the original brands and carry out all the intensive research. Generic companies don't carry out research and although their place on the market is important, unless the branded companies sell, they won't be able to sustain the extremely high costs of research and lab trials. Neither will they be able to offer training and related educational materials which look into specific illnesses and health conditions.”

“I joined the team in the early 80s and effectively capped every Sliema boy’s dream of becoming a key player with the very same team of which I was an ardent fan.”

**QUIZ**

**LAST AUGUST, 8 STUDENTS FROM THE MALTA MEDICAL STUDENTS’ ASSOCIATION (MMSA) JOURNEYED TO WHICH COUNTRY TO REPRESENT MALTA IN THE INTERNATIONAL FEDERATION OF MEDICAL STUDENTS ASSOCIATION (IFMSA) 63RD GENERAL ASSEMBLY AUGUST MEETING?**

SEND YOUR ANSWERS BY 10TH OCTOBER TO IAN.C.ELLUL@GMAIL.COM

The 5th correct entry will win a medical language translator book published by MMSA.

**QUIZ WINNER**

**WINNER OF THE MEDICAL LANGUAGE TRANSLATOR BOOK PUBLISHED BY MMSA**

Dr Mario Saliba is the lucky winner of the medical language translator book published by MMSA. He was the 5th participant who replied correctly to the question, “a training post open to family doctors and doctors with MRCOG is being advertised in this issue. In which specialization it is being offered?” The correct answer is genito-urinary medicine.
Ultrasound (US)-guided FNA lends itself particularly well to lesions in superficial organs such as the thyroid, lymph nodes and the breast. However, since it is less traumatic than core biopsy, it is safer for use in highly vascular organs such as the thyroid gland. Smaller nodules are more amenable to FNA, while larger nodules are better sampled with core biopsy.

**Focal Thyroid Lesions**

The Society of Radiologists in Ultrasound suggests that FNA should be considered for a thyroid nodule 1.0 cm or more at the largest diameter if microcalcifications are present and for a nodule 1.5 cm or larger if the nodule is solid or if there are coarse calcifications within the nodule.

In cases of multiple thyroid nodules, the risk of an individual nodule being cancerous is decreased but the prevalence of thyroid cancer does not differ between patients with a solitary nodule and those with multiple nodules. Recent literature indicates that patients with multiple thyroid nodules have the same risk of developing thyroid malignancy as patients with solitary thyroid nodules. Therefore in the presence of multiple nodules, FNA is indicated. However a meticulous search for suspicious ultrasound features should be made in order to identify the more suspicious nodules as sampling of all nodules is frequently not practical.

US features that are suggestive of malignancy include microcalcifications (Fig 1), marked hypoechogenicity (Fig 2), an irregular or microlobulated margin (Fig 3), a longitudinal dimension larger than the transverse dimension (Fig 4), high intrinsic vascularity (Fig 5), direct tumor invasion of adjacent soft tissue (Fig 6), and metastasis to one or more lymph nodes (fig 7).

In cases with multiple thyroid nodules, US characteristics are more useful than nodule size for identifying nodules that are likely to be malignant. If only the dominant or largest nodule is aspirated, a thyroid cancer may be missed (Fig 8 a, b). Diagnostic US therefore should be performed to characterize all thyroid nodules prior to considering which one(s) to biopsy.

**Figure 1.** Transverse ultrasound scan through the right thyroid lobe and isthmus showing multiple microcalcifications (arrows) in an ill-defined hypoechoic lesion.

**Figure 2.** Transverse scan through at left thyroid lobe lesion (arrow) that shows marked hypoechogenicity.

**Figure 3. (a)** Transverse scan through the left thyroid lobe showing a hypoechoic lesion with irregular microlobulated margins (arrowheads) and (b) longitudinal scan through the left thyroid lobe showing a moderately echogenic lesion with one ill-defined margin (arrowheads).
Diffuse Thyroid Lesions

Among patients with autoimmune diseases such as Hashimoto thyroiditis, the rate of thyroid malignancy is similar to that among patients with a non-symptomatic thyroid gland. In cases in which Hashimoto thyroiditis manifests as a nodular lesion mimicking a thyroid neoplasm, FNA must be performed to rule out lymphoma and papillary carcinoma, either of which may coexist with Hashimoto thyroiditis (Fig 9 a, b). FNA is also required in cases of diffuse rapid enlargement of the thyroid gland, especially in patients older than 50 years, to rule out anaplastic carcinoma, metastasis, and lymphoma (Fig 10 a, b).

High Risk of Thyroid Cancer

The threshold for biopsy of a thyroid nodule in a patient with one or more risk factors for thyroid cancer is lower than that for biopsy in a patient without such risk factors. Risk factors for thyroid cancer include a family history of thyroid cancer, a history of head and neck irradiation, male gender, age of less than 30 years or more than 60 years, and a previous diagnosis of type 2 multiple endocrine neoplasia.

Procedure for Performing an US-Guided Thyroid FNA

Prior to performing thyroid FNA, the reasons for performing the procedure should be explained to the patient. These are (1) to reach a diagnosis and (2) possibly avoid surgery. The procedure for performing a thyroid FNA must be explained and informed consent obtained from the patient.

One should ask about known coagulation disorders and whether the patient is taking anticoagulation treatment; if no history of coagulation disorder or anticoagulation medication exists, it is not necessary to perform coagulation studies prior to FNA. If core biopsy is contemplated, coagulation studies are best performed prior to the biopsy.

Significant complications are rare. Most frequent (but also rare) complications are subcapsular haematomas (Fig 11). Even rarer is extensive extracapsular bleeding into the neck. Both complications are treated conservatively.

At the start of the procedure, the patient is placed in the supine position with a pillow under the shoulders to improve neck extension. The skin is cleansed with chlorhexidine solution, which is also used as the US medium (replacing US gel). Local anaesthetic is administered to skin and subcutaneous tissues with 1-2mL 1% lidocaine hydrochloride solution.

Initial scanning in the horizontal plane is performed to locate the lesion and evaluation with Colour Doppler Ultrasound identifies the location of large blood vessels that need to be avoided to minimize the likelihood of blood contamination of the specimen. The patient is instructed not to swallow or speak while the needle is in the thyroid gland.

The probe is placed in the transverse plane with the needle/syringe parallel to the plane of the probe with a medio-lateral or latero-medial approach (Fig 12a). Having the needle parallel to the plane of the beam improves visualisation of the needle tip (Fig 12b).

A 24-gauge needle is inserted into the solid portion of the nodule under US visualisation and when the needle tip is in position, it is moved vigorously in and out while being rotated to dislodge as much tissue as possible from the nodule into the needle bore. This is ideally performed until a small amount of tissue is seen in the hub of the needle. Aspiration may or may not be

Figure 4. Transverse scan through the left thyroid lobe showing a hypoechoic lesion with a height measurement (arrows) greater than the width measurement.

Figure 5. Longitudinal scan through a left thyroid lobe lesion showing marked intrinsic hypervascularity (arrows) on Colour Doppler imaging.

Figure 6. Transverse scan through the right thyroid lobe showing a hypoechoic lesion (between calipers) with direct invasion (arrowheads) of the adjacent sternohyoid muscle (SHM).

Figure 7. Longitudinal scan through an enlarged right carotid lymph node (arrows) that also shows central necrosis (*).

Figure 8 (a) & (b). Sagittal scan through the left thyroid lobe showing the clinically palpable thyroid mass as a 2.5-cm well-circumscribed isoechoic nodule (*) in a), a finding suggestive of a benign nodule. Superior to the said nodule however, was an 0.8cm non-palpable hypoechoic mass with a height exceeding its width (arrow in b). FNA confirmed papillary carcinoma in the non-palpable mass and adenomatous hyperplasia in the palpable mass.

Figure 9. A rapidly growing mass was seen in the left thyroid lobe in a man with chronic Hashimoto thyroiditis. (a) Transverse US scan shows a diffusely enlarged and heterogeneously hypoechoic thyroid gland. (b) Coronal PET-18FDG scan shows increased uptake in the left thyroid lobe (arrow). FNA biopsy showed findings characteristic of diffuse large B-cell lymphoma.
performed during the to-and-fro movement, but is best avoided in very vascular lesions as it is likely to cause specimen contamination with blood.

During the procedure, the needle tip should be placed into different parts of the nodule avoiding blood vessels; this will improve sample quality and reduces the sample inadequacy rate. Aspiration should not be performed while the needle is withdrawn.

The procedure may be repeated especially if the sample obtained appears bloody.

After the procedure, adhesive plaster is applied, and the patient should be instructed to manually compress the skin entry site for a minimum of 30 minutes. The patient should be instructed to contact hospital staff or visit the emergency room if neck swelling occurs on the way home or at home.

If a lesion contains both cystic and solid components, the solid component should be sampled (Fig 13). If the lesion contains a large fluid component, this is best to aspirate the fluid first and then perform a FNA on the remaining solid component (Fig 14).

A repeat FNA biopsy should be considered if there is discordance between the findings at imaging and those at cytologic analysis (Fig 15), a growing mass, a recurrent cyst, or an inadequate FNA sample. At least 3 months should be allowed to elapse after the initial FNA biopsy. The 3-month time lag before repeat FNA is recommended to avoid problems in cytologic interpretation that may be posed by reparative cellular atypia (e.g. marked nuclear chromatin clearing, grooves, or inclusions that may be mistaken for evidence of papillary carcinoma).

For follow-up of thyroid nodules with an initial benign cytologic diagnosis and without clinical or radiologic findings suggestive of malignancy, imaging surveillance is recommended rather than repeat US-guided FNA biopsy. If nodule size is stable, the interval before the next follow-up clinical examination or US evaluation may be prolonged.

CONCLUSION

US-guided FNA is useful for the diagnosis of palpable or non-palpable thyroid nodules. The routine use of this biopsy procedure has caused profound changes in the management of thyroid nodules. FNA biopsy allows prompt identification and treatment of thyroid malignancies and avoidance of unnecessary surgery in patients with benign lesions, thereby improving the overall quality of life for patients with thyroid nodules. Furthermore, FNA helps guide treatment and helps reduce the cost of care.

The adequacy of cytologic specimens depends on several factors, including the nodule characteristics and the FNA technique used. As the person performing FNA gains experience and as lesion targeting and localization with US become more accurate, the rate of sample inadequacy should decrease.

To optimize the usefulness of FNA, every centre should strive to attain and maintain a high level of expertise in all aspects of aspiration and interpretation and, toward that end, should establish clinical guidelines tailored to its patient population and FNA biopsy results.
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COMPOSITION: Natrixam 1.5 mg / 5 mg: indapamide 1.5 mg – amlodipine 5 mg.

INDICATIONS: Substitution therapy for treatment of essential hypertension in patients already controlled with indapamide and amlodipine given concurrently at the same dose level. DOSAGE AND ADMINISTRATION: One tablet per day as single dose, preferably to be taken in the morning. Natrixam is not suitable for initiation therapy. If a change in the posology is required, titration should be done with the individual components. Children and adolescents: efficacy and safety not established. Severe renal impairment (creatinine clearance < 30 mL/min): contraindicated. Older people: to be treated according to renal function. Hepatic impairment: contraindicated in severe hepatic impairment; in mild to moderate hepatic impairment, treatment start with the lowest dose. CONTRAINDICATIONS: Hypersensitivity to the active substances, to other sulphonamides, to dihydropyridine derivatives or to any of the excipients. Severe renal failure (creatinine clearance below 30 mL/min). Hepatic encephalopathy or severe impairment of liver function. Hyponatraemia. Lactation. Severe hypotension. Shock (including cardiogenic shock). Obstruction of the outflow tract of the left ventricle (e.g., high-grade aortic stenosis). Haemodynamically unstable heart failure after acute myocardial infarction. WARNINGS: Special warnings: Hepatic encephalopathy: stop treatment. Phototoxicity: stop treatment. Precautions for use: Hypertensive crisis: efficacy not established. Water and electrolyte balance: Sodium and potassium levels: to be measured before and during treatment. Hyponatraemia: high risk for elderly, malnourished and/or polymedicated, chronic patients with oedema and ascites, patients with coronary artery disease, cardiac failure and long QT interval: first measurement of plasma potassium one week after start of treatment and more frequent monitoring required. Calcium levels: stop treatment before investigating parathyroid function. Blood glucose: to be monitored in diabetic patients especially in case of hypokalaemia. Cardiac failure: use with caution. Renal function: pre-existing renal insufficiency may worsen at start of the treatment due to reduction in glomerular filtration; amlodipine not dialysable. Hyperuricaemia: increased tendency of gout attacks. Hepatic function: caution to be exercised in mild to moderate hepatic impairment, start at the lowest dose. Older people: to be treated according to renal function. Galactose intolerance/Lapactose deficiency/glucose-galactose malabsorption: should not be taken. INTERACTION(S): Not recommended: lithium, dantrolene, grapefruit or grapefruit juice. Precautions for use: to be taken into consideration: potassium-sparing diuretics, metformin, enalapril, furosemide, omeprazole, iron preparations, ciclosporine, tacrolimus, corticosteroids, tetracoside (systemic route), other medicinal products with antihypertensive properties. FERTILITY / PREGNANCY / BREASTFEEDING: Not recommended during pregnancy. CONTRAINDICATED during lactation. DRIVE & USE MACHINES: May be impaired due to the decrease in blood pressure or in case of dizziness, headache, fatigue or oedema. UNDESIRABLE EFFECTS: Common: hypokalaemia, somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, maculopapular rashes, ankle swelling, oedema, fatigue. Uncommon: insomnia, mood changes (including anxiety), depression, tremor, dyspepsia, syncope, hypotension, paresthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dizziness, altered bowel habits (including diarrhea and constipation), dry mouth, constipation, purpura, alopecia, skin discoloration, hyperhidrosis, pruritus, rash, alopecia, arthralgia, myalgia, muscle cramps, back pain, twitching, disorders of cardiac conduction, nocturia, increased urinary frequency, impotence, depression, fatigue, headache, palpitations, flushing, abdominal pain, nausea, maculopapular rashes, ankle swelling, oedema, fatigue. UNDESIRABLE EFFECTS: Common: hypokalaemia, somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, maculopapular rashes, ankle swelling, oedema, fatigue. 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