Keeping updated
Maria Cordina 3

Lung health and outdoor air pollution - a review
Joseph Cacciottolo 4

Treatment of lower urinary tract infections in an era of increased antimicrobial resistance
Ian Mifsud 8

Metformin revisited – an ‘old’ drug with a ‘new’ beginning
Sandro Vella 12

Medicinal product quality defects reporting
Karl De Marco 16

Asian mosquito tiger: a nuisance, threat or both?
Tanya Melillo 17

The pill in the future - pharmacological contraception in science fiction
Victor Grech, Clare Thake-Vassallo, Ivan Callus 21

Hypopituitarism: a review on the diagnosis and management of central hypoadrenalism and hypothyroidism
Mark Gruppetta 25

The extemporaneous compounding of paediatric medicines at Mater Dei Hospital
Antonella Aquilina 28
Presentation and composition:
Micronized, purified flavonoid fraction 500 mg: diosmin 450 mg; hesperidin 50 mg. Therapeutic properties:
Vascular protector and venu-tonic. Daflon 500 mg acts on the return vascular system: it reduces venous disten-
sibility and venous stasis; in the microcircula-
tion, it normalizes capillary permeability and rein-
forces capillary resistance. Pharmacokinetics: Microniza-
tion of Daflon 500 mg increases its gastrointestinal absorp-
tion compared with nonmicronized diosmin (urinary excretion 57.9% vs. 32.7%). Therapeutic indications: Treatment of organic and idi-
opathic chronic venous insufficiency of the lower limbs with the following symptoms: heavy legs; pain; nocturnal cramps. Treatment of hemorrhoids and acute hemorrhoidal attacks. Side effects: Some cases of minor gastrointestinal and autonomic disorders have been reported, but these never required cessation of treatment. Drug Interactions: None. Precautions: Pregnancy: experimental studies in animals have not demonstrated any teratogenic effects, and no harmful effects have been reported in man to date. Lac-
tation: in the absence of data concerning the diffusion into breast milk, breast-feeding is not rec-
commended during treatment. Contraindications: None. Dosage and administration: In venous dis-
 ease: 2 tablets daily. In acute hemorrhoidal attacks: the dosage can be increased to up to 6 tablets daily. As prescribing information may vary from country to country, please refer to the complete data sheet supplied in your country.

Keeping updated

Maria Cordina BPharm (Hons) (Melit) PhD (QUB)
Editor
Email: president@mcppnet.org

In today’s exceptionally fast-paced world, one of the main laments that health care professionals have is that they have difficulty finding time to keep up with the barrage of new knowledge available. It is indeed because there is so much new information out there that keeping updated is essential since we are bound to make the best decisions for the optimal health outcomes of our patients.

The Malta College of Pharmacy Practice, which is an autonomous institution and whose council is made up of members who voluntarily dedicate their time to supporting professional development, offers a service to health care professionals by addressing issues of particular relevance to the local situation.

This issue of the Journal is evidence of this. Our opening paper by Cacciottolo addresses an issue of national concern which is very topical, namely lung health and outdoor air pollution. It is an issue in which we need to be well versed in order to advise our patients. Antibiotic resistance has been addressed on numerous occasions. However this is a subject which requires repeated attention. Mifsud presents a very interesting paper with a very practical approach based on years of experience. Metformin is a drug that has been around for quite some time yet is being prescribed and dispensed for indications other than that for which it was originally licensed. The present paper gives us a comprehensive overview of this.

We are all familiar with the Asian Tiger Mosquito. Melillo traces its entry into Malta, highlights the threat that it poses and provided information on avoidance and management which we should do well to heed. Victor Grech and colleagues once again transport us into the realm of science fiction this time addressing pharmacological contraception in science fiction - a very enjoyable read!

Grupetta presents a highly evidence based review of hypopituitarism. This paper provides solid practice information on diagnosis and management.

Our last contribution by Aquilina provides a showcase of the essential services of extemporaneous compounding that is provided at Mater Dei Hospital. This service provides the medication in the required formulation to both children and adults whose access to medication would otherwise be hampered.

I would like to take this opportunity to thank not only our authors for their excellent contributions but also our list of anonymous reviewers whose service ensures the quality of our journal.
Lung health and outdoor air pollution - a review

Joseph Cacciottolo MD, DSc, FRCP
Environmental Management and Planning Division
Institute of Earth Systems, University of Malta
Email: joseph.cacciottolo@um.edu.mt

Educational aims
- To review the relationship between air pollution and lung health
- To increase awareness of the hazards of air pollution, particularly on lung health
- To discuss the impact of air pollution on three common lung diseases
- To provide a list of references as a base for further reading

Key words
Lung health, pollution, particulate matter, ozone

Abstract
The lung is one of the interfaces between the body and the exterior environment. The maintenance of lung health depends on several factors, among them one’s genetic makeup, the environment, socioeconomic circumstances and natural ageing. Persons respond differently and uniquely to environmental circumstances, and this often makes the exposure-disease relationship difficult to assess.

Air pollution most commonly causes irritation of the respiratory tract, resulting in discomfort, cough and breathlessness. It is also a major factor in exacerbating existing respiratory diseases and may also be the potential cause of lung disorders. The relationships between air pollution, increased incidence of respiratory conditions and severity of airway diseases are well recognized and robustly supported by epidemiological, toxicological and clinical studies.

Outdoor air pollution is caused by aerosols and gases in amounts that may affect health, and the major contaminants in urban environments are a wide variety of particulate matter and ozone.

Common specific lung disorders are known to be linked with urban air pollution: asthma and chronic obstructive pulmonary disease are frequently exacerbated following exposure to contaminated air, while with regard to lung cancer, the relationship is a causal one. Air pollution also poses a significant public health problem and concomitant approaches are necessary in order to improve air quality and to lessen the negative impact of airborne pollution on lung health. Control and mitigation of this problem requires effective health education, and sound preventive strategies through a combined community, administrative and political approach.

Introduction
The human body interfaces with the outside milieu through skin, respiratory tract and the alimentary canal. The lungs are the most sensitive and delicate interface with the exterior environment; as such they react rapidly to irritation and are susceptible to harm, causing long term impairment and possible disability. The effects of interaction of the lungs with the environment depend on a wide variety of extrinsic and intrinsic factors, among them such personal factors as one’s genetic makeup, socioeconomic circumstances and ageing itself.

A spectrum of personal and general adverse environmental factors, as well as certain occupations and working conditions influence lung health and may possibly lead to the development of pulmonary disorders. Persons respond differently and uniquely to identical environmental circumstances and an accurate assessment of risk may be confounded by genetic predisposition and interaction. The exposure-disease relationship may not be easy to identify and assess, not only because of the usually long-term and possibly variable exposure, but also because of the difficulty to separate the impact of comorbid conditions in the same individual.

A moderately active adult inhales about 20m$^3$ of air daily, of varying quality, and weighing more than 24kg. The respiratory tract itself is protected by various mechanisms. The nose, acting as a coarse pre-filter, traps relatively large particles (>5μm) and the epithelial lining acts as a filtration mechanism to trap smaller (>3-5μm) inhaled particles which are then moved out of the airways by the mucociliary process. The layer of mucus within the respiratory bronchioles traps very small particles and the alveolar fluid also affords a medium where particles are engulfed and destroyed by macrophages. The coughing and sneezing reflexes both act as protective mechanisms, as well as efficient systems for rapidly cleansing the respiratory tract from relatively large particulate matter, however they are ineffective with regard to gaseous air pollutants.

In clinical terms, exposure to polluted air impacts negatively on lung health by causing respiratory symptoms, principally coughing, breathlessness and chest tightness. It is also a major factor in exacerbating existing respiratory diseases and may also be the potential cause of lung disorders. Repeated
Key points

- Healthy lungs have extremely efficient protective mechanisms.
- Lung function and structure may be compromised by repeated exposure to contaminated air.
- Ambient air in urban areas with heavy traffic flow may be polluted by particulate matter and ozone.
- Exposures to both particulate matter and ozone have a negative impact on lung health, varying from discomfort to serious disability.
- Air pollution frequently causes exacerbation and deterioration of both asthma and chronic obstructive pulmonary disease, and may be a potential cause for lung cancer.
- Control of airborne pollution requires effective health education and preventive strategies, through combined community, administrative and political approaches.

Exposure may lead to decline in lung function, increased susceptibility to chest infections, and permanent damage leading to premature death. Children, the elderly and persons with pre-existing cardiovascular disease, respiratory problems and diabetes mellitus appear to be at a greater risk to develop complications related to air pollution.1, 2

The urban environment and outdoor air pollution

Outdoor air pollution is caused by solids, liquids, or gases in amounts that may adversely affect health, and the environment itself. In its milder form, air pollution often interferes with the comfortable enjoyment of life and property and most commonly causes irritation of the respiratory tract and the eye.

For many centuries, airborne dust, smoke and obnoxious fumes have been known to be sources of discomfort and illness. In the United Kingdom, the Industrial Revolution, beginning around 1730, was fueled primarily by the use of coal, and furnaces were often in close proximity to densely populated areas. Industrial use of coal, together with its use as a source of domestic heating, caused very high levels of air pollution, which were made worse when the weather was foggy.

The first well-documented widespread occurrence of airborne pollution happened in December 1952 in the Meuse valley, Belgium. Then, a lethal combination of industrial air pollution and thermal inversion, trapping fog over the heavily populated area of the narrow valley caused ‘several thousand cases of acute pulmonary attacks’ and 60 deaths. The Commission investigating this disaster was of the opinion that sulphur dioxide or its oxidation products were the cause for this disaster, however later studies suggest that the probable cause was acute intoxication by gaseous fluorine compounds.3

In December 1952, the London smog episode was the result of pollution from domestic coal use and industrial furnaces, together with adverse atmospheric conditions. Over a short period, tons of particulate matter filled the air, eventually turning the sky almost black, stinging eyes and causing acute respiratory symptoms. Visibility was so much reduced, that traffic flow was practically brought to a standstill. This episode was the immediate cause of around 4000 deaths, together with an indeterminate number due to delayed effects. Most of those who succumbed were elderly or already infirm.4

The damage that urban air pollution causes to health is multifactorial and usually follows exposure to multiple contaminants present concurrently. With regard to lung disorders, the relationship between air pollution, increased incidence of respiratory conditions and severity of airway diseases is well supported by epidemiological, toxicological and clinical studies.5

In European Union states, quite significant segments of urban dwellers are exposed to unacceptably high levels of airborne pollutants (Figure 1).6 In a general European context, aerosol particles and to a lesser extent ozone, are the pollutants that mostly compromise lung and cardiovascular health.7 There are no established safe levels for exposure to either particulate matter or ozone and they pose a risk to health even at concentrations below current guidelines for air quality.8

Particulate matter

Atmospheric particulate matter (PM) refers to a wide range and mix of particles of varying sizes and chemical composition: they may derive either from natural sources, or as a result of human activities and industry. Suspended dusts, pollen and sea-spray are the commoner natural PM, while combustion of fossil fuels in vehicles and power-generating plants are the source of most of ‘man-made’ or anthropogenic PM. The finer particles are classified as having an aerodynamic diameter of 2.5 μm or less (PM<sub>2.5</sub>).

The effects of chronic exposure of airborne PM on lung function and overall health are complex and to a very large extent beyond control of individuals. The negative effect of particulate air pollution on respiratory well-being is independent and consistent among different communities. Such a causal relationship holds for acute respiratory infections in children, obstructive pulmonary disorders, lung cancer, and for mortality from cardiopulmonary problems.9 Children are especially vulnerable, as there is clear association between decreased growth in lung function and exposure to airborne PM. This association is consistent across communities that are ethnically different and geographically separate.10, 11

In the European Union, the average life expectancy is 8.6 months lower due to exposure to anthropogenic PM<sub>2.5</sub>, while mortality rates due to air contamination are higher by 15–20% in cities with levels of pollution that exceed those observed in cities with relatively cleaner air.12

Ozone

Ozone (O<sub>3</sub>) is formed as a result of chemical reactions involving daylight UV rays, following emission of precursor gases resulting principally from fuel combustion. Ozone is a powerful oxidizing agent that not only irritates the respiratory tract, but also reduces lung function. High ambient ozone concentrations are also clearly and independently associated with a significant risk of death from respiratory causes: the evidence is particularly compelling when considering results deriving from a large-scale study over an 18-year period and involving over 448000 subjects.13

Both acute and long-term exposures to ozone are associated with increased morbidity and mortality and the absolute effect of the gas on mortality is higher among older adults and during warmer weather.14 Children, persons who work or exercise outdoors, persons with pre-existing respiratory disorders and persons suffering from cardiovascular conditions are especially vulnerable to damage caused by breathing ozone.15, 16, 17
Specific lung diseases and air pollution

Asthma

Air pollution is a recognized cause for destabilizing well-controlled asthma, and for exacerbating this inflammatory condition. This is especially so among children, who are more susceptible to air pollution than adults, even when levels of pollution are relatively low and within ‘acceptable’ ranges.\(^4,15\)

Hospital admissions because of acute asthma may be due to a variety of provoking factors, among them exposure to air polluted with a wide range of PM. The causal relationship between hospitalization rates for asthma and ambient air contamination is both consistent and widespread across all age-groups and among different communities. Exposure to traffic-related air pollution over a long period also increases the risk of hospitalization because of unstable asthma among older persons, however children are probably at an even higher risk.\(^20\)

There is a clear relationship between ambient ozone concentrations and increased symptoms of asthma. Persons with asthma might be more sensitive to ozone, and may therefore develop respiratory symptoms either at lower concentrations of the gas, or with greater magnitude than persons who do not have this condition. Admissions to hospital for control of asthma have been found to be more frequent on days following exposure to raised ambient ozone levels, while minor adverse respiratory symptoms and decreased lung function also persist for several days. Predictably, the effects tend to be more pronounced during the warm season.\(^21\)

While the role of air pollution as a trigger factor for exacerbating pre-existing asthma is well documented, there is no evidence that it may actually cause asthma, and any role that it may possibly play in initiating it, is yet undetermined.

Cancer of the lung

Several large epidemiological studies have documented a link between air pollution and lung cancer in non-smokers. Persons who live in areas with high ambient air pollution are more likely to develop lung cancer than those who live in areas with cleaner air. Recent evidence shows a clear relationship between concentrations of ambient PM\(_{2.5}\) over a 26-year period and mortality from lung cancer among persons who never smoked.\(^22\)

The relationship between ambient diesel exhaust specifically and lung cancer is less clear, and most of the evidence derived from population studies is not considered adequate to prove the diesel-lung cancer hypothesis.\(^23\) However, with regard to occupational exposure to diesel fumes, a large multicentre study showed a consistent association between cumulative diesel motor exhaust and increased risk of lung cancer: this association was well-adjusted for bias and confounding factors.\(^24\)

Chronic obstructive pulmonary disease

The role of air pollution as a direct cause of chronic obstructive pulmonary disease (COPD) has been explored by several studies, however any possible causal relationship is still unclear.\(^25\) A large Danish cohort study suggests that exposure to high levels of air pollution in the long-term may itself contribute to the development of COPD. Persons who were exposed for more than 25 years ran a 7\% higher risk, while the impact of air pollution on persons who also had asthma and diabetes was greater.\(^26\)

The role of air pollution as a complicating factor in COPD as a pre-existing lung condition is however not in any doubt, and the relationship has been well-defined.\(^27\) There is evidence to suggest that some patients are more susceptible than others to this environmental trigger and react with increasing symptoms and acute exacerbations: this has a cumulative effect on emergency department visits, hospital admissions and even mortality.\(^28,29\)

Conclusion

Air pollution poses clear and multiple health hazards to individuals; however it is also a
significant public health problem. Several concurrent approaches are necessary in order to improve air quality and lessen the negative impact of airborne pollution on lung health. Control of this problem requires effective health education, and sound preventive strategies through a combined community, administrative and political approach.

References

Treatment of lower urinary tract infections in an era of increased antimicrobial resistance

Ian Mifsud  B.Pharm (Hons), MSc. Env. Mgt . PG Cert Clinical Pharmacy
Senior Pharmacist – Rehabilitation Hospital Karen Grech
Email: ian.a.mifsud@gov.mt

Educational aims

- To provide an overview of the OTC preparations available for the prophylaxis and treatment of acute uncomplicated cystitis
- To highlight the reasons as to why nitrofurantoin and co-amoxiclav are the antimicrobials of choice in the empirical treatment of lower urinary tract infections
- To illustrate the limitations of nitrofurantoin treatment
- To demonstrate why fluoroquinolones are not the ideal choice in the treatment of lower urinary tract infections

Key words
lower urinary tract infection, bacteruria, nitrofurantoin, co-amoxiclav, ESBL positive pathogens

Abstract
The antibiotic arsenal for treatment of lower urinary tract infection is becoming increasingly limited. Co-trimoxazole has been lost in the empirical treatment of urinary tract infection. Other agents particularly fluoroquinolones are becoming ineffective. Locally, the empirical treatment of such infection focuses on two antibiotics – nitrofurantoin and co-amoxiclav. Carbapenems are increasingly being prescribed due to the emergence of ESBL (extended spectrum beta lactamase) positive pathogens.
Other OTC preparations that are commonly associated with cystitis are cranberry products. Evidence to support the use of these products for treatment of cystitis is lacking. The recommendation of such products should be restricted to the prevention of such infections in premenopausal women with a history of recurrent infections. Evidence is also lacking for the effectiveness of cranberry products for their prophylactic effect in the elderly and catheterised patients. The optimal dose has not been established but giving a minimum of 36 mg/day proanthocyanidin A (the active compound), is favoured. It might be appropriate to recommend cranberry capsules as an alternative to the juice as a solid dosage form may be more convenient to the patient. The use of cranberry products is not generally recommended in patients on warfarin as interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice. The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching the interactions resulting in an increase the INR can occur.

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazol...
should be considered a risk for infection with ESBL-producing pathogens. An increasing proportion of patients would have acquired such organisms before hospital admission, reflecting the regrettable over-prescribing of antibiotics in the community. Treatment with co-amoxiclav in such cases is likely to fail and these pathogens could also have acquired resistant to quinolones and aminoglycosides. Carbapenems are increasing becoming the only practical alternative treatment available locally. Ertaopenem has an advantage over other carbapenems in that it is given on a once daily basis; it also has a narrower spectrum than other carbapenems, it does not cover Pseudomonas and Acinetobacter species. In Europe it is used off-licence for urinary tract infection, however it is registered for this indication in the US.\textsuperscript{17,18} Carbapenems are not available as oral formulations. Patients requiring such antimicrobials have to undergo IV therapy, an invasive procedure which in its own characteristics include the convenience of a single-dose regimen for acute uncomplicated cystitis, very good activity against a range of multi-drug resistant organisms including resistant Enterobacteriaceae and minimal propensity to induce resistance.\textsuperscript{23}

**Conclusion**

Although antimicrobial resistance is an inevitable natural phenomenon, our professional behaviour is crucial in determining the rate and extent to which pathogens develop resistance. The emergence of ESBL-positive pathogens is challenging our practices and constraining the health care professional to rely increasingly on second-line agents such as carbapenems. Clinical judgement in the choice of antibiotics, when indicated, is pivotal in ensuring therapeutic success while minimising the negative consequences of therapy.

### References


Metformin revisited – an ‘old’ drug with a ‘new’ beginning

Sandro Vella  MD, MSc (Roehampton), MRCP (UK)
Consultant Physician, Diabetologist and Endocrinologist, Mater Dei Hospital, Malta
Visiting Assistant Lecturer, Department of Medicine, University of Malta Medical School, Malta
Email: svell11@um.edu.mt

Educational aims
- To highlight the mechanism of action of metformin
- To identify metformin’s role as an oral glucose lowering agent with favourable pleiotropic effects on cardiovascular outcomes.
- To discuss potential new roles for this drug in type 1 diabetes, as well as in the fields of obstetrics and gynaecology, nephrology, hepatology and oncology
- To discuss the cost-effectiveness and safety of metformin pharmacotherapy, with particular reference to established prescription guidelines

Key words
metformin - diabetes - cardiovascular - pregnancy - cancer

Abstract
Acting as a weak activator of AMP-activated protein kinase, metformin has established itself as a cost-effective first line agent in the management of type 2 diabetes (T2DM). Besides slowing progression to this condition, its use is associated with improved survival and lower rates of myocardial infarction in T2DM, as well as benefits in stable patients with heart failure. Metformin may play a valuable role in early nephropathy, non-alcoholic fatty liver disease and as adjunct therapy in type 1 diabetes. It is increasingly advocated in patients with gestational diabetes and polycystic ovary syndrome. Its role as an anti-cancer agent remains controversial.

Introduction
Derived from the French Lilac plant Galega Officinalis, metformin (N,N-dimethylimidodicarbonimidic diamide) has widely established itself as a safe as well as clinically effective oral glucose lowering agents. Used for 55 years in the United Kingdom (although for only the last eighteen years or so in the United States),1,2 this drug has been virtually uniformly advocated as a first line agent in the management of type 2 diabetes (T2DM) by local, national and international treatment guidelines. This review will seek to address the evidence underpinning its widespread use in T2DM patients, as well as potentially exciting new roles in type 1 diabetes (T1DM) and beyond.

Pharmacology
Perhaps surprisingly, the mechanism of action of metformin had remained obscure until relatively recently. This biguanide is now recognised as a weak activator of an important, ubiquitous, phylogenetically conserved serine/threonine protein kinase called AMP-activated protein kinase (AMPK).3 Acting as a gauge of systemic and cellular energy status, AMPK is activated by an increase in intracellular adenosine monophosphate / adenosine-5’-triphosphate (AMP/ATP) ratio, and serves to protect cellular functions under energy restricted conditions by switching from an anabolic to a catabolic state. The latter is achieved through phosphorylation of key metabolic enzymes and transcription factors/co-activators modulating gene expression.4 Following hepatic uptake through the organic cationic transporter 1 (OCT1),5 metformin exerts additional specific and AMPK independent inhibition of complex 1 of the respiratory chain,6 leading to an acute increase life expectancy by 0.2 year and reduce cumulative incidence of coronary artery disease, stroke, amputation, end-stage renal

Cost effectiveness
Data from the Diabetes Prevention Programme (DPP) suggests that metformin is cost-effective in individuals below the age of 65. Intervening with this drug over a lifetime is expected to prevent diabetes in 8%, delay onset of T2DM by 3.4 years, increase life expectancy by 0.2 year and reduce cumulative incidence of coronary artery disease, stroke, amputation, end-stage renal

Abbreviations
AMP adenosine monophosphate
AMPK AMP-activated protein kinase
ATP adenosine-5’-triphosphate
BMI body mass index
DARTS Diabetes and Audit in Research Tayside Scotland
DPP Diabetes Prevention Programme
eGFR estimated glomerular filtration rate
HbA1c glycosylated haemoglobin
HF heart failure
HOME Hyperinsulinaemia: the Outcome of its Metabolic Effects
IGT impaired glucose tolerance
MIG Metformin in Gestational Diabetes
mTOR mammalian Target Of Rapamycin
NAFLD non-alcoholic fatty liver disease
NASH non-alcoholic steatohepatosis
OCT1 organic cationic transporter 1
OR Odds ratio
PRESTO Prevention of Restenosis with Tranilast and its Outcomes
QALY quality-adjusted life year
RR relative risk
T1DM type 1 diabetes mellitus
T2DM type 2 diabetes mellitus
UKPDS United Kingdom Prospective Diabetes Study

References
Metformin in pre-diabetes and obesity

The DPP reported that metformin prescribed at a dose of 850mg twice daily decreased progression from impaired glucose tolerance (IGT) to diabetes by 31% over three years. Benefits were greater in patients with a body mass index (BMI) exceeding 35 kg/m$^2$ (mean reduction of 53%) compared with those with a BMI ranging between 22 and 30 kg/m$^2$ (mean reduction 3%). Metformin therapy was as effective as lifestyle intervention in younger individuals and those with a higher BMI. These effects appear to be durable, as demonstrated in the ten-year follow-up data of the DPP, resulting in comparable diabetes incidence rates between metformin-treated individuals and those adopting intensive lifestyle interventions.

Metformin in type 2 diabetes

The United Kingdom Prospective Diabetes Study (UKPDS) was the first major study to suggest a cardiovascular benefit in T2DM. Randomising 1704 overweight T2DM patients to initial treatment with metformin (342 patients), sulphonylurea or insulin (951 patients), or dietary measures alone (411 patients), metformin therapy (but not sulphonylurea/insulin therapy) was associated with a 32% lower incidence of any diabetes related endpoint (micro- and macrovascular) compared with sulphonylurea therapy after five years of follow-up. Use of metformin in higher risk T2DM patients with heart failure was associated with a significant reduction in all-cause hospitalization at one year (OR 0.85 [95% CI 0.76, 0.95]; p = 0.004) compared with non-sensitisers (sulphonylureas, non-sulphonylurea insulin secretagogues, alpha glucosidase inhibitors or insulin) in a systematic review and meta-analysis of eight controlled studies. In a similar vein, Eurich et al reported that metformin monotherapy in this setting translates into a lower risk of mortality (HR 0.70 [95% CI 0.54, 0.91]) as well as a lower risk of the composite outcome of deaths or hospitalization (HR 0.83 [95% CI 0.70, 0.99]) compared to sulphonylurea therapy. In a retrospective study of 8063 insulin-treated patients with no prior history of heart failure (HF), Nichols et al, reported that metformin therapy reduced the congestive HF rate ratio to 0.63 (95% CI 0.37, 1.07), a development which is particularly desirable given that initial insulin therapy was associated with a higher incidence of HF.

Is there a role for adjunct metformin in type 1 diabetes?

An ever increasing proportion of T1DM patients harbour a phenotypic and metabolic profile typical of patients with the metabolic syndrome. Indeed insulin resistance has been shown to accelerate progression to macrovascular and microvascular outcomes in T1DM. These observations generated considerable interest in a potential role for adjunct metformin use in pregnant women with the polycystic ovary syndrome and gestational diabetes. A recently published systematic review of metformin use in pregnant women with the polycystic ovary syndrome reported lower pooled risks of early pregnancy loss (OR 0.32; [95% CI 0.19, 0.55]), gestational diabetes (OR 0.37; [95% CI 0.25, 0.56]), pre-eclampsia (OR 0.53; [95% CI 0.30, 0.95]) and preterm delivery (OR 0.30 [95% CI 0.13, 0.68]). Current guidelines tend to advocate a role for metformin in the management of gestational diabetes. Despite concerns that metformin crosses the placenta, two meta-analyses (one in women prescribed metformin monotherapy, and the other recruiting women using metformin prescribed metformin monotherapy, and the other recruiting women using metformin and/or a sulphonylurea) have not reported an increase in congenital malformations or neonatal deaths. The Metformin in Gestational Diabetes (MIG) trial reported no significant difference in the composite neonatal outcome of neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score < 7, or prematurity, albeit higher rates of preterm births and less weight gain among the 363 patients treated with metformin (±
supplemental insulin) compared to patients randomised to insulin therapy (n = 370). A recently published, albeit smaller (n = 94), trial largely showed that metformin improved glycaemic control (lower mean glucose levels throughout the day), with the added advantage of including studies with ‘immortal time bias’ reported no association between cal techniques which avoided immortal bias’. At least one study employing statistical methods which avoided immortal time bias reported no association between cal techniques which avoided immortal bias’. At least one study employing statistical methods which avoided immortal bias’.

Data from several studies suggests that metformin use is associated with significantly lower incidence rates across multiple cancers. Two meta-analyses, integrating results from several observational and randomised controlled trials, reported relative risks of 0.69 (95% CI 0.61, 0.79) 30 and 0.67 (95% CI 0.53, 0.85) 31 respectively. While impressive, such results should be interpreted with caution, given the inherent limitations of observational studies, and the potential of including studies with ‘immortal time bias’. At least one study employing statistical techniques which avoided immortal time bias reported no association between metformin use and cancer incidence. At a cellular level, the anti-neoplastic action of metformin appear to be mediated by both AMPK-dependent and -independent mechanisms, leading to an inhibition of the cell cycle (through a reduction in cyclin D1 level) and mammalian Target Of Rapamycin (mTOR) signalling, a stimulation of the p53/p21 axis, and a suppression of fatty acid synthesis, angiogenesis, inflammation, hyperinsulinaemia and prevalent insulin growth factors.

Metformin and non-alcoholic fatty liver disease

The majority of patients with T2DM are characterised by non-alcoholic fatty liver disease (NAFLD) and up to 50% may develop non-alcoholic steatohepatosis (NASH), a harbinger of cirrhosis. Metformin prescription in patients with NAFLD may translate into a reduction in plasma aminotransferases, albeit without evidence of improvement in liver histology. 36-38

Metformin and nephropathy

Metformin should be prescribed with caution in individuals with an estimated glomerular filtration rate (eGFR) ranging between 30 and 45 mls/min/1.73m² and is absolutely contraindicated if eGFR <30 mls/min/1.73m². Nonetheless, data from animal models suggest that metformin pharmacotherapy ameliorates tubular injury associated with hyperglycaemia (partly by reducing oxygen consumption and hypoxia-inducible factor-1 expression) as well as reactive oxygen species-mediated lipotoxicity of renal podocytes. Both mechanisms underpin the development of diabetic nephropathy. Additionally, data from murine models suggest that metformin reduces cystic growth in autosomal dominant polycystic kidney disease. Such promising roles remain to be confirmed in clinical studies.

Adverse effects

A Cochrane review has largely dispelled the myth that the benefits of metformin may be offset by an unacceptably high risk of lactic acidosis. Indeed, the authors reported no additional risk of developing this complication in prospective comparative trials or from observational cohort studies, provided metformin is prescribed in the appropriate setting. To this effect, use of this oral glucose lowering agent is not recommended in acute situations associated with hypoxia or a tendency for acidosis (such as sepsis, acute heart failure, cardiogenic shock, respiratory failure) as well as in moderate to severe renal impairment (as outlined earlier). Gastro-intestinal adverse effects (bloating, diarrhoea, abdominal cramps, flatulence) are best avoided if metformin is dosed gradually over a few days to weeks. Tolerability may be improved by switching to an extended release formulation. Vitamin B12 deficiency is a recognised, albeit rare, adverse effect, and should be borne in mind in patients with macrocytic anaemia, peripheral neuropathy and cognitive impairment.

Conclusion - the way forward

Metformin’s pivotal role in the management of T2DM is clearly established, and likely to remain undisputed, at least in the near future. Available evidence suggests that it is safer than initially thought, particularly if prescribed in the right clinical setting. A better understanding of the mechanisms underpinning its diverse actions at a cellular level, particularly in humans, is likely to unravel exciting new roles for this cheap, widely prescribed, biguanide.

References

Medicinal product quality defects reporting

Karl De Marco  B.Pharm (Hons)
Medicines Inspector
Inspectorate and Enforcement Directorate, Medicines Authority
Email: karl.de-marco@gov.mt

Introduction
One of the ways in which the Medicines Authority protects public health is by minimising the risk to patients arising from the distribution of defective medicinal products. It achieves this by managing an assessment and communications system, between suppliers of medicinal products, the regulatory authorities and the users including patients, and when required oversees the removal of the defective medicinal products from the local market.

Holders of a manufacturer’s, importer’s and wholesale dealer’s licence are obliged to report to the Medicines Authority any defect in a medicinal product handled under their authorisation that could result in a recall or abnormal restriction in supply. This includes possibly faulty manufacture, product deterioration, detection of falsified medicines or any other serious quality problems with a product.

Reporting of suspected product quality defects
Reports of suspected defects may also be sent to the authorities by other competent authorities, healthcare professionals and members of the general public.

If a member of the general public has reason to believe that their medicine is not of an acceptable quality, they should, in the first instance, consult with their doctor or pharmacist who may then decide to refer the matter to the Medicines Authority, since the doctor or pharmacist may be in a better position to provide prompt advice and/or reassurance to the patient. However, if it is not possible to speak to a doctor or pharmacist and the patient feels that the matter is urgent, they may contact the Medicines Authority directly.

The role of the Medicines Authority is to provide an assessment and communicate between suppliers of medicinal products, the regulatory authorities and the users. Where a defective medicine is considered to present a risk to public health, the marketing authorisation holder, the manufacturer or wholesale dealer as appropriate, is responsible for recalling the affected batch(es) or, in extreme cases, removing all batches of the product from the market. The Medicines Authority will normally support this action by the issue of a drug alert notification to healthcare professionals.

Product recalls
A product recall is defined as the retrieval from the marketplace of a batch or batches of any medicinal product which is/are the subject of a quality defect.

Product recalls are categorised according to the potential impact of the issue giving rise to the need for a recall, on patients and public health. There are three classes of recalls:

- **Class I recalls** – generally for critical quality defect issues. These are recalls which result from quality defects of medicinal products which are potentially life-threatening or could cause a serious risk to health;
- **Class II recalls** – generally for major quality defect issues. These are recalls due to quality defects which could cause illness or mistreatment but are not Class I;
- **Class III recalls** – generally for minor quality defect issues. These are recalls due to quality defects which are not likely to pose a significant hazard to health but where a recall has been initiated for other reasons.

In the case of Class I and Class II recalls, the Medicines Authority will notify regulators in other countries using the European Rapid Alert System.

Reporting of suspected quality defects
Suspected quality defects can be reported by using the Medicinal Product Defect Reporting Form.

Email: inspectorate.adm@gov.mt
Tel: 00356 2343 9000
medicinesauthority.gov.mt/recallsrapidalerts
Asian Mosquito Tiger: a nuisance, threat or both?

Tanya Melillo  MD MSc(HSM)Dip (HSM)
Consultant in Public Health
Head of Infectious Disease Prevention and Control Unit
Department of Health Promotion and Disease Prevention, Msida
Email: tanya.melillo@gov.mt

Educational aims
• To identify diseases caused by the Asian Mosquito Tiger
• To highlight methods of preventing bites
• To familiarise with ways of minimising mosquito proliferation

Key words
Mosquito, Asian Mosquito Tiger, mosquito borne diseases, Dengue, Chikungunya

Abstract
Asian Mosquito Tiger or Aedes Aldopictus is a mosquito which reached the Maltese Islands towards the end of summer of 2009 and has since spread and proliferated all over Malta and Gozo. It is a nuisance because of its ferocious biting on humans but it can also be a carrier of a number of diseases which may eventually be introduced to our islands causing outbreaks and resulting in a negative impact on our tourism and jeopardizing agricultural development resulting in major economic consequences.

The local situation
In the beginning of September 2009, Dr Paul Gatt, an entomologist, discovered the first Aedes (stregomyia) Aldopictus (Skuse) mosquito (Insecta Diptera Culicidae) in Malta in Mellieha. The presence of this mosquito in Malta added to the total mosquito fauna documented in Malta, which now incorporates all of the subfamily Culicinae. The Aedes Aldopicutus, popularly known as the Asian Mosquito Tiger originated from the forests of Southeast Asia where it was found to breed mainly in rotting tree holes. It was first described by Skuse (1984) in India but has since found it's way all over the world due to its ability to breed successfully in both natural and artificial habitants since it requires only a small amount of water to breed.

A second record of the same species was confirmed by Dr J Buhagiar during the period of September and October of the same year in Marsascala. With two sightings in two different localities of the same mosquito which was previously never documented, the likely conclusion was that this mosquito had finally reached our shores during the summer of 2009.

Both Gatt and Buhagiar postulated that the likely mode of how this mosquito reached our shores was from Italy due to the large amount of sea traffic and close proximity between Italy/Sicily and Malta. On a daily basis, the Malta Freeport acts as a transhipment centre in the Mediterranean where large volumes of containers arrive, in addition there is a daily ferry link between Malta and Sicily, where there is a large flow of vehicles, both private and commercial which cross over between May and November, a large number of cruise liners touring the Mediterranean, stop for a day at Valletta Grand Harbour. The Aedes Aldopictus mosquito inhabits large parts of Italy and Sicily and Italy is in fact the country most infested with this mosquito in all of Europe.

During the winter of 2009/2010, surveillance was conducted to investigate the mosquitoes’ presence and behaviour following its discovery and to see whether the species would survive our winter. Larvae and pupae were found to develop in the ovitraps throughout the winter and a few adult mosquitoes were also observed.

The results obtained from this surveillance confirmed that Malta had the ideal climate conditions during the winter months to allow the mosquito to develop...
both in the egg and larvae stage with the development of the adult form once Spring arrives.\textsuperscript{7}

A steering committee between the Infectious Disease Prevention and Control unit (ICDU) and the Institute of Earth Systems within the University of Malta was set up to develop a strategy for the surveillance of \textit{Aedes Albopictus} in Malta.

The insect’s distribution on the Maltese islands since reaching our shores was monitored throughout a whole year from September 2010 up to September 2011 using ovitraps placed in potential introduction sites and within localities that harbour potential habitats for the species. The Maltese islands were geographically split into 7 regions and ovitraps were placed in each region.

Every week they were checked for eggs and larvae. Scientific data was gathered from the ovitraps placed. The results following a full year monitoring showed that the mosquito proliferated and spread across all of Malta and was found in all regions except Gozo, but was then confirmed in December 2011. These results were also confirmed by reporting of public sightings during the same year whereby the general public was asked to provide information to ICDU if they were bitten by the mosquito and to also provide specimens of the mosquito when possible.\textsuperscript{9}

**The Asian Mosquito Tiger**

It is a striking mosquito approximately 2-10mm in length, characterised by its black and white striped legs and small black and white body. The head consisting of eyes and a pair of long segmented antennae, is responsible for receiving sensory information and for feeding. The antennae’s role is used to detect host odours.

It typically flies and feeds during the daytime unlike other mosquitoes. \textit{Aedes albopictus} feeding peaks in the early morning (dawn) and late afternoon (dusk). It is an opportunistic and aggressive biter with a wide host range including man, domestic and wild animals.\textsuperscript{10} Since it has a short flight range (around 200m), it tends to remain close to its breeding site. The male has a short life expectancy but the female can live from 3 weeks to 3 months. Water is the essential element for mosquito development because the female lays her eggs just above the surface of the water.\textsuperscript{11,12}

**Life cycle**

The female mosquito, after birth, looks for a male to mate. Mating occurs soon after emergence during a swarm flight. Once this is done, which only occurs once in their life, the female looks for a blood meal which is necessary to fertilise its eggs. About four or five days after feeding on blood, the female mosquito lays her eggs just above the surface of standing water.

Around 150 to 250 eggs are laid per oviposition (egg-laying event). Each female can have 1 to 4 ovipositions. When rain covers the eggs with water, the larvae hatch. The active reproductive period occurs from late Spring (May) to early Autumn (October).\textsuperscript{10,12}

Eggs are laid singly on the sides of water-holding containers such as tyres, animal watering dishes, birdbaths, flowerpots and natural holes in vegetation.\textsuperscript{13}

They are black and oval with a length of 0.5 mm. Eggs can withstand desiccation for up to one year. Larval emergence occurs after rainfall raises the water level in the containers. The eggs may require several submersions before hatching. Larvae development takes 3-8 weeks and adults can live for a period of 3 weeks to 3 months.\textsuperscript{10,13}

Asian Tiger Mosquitoes spend the winter in the egg stage, hatching into larvae when the eggs get covered with water in the spring. The larvae feed on small bits of debris and bacteria in the water. Its life cycle is closely associated with human habitat, and it breeds in containers with standing water.\textsuperscript{14}

Asian Tiger Mosquitoes are known to be attracted to carbon dioxide, dark clothing, perspiration, and particular odours.\textsuperscript{14}

Female mosquitoes hunt their blood host by detecting organic substances such as carbon dioxide and 1-octenol-3-ol produced from the host. Some persons are preferred to others by mosquitoes and that is why some are bitten while others are not. This is due to the smells produced by the victim’s sweat which attracts the mosquito because of the proportions of carbon dioxide, octenol and other compounds that make up body odor.\textsuperscript{28}

**Medical significance**

\textit{Aedes albopictus} is a known competent vector for at least 22 Arboviruses.\textsuperscript{15} These include Dengue, Chikungunya, West Nile fever, Yellow fever and Japanese Encephalitis. It can also transmit Dirofilariasis to dogs. In order for the mosquito to be able to transmit infections, it has to be carrying the pathogen within itself first and then through biting its host, it transmits the virus, causing the host to develop the viral illness.

The two most likely viral illnesses transmitted by \textit{Aedes Albopictus} within the Mediterranean region are:

- Chikungunya
- Dengue

---

*Figure 1: Adult Asian Tiger Mosquito, \textit{Aedes albopictus} (Skuse).*

Photograph: J.L. Castner, University of Florida

*Figure 2: Adult Asian Tiger Mosquito, \textit{Aedes albopictus} (Skuse).*

Photograph: Michele M. Cutwa, University of Florida

*Figure 3: Larva of the Asian Tiger Mosquito, \textit{Aedes albopictus} (Skuse).*

Photograph: Michele M. Cutwa, University of Florida
Chikungunya virus is a member of the genus alphavirus. It is spread by the bite of an infected mosquito. The incubation period is between 2-12 days but usually occurs within 3-7 days. It can cause a debilitating illness and is characterised by fever, headache, fatigue, nausea, vomiting, muscle pain, rash and joint pain. Acute Chikungunya fever can last from a few days to a few weeks but some patients have prolonged fatigue or develop incapacitating joint pains or arthritis which lasts for weeks or months. 

Dengue is an acute febrile viral disease caused by Flavivirus serotypes. It presents with sudden fever for 2-7 days together with two or more of the following: intense headache, retro-orbital pain, myalgia, arthralgia, rash or haemorrhagic manifestation. Anorexia, nausea, vomiting and persistent abdominal pain may also be present.

Some patients with dengue fever go on to develop a severe and sometimes fatal form of the disease called Dengue Haemorrhagic Fever. This is characterised by a fever and evidence of haemorrhagic manifestations. The symptoms of infection usually begin 4-7 days post being bitten and last between 3-10 days. 

Ways to control mosquitoes

All mosquitoes need water in order to reproduce. Each female mosquito may lay as many as 200 eggs that will transform into larvae and then into adults. Therefore the control of these mosquitoes should be aimed at destroying the places where they lay their eggs which are never far from where people are being bitten.

- Remove all water filled containers like flower pots, old buckets, food containers and tires.
- Keep mosquitoes from breeding in bird’s baths, pet water dishes and paddling pools by emptying them at least every 3 days.
- Any puddles, inlets to sewers and drainage systems should be drained not to allow water to stagnate for more than 3 days.
- Gutters should be kept clean from fallen leaves and other debris so that water does not collect in them.
- Man made outdoor features especially fish ponds should contain fish like gold fish, carp or killifish as these feed on the mosquito’s immature stages.
- Litter can also hold rain water and should be removed.
- Any standing water in catchment basins etc that cannot be drained must be regularly treated with properly labelled insecticides.
- Always place a tight lid on containers used for water storage like water tanks.
- In cases where fish cannot be kept in open water reservoirs or wells, they need to be covered.
- Swimming pools must be maintained with regular chlorine or emptied if not is use.
- Do not leave toys in the garden which can store rain water.
- Protect boats and vehicles from rain with tarps that do not accumulate water.

Treatment when bitten

Once bitten, the clinical manifestation is characterised by an area of erythema around the bite, pruritus and moderate to extensive swelling of the area. This is largely due to a local chemical cellullites rather than hypersensitivity caused by the contact of the mosquito’s saliva with human skin.

It is recommended that a cold compress is applied initially followed by an antiseptic cream. Oral antihistamines should be given and if gross swelling is present, topical and/or oral corticosteroid might be indicated following specialist advice. Antibiotics should not be prescribed as the bites are not infected. If evidence of secondary bacterial infections develops characterised by pain, tenderness, pus and an extension of the erythema beyond the bite, than an oral antibiotic primarily aimed against staph aureus and strep.pyogenes should be given. Topical antibiotics should be avoided.

Conclusion

The Asian Mosquito Tiger will use almost any container that holds enough water to complete its life cycle including flower pots, tin cans, plastic buckets, cemetery urns and discarded tyres. Control is difficult because a proportion of mosquitoes still deposit their eggs in natural containers like tree holes which are impossible to eliminate. However the reduction of container breeding sites has shown to be an effective way for people in the community to manage its control near where they live.

The discovery of Aedes Aldopicus in Malta is of public health importance because it is a competent vector which can result in spread of diseases like Dengue and Chikungunya. Since it is now established locally, the risk of the mosquito becoming infected and starts transmitting disease locally increases. Outbreaks of Chikungunya occurred in Italy in Taranto in 2007 in La Reunion in France in 2010 while cases of Dengue have occurred in Croatia and France in 2010. An outbreak of Dengue occurred in Madeira, Portugal between October and December of 2012 following the discovery of two cases of autochthonous Dengue virus infections with over 1,357 cases of Dengue fever-the first sustained transmission of disease since the last outbreak in Greece in 1927.

Outbreaks of mosquito borne disease have a considerable economic impact. A cost illness analysis performed on the Chikungunya epidemic in La Reunion island.
(2005-2006) where 204,000 cases were infected, estimated the total cost of medical expenses at 42.0 million Euro, of which 60% were direct medical costs and 40% to disease related loss of productivity.20

The most effective means of vector control is environmental management with the aim to modify or manipulate environmental factors with the view to prevent and reduce vector propagation and human-vector-pathogen contact. The methods involved will include improving the water supply and storage, solid waste management and modification of man-made larval habitats. Chemical control using insecticides and also biological control using biocides or larvivorous fish are used to destroy larvae.21

Control measures would need to be applied throughout the whole year since the mosquito continues to breed locally throughout the whole year but can be most effective during the winter period during larval development. Adult biting activity in winter is very low so the potential transmission of Arboviruses will take place in the period of May and November when adult mosquitoes are present in large numbers.22

References


25. ECDC mission report on Dengue outbreak in Madeira, Portugal October-December 2012.

26. CDC Guidelines for the surveillance of invasive mosquitoes in Europe, 2012


The pill in the future - pharmacological contraception in science fiction

1Victor Grech MD, PhD (Lond.), PhD (Melit), FRCPCH, MRCGP(UK), DCH
2Clare Vassallo B.A. (Gen.), B.A. (Hons) PhD (Bologna)
3Ivan Callus B.Ed. (Hons), B.A. (Hons) (Lond.), M.A., Ph.D. (Cardiff)

Abstract
Contraception dates back to Mesopotamian times. Science fiction (SF) has utilised many contraceptive plot devices and this paper will explore these stratagems from the pharmacological point of view. It will be shown that the oral contraceptive pill and the contraceptive implant were both predicted in SF as well as other forms of contraception of which we only, as yet, have tantalising research possibilities.
cognition, and whose main formal device is an imaginative framework alternative to the author’s empirical environment.”

SF has utilised many contraceptive plot devices and this paper will explore these stratagems from the pharmacological point of view. This work arises from a Ph.D. dissertation dealing with the wider topic of infertility in SF. 1

Contraception
Natural methods
Voluntary infertility is used to prevent overpopulation on the island of Parz in the far future in One Million Centuries (1967) where a delicious, naturally occurring fruit severely curtails libido, ensuring that few children are born. 6

The oral contraceptive pill
Many texts, such as The Twilight of Briareus (1974) mention the pill in everyday use, 7 but earliest mention of the equivalent of an oral contraceptive pill appears to have been in Brave New World (1932) where procreation and sex are completely divorced. Sex is solely procreative and safeguarded from conception in fertile women by the permanent and regulation carriage of a supply of contraceptives on a fashion accessory known as a ‘Malthusian belt’, which they are conditioned to wear from birth. 8

More urgently, the pill may be used where it is crucial to avoid pregnancy, such as in astronaut crews. Titan (1979) empowers female astronauts with monthly implants and ever-wear diaphragms. 9 Contraception for spaceship crews is also outlined in The Wind People (1959) wherein artificial gravity conditions are said to completely preclude female crew conception but have no effect on libido or potency, and this effect wears off after approximately three months. Automatic contraception is naturally a desired side effect of interstellar travel and on long planet layovers between trips, spaceship crews are routinely administered a contraceptive drug called ‘anticeptin’ to further continue to prevent pregnancies. 10

Likewise, in Luna One (1973), women who form part of the first moon colony are given a contraceptive pill called ‘P-C pill’. 11 On a different tack, in the interest of cementing friendship between the various branches of the armed forces, in Short in the Chest (1954), sex between men and women is by roster, with women taking an ‘oestric’ drug in order to increase libido, and men take the equivalent ‘priapic’, with contraception ensured through women also taking an ‘anti-concipient’. 12

Contraceptive Patch
In The Eleventh Commandment (1962), anti-contraceptive matters are taken even further when the Vatican is vapourised in a nuclear exchange and a new pontiff is chosen from among the American cardinals resulting in a schism, with the establishment of an eleventh commandment: ‘be fruitful and multiply and replenish the Earth’, and contraception is made illegal. The protagonist, a human colonist from Mars, visits Earth and wears a contraceptive patch, but this fails, and the reason given is that the higher gravity of Earth rendered the patch ineffective. 13

Contraceptive Implants
Islands of Tomorrow (1994) depicts humans travelling back in time and abducting humans into the future for breeding purposes, and one of the women has a contraceptive implant and hence, initially, fails to become pregnant. 14

In A Reasonable World (1991), the impact of a totally foolproof contraceptive leads to the development of sexual intercourse as a performance art form. 15 In The Group (1973) extrapolates the consequences of such technology into entertainment, where sexual experiences (including the input of all senses) during copulation are transmitted through technological means to the rest of the members of an entire group, a group that is dispersed around the world. 16

The state subversion of population control into eugenics is also used in the Known Space stories. In this future, complete contraceptive birth control is achieved by the annual subcutaneous administration of a crystalline drug, a crucial system in the heavily overpopulated dystopia that comprises this future Earth. 17

A greater level of detail with regard to population control in the closed environment that constitutes a huge spaceship is given in Paradises Lost (2002), where ‘conshots’ are given to both genders by the medical staff, and individuals who fail to show up for their shots are tracked down by the ship’s authorities. Exempt individuals include postmenopausal females, sterilised crew and those who are strict homosexuals or who have taken a pledge of strict chastity. The intention to conceive must be formally declared beforehand by both partners, and each individual is only allowed to have one child. Irregular or extra pregnancies are stopped by a morning after drug or by forcible termination and indeed, in White Mars (1999), the perils of inadequate contraception are shown when stranded colonists run out of contraceptives. 18

More practically, in the Vorkosigan novels, women who have had a contraceptive implant wear a distinguishing earring to state that they are consenting and contraceptive-protected adults. 20

Iatrogenic chemical infertility
Widespread infertility may be a completely accidental and involuntary iatrogenic event in SF, a flawed cure as depicted in The Douglas Convolution (1979) and its sequels, set in a 22nd century Earth suffering from widespread female infertility brought on by the use of a contraceptive agent. 21 Similarly, in The Wind Obey Lama Toru (1967), fertility and sterility drugs act and counteract, driving human population levels up and down in a chaotic fashion. 22 Likewise, in They Shall Not Die (1939), a drug is available that prevents all disease but sterilises all those who take it. 23

Deliberate and widespread state-induced infertility
Benefits (1979) traces the progress from state benefits for mothers to an overpopulation-prevention program, with the state ultimately dumping a universal contraceptive in drinking water, a drug which, when combined with the antidote that is given to approved mothers, proves to be a potent mutagen. 24 An identical population-control strategy is mentioned in The Year of the Comet (1955), where an anti-fertility agent is added to drinking...
water, which, however, is said to have up to two percent mortality, with the majority of deaths conveniently being women, further reducing the population’s reproductive potential.25

**Chemical infertility inflicted on animals**

In *Auto da fe* (1966), a future humanity modifies dogs, giving them intelligence, speech, the ability to walk upright and lengthening their lifespan to some five centuries. However, these gifts come at a price in that the story depicts the world’s last dog among a troupe of bitches, and their fertility is at a complete standstill because of contraceptive drugs that are dripped into their food at the behest of the last surviving human.26

**Aliens**

In the *Star Trek* episode *The Mark of Gideon* (1969), the *Enterprise* crew discover a grossly overpopulated planet. Captain Kirk suggests to the rulers that his United Federation of Planets would be willing to provide any kind of contraceptive devices that the populace would need.27

**Contraception failure**

Contraceptive failure is not uncommon in SF television series, and in the *Farscape* episode *Natural Election* (2002),28 one of the protagonists, a military peacekeeper, becomes pregnant, and the only positive aspect is that the possibility of an arrested pregnancy is mentioned, implying that pregnancy may be temporarily suspended and gestation later resumed. However, the nature of any contraception used in this society is not discussed. The scenario posed in the *Star Trek Deep Space Nine* episode *The Dogs of War* (1999) is even more implausible as one of the protagonists finds herself pregnant since her partner forgot to take his birth control injection, and yet both are meant to be taking their injections.29

**Discussion**

The daily contraceptive pill was developed in 1951 by Djerassi and colleagues, earning him the 1973 National Medal of Science,10 and the concept of the pill itself appears to have been first mentioned in SF in 1932, twenty years earlier. It is typical of medicine that a Nobel prize was also given to the scientists to who made great inroads into infertility treatment.31

Contraceptive implants were utilised in SF in the 1970s, prefiguring the actual development of long-acting implantable contraceptive agents, such as Norplant (developed in 1991 with a pregnancy rate of <1% over a five-year period) by twenty years. Injectable depot contraceptive hormones are now available for both sexes.32,33 With an estimated 60% of all unplanned pregnancies in the developed world occurring in women using some form of birth control, it is anticipated that this range of options will provide more effective contraception, albeit without preventing sexually transmitted diseases due to the lack of the barrier nature of these systems. Some American states are actually attempting to persuade certain sectors of the populace to implant such agents in order to curb the population growth of the underprivileged.34

Interestingly, there are also several naturally occurring candidate compounds that could be added to food or drink in order to induce infertility or produce outright sterility. For example, the short term, oral administration of an aqueous or chloroform extract of Carica papaya seed has been shown to induce complete and reversible sterility in male rats and rabbits with no effect on libido, and this has been attributed to a decline in sperm motility and alteration in sperm morphology, as well as to reduced contractile response of the vas deferens, the conduit by which sperm is ejaculated out of the testis.35,36

This brief sampling of SF stories demonstrates a typical and important property of the genre: the ability to predict the future, if for no other reason, then through the sheer multitude of stories and the inevitability of such narratives prefiguring future turns of events. In this way, SF prepares us for ‘future shock’, which has been described as ‘a time phenomenon, a product of the greatly accelerated rate of change in society… the dizzying disorientation brought on by the premature arrival of the future. It may well be the most important disease of tomorrow’.37 It is also simultaneously evident that SF also offers ‘inspiration to would-be inventors, spurs on technological progress’.38

The genre also continually inflicts a ‘reality-test’ on itself, and does not break with the Aristotelian admonition that ‘we must presuppose many things that accord with our highest hope, although the existence of none of them must be impossible’.39 This returns us to back to the concept of novum in SF, in this case, a chemical contraceptive agent, a novel scientific/technological plot device that is validated by cognitive logic, that is, made to appear scientifically plausible, thereby making an SF narrative not only possible but also plausible.

**References**

Hypopituitarism: a review on the diagnosis and management of central hypoadrenalism and hypothyroidism

Mark Gruppetta  MD, MRCP(UK)
Department of Medicine, Faculty of Medicine and Surgery, University of Malta, Msida, Malta; Department of Medicine, Mater Dei Hospital, Msida, Malta. Email: mark.gruppetta@gov.mt

Introduction
The pituitary gland is situated at the base of the brain and is divided into the anterior and posterior lobes. The anterior pituitary is responsible for the synthesis and secretion of adrenocorticotropin hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH) and prolactin. It has a crucial role in the control of the hypothalamo-pituitary-adrenal axis through its secretion of ACTH, released under the influence of hypothalamic corticotropin-releasing hormone (CRH), ACTH being responsible for the control of cortisol secretion by the adrenals. Control of thyroid hormone production by the thyroid through the secretion of TSH, released under the influence of hypothalamic thyrotropin-releasing hormone (TRH) is another key role of the anterior pituitary. Partial or complete insufficiency of anterior pituitary hormone secretion termed hypopituitarism may result from pituitary or hypothalamic disease. A variety of conditions can result in hypopituitarism besides developmental and genetic causes, including various tumours such as pituitary adenomas and craniopharyngomas, head trauma, irradiation, pituitary infarction, empty sella syndrome and infiltrative diseases. In acquired hypopituitarism, failure of pituitary hormones usually follows a particular order with loss of GH first, followed by LH and FSH, than TSH and lastly ACTH. This order may reflect their relative importance for survival and in fact the more severe clinical condition occurs with ACTH deficiency which if left untreated can be fatal. This review will focus on the diagnosis and management of ACTH and TSH deficiencies (central hypoadrenalism and hypothyroidism respectively).

Central hypoadrenalism
Diagnosis of central hypoadrenalism
Since serum cortisol levels usually reach a peak value at about 0800h, a level less than 100nmol/L at this time is taken to mean that there is cortisol deficiency. Levels of serum cortisol taken at other times of the day are not very significant in terms of the diagnosis of hypoadrenalism. Hence a number of dynamic function tests have been devised to assess whether a patient can mount a suitable elevation in serum cortisol in response to stress as happens physiologically in a normal person. The test which has been available for many
years and still considered to be the gold standard is the insulin tolerance test (ITT) in which an insulin dose is given to induce a hypoglycaemic episode and proven to repeated measurements of serum cortisol are taken.1

Due to the nature of the test, it needs to be carried out under medical supervision and has some important contraindications such as a history of epilepsy, ischaemic heart disease or cardiac dysrhythmias. A peak value of 550nmol/L or above has to be achieved for the test to indicate adequate cortisol stress response. 1 A test which is simpler and shorter to do and for most cases provides adequate results which correlate well with an ITT, is the short synacthen test (SST). In this test 0.25mg of ACTH[1-24] [tetracosactrin (Synacthen*)] are injected intramuscularly (i.m.) or intravenously (i.v.) and serum cortisol levels are measured at 0, 30 and 60 minutes. Since the use of the SST for evaluation of central hypoadrenalism works on the principle that adrenal glucocorticoid producing cells will have their cortisol producing ability attenuated as a result of chronic ACTH deficiency, there is a time lag until this develops and thus this test should not be used to assess patients in their early stages after a pituitary insult.1,5

Another alternative test which could be used when an ITT is contraindicated, is the glucagon test where 1mg of glucagon is injected subcutaneously and measurements of serum cortisol are carried out every half hour for 4 hours.1,2,4

**Treatment of central hypoadrenalism**

In the acute setting when central hypoadrenalism is present or suspected, the treatment of choice is hydrocortisone given through the i.v. or i.m. route. Before administering the first dose of hydrocortisone, if possible a serum sample for estimation of cortisol level is taken. Usually the dose is 100mg every 6-8 hours, together with i.v. saline infusion. After 24 hours the dose of hydrocortisone can be reduced to 50mg 6 hourly and then, if clinically tolerated, changed to oral hydrocortisone.1,9

Long term treatment involves lifelong supplementation of glucocorticoids. Previously most patients used to be given hydrocortisone 20mg as soon as they wake up and 10mg in the late afternoon. Following studies10 that determined that the average daily dose of cortisol secreted is 5.7mg/m² per day or 9.9 ± 2.7 mg/day, which is equal to a daily delivered dose of 15-20mg, usual supplementation dosages were revised down to this level. With the knowledge that mimicking the normal circadian cortisol rhythm has proven to be very difficult, different approaches were adopted by various experts: either starting with a twice daily dose of hydrocortisone and if on clinical assessment, the patient is still feeling unwell going up to thrice daily dosing or advocating that the replacement dose of hydrocortisone be divided into 3 doses from the start with typical dosages being a 10mg dose taken on rising, 5mg at midday and 5mg in the early evening.1,11-13 Some experts advocated that this thrice daily regime be further fine tuned by adopting a weight adjusted dosage.11 It is important to note that the first morning dose of hydrocortisone is best taken as soon as the patient wakes up with a glass of water and the last dose should be taken in the late afternoon rather than the evening to prevent unphysiological high levels of cortisol in the evening and possibly insomnia.1,12 Studies on the relation between hydrocortisone dosage and health-related quality of life suggest that a twice daily regimen is superior to a once daily dose and perhaps a thrice daily better than twice daily although the evidence here is not as strong.12,13 In a large study14 on 2424 hypopituitary patients of whom 1186 were on hydrocortisone, it was shown that while patients who were on hydrocortisone had higher levels of total cholesterol, triglycerides, HbA1c and a higher waist circumference, compared to ACTH-sufficient patients, those who were taking a dose of hydrocortisone less than 20mg/day did not have statistically significant differences in the metabolic parameters mentioned when compared to patients who had an intact hypothalamic-pituitary-adrenal axis. To try to mimic the physiological cortisol circadian rhythm better, modified release oral formulations of hydrocortisone are currently being developed. The total replacement dose needed might be less for those patients who have some residual pituitary function as evidenced by a subnormal peak response on a stimulation test but a normal basal level of cortisol. Some patients would even just require steroid cover for periods of increased stress.2 Mineralocorticoid replacement (Ex. Fludrocortisone) is not needed in central hypoadrenal patients.

An important dimension of the assessment of proper glucocorticoid replacement treatment is regular clinical assessments aiming to highlight symptoms/ signs of under or over treatment, although one has to appreciate that minor degrees of over/under treatment might prove very difficult to diagnose on clinical grounds.12,13 In this context the role and value of cortisol day curves is debated by various experts, though they may have a role in monitoring adequate replacement and avoiding over treatment of patients1 or in those who are on other drugs which interfere with the metabolism of hydrocortisone.12 Another method advocated by some experts to help assess adequate glucocorticoid replacement is taking a serum cortisol level 4 hours after ingestion and comparing this level to a dosing nomogram.13 Although the effect on bone mineral density of patients who are on glucocorticoid is debatable, there are some studies which suggest a lower bone density in such patients particularly in post-menopausal women. Hence it is reasonable to suggest that patients are to be kept on the lowest dose of hydrocortisone possible and have their bone mineral density followed up.12,13

An important dimension in the management of patients who are glucocorticoid deficient is their education. Patients who are on replacement steroids are advised to carry a Steroid Card with them at all times and emphasis made on the fact that they should not stop taking this treatment unless advised otherwise by their doctor. On a practical level, patients should be advised to think ahead so that they do not run out of the replacement steroid tablets. They are also provided with a phial of hydrocortisone 100mg to be available for administration in emergency settings and adequately educated on how this is given if the need arises. These patients are advised that they should double their usual dose of hydrocortisone if they have a major stressful event such as a febrile illness unless they are severely ill when they might need hydrocortisone administration through the i.v. route.1,9,12

**Central hypothyroidism**

_Diagnosis of central hypothyroidism_

The biochemical diagnosis of central hypothyroidism is done when a low thyroxine (T4) level is noted together with an inappropriately normal or low TSH level. It is worth noting that tri-iodothyronine (T3) levels often remain within normal limits even when T4 levels are low and thus the measurement of its level might not be helpful for diagnosis. A high index of suspicion should be maintained in
Key points

- A combination of basal serum cortisol levels and various dynamic function tests have been devised to establish whether a patient has an adequately functioning hypothalamo-pituitary-adrenal axis.
- Typical daily glucocorticoid supplementation dose is 15-20mg hydrocortisone divided into twice or thrice daily doses.
- The first morning dose of hydrocortisone is best taken when the patient wakes up and the last dose should be taken not later than in the late afternoon.
- Vital to educate patients on the importance of drug compliance and what to do during major stressful events.
- Biochemically patients with central hypothyroidism have low thyroxine levels with an inappropriately normal or low TSH level.
- Serum TSH level is not a good indicator of adequate thyroxine supplementation dosages in central hypothyroidism and changes in dose should be done according to serum thyroxine levels and on clinical grounds.

those patients who have conditions which could result in hypopituitarism and thus central hypothyroidism, such as a history of pituitary tumours, previous cranial irradiation or cranial injuries.\textsuperscript{15,16}

Treatment of Central Hypothyroidism

The treatment of central hypothyroidism is life long thyroxine. It is important to ascertain before starting T4 treatment in a patient, that the possibility of coexistent hypothalamic involvement has been excluded or if present is adequately replaced since it is well known that T4 increases cortisol clearance and thus an adrenal crisis might be precipitated in patients who are cortisol deficient. Usually it is advisable to start with low doses of T4 such as 25-50μg daily and then titrating the dose every few weeks until the correct dose is found. Elderly patients and those with a history of ischaemic heart disease deserve special attention in titrating the dose of T4. Several drugs including iron, calcium, mineral supplements, aluminium hydroxide and sucralate are known to interfere with T4 absorption. Adverse reactions to T4 treatment have to do with over replacement of T4 and thus will include symptomatic or subclinical thyrotoxicosis. It is important to note that in central hypothyroidism TSH levels cannot be used as an indicator of correct dosage as is done in primary hypothyroidism since the TSH response is inappropriate. Thus changes in dosages should be done on clinical grounds and according to serum T4 levels, aiming to keep these in the upper half of the normal reference range.\textsuperscript{15,16}

Conclusion

While not very common, hypopituitarism, especially central hypoadrenalism and hypothyroidism need to be promptly diagnosed and appropriately treated. While aiming to restore normal physiological hormonal levels, a structured monitoring system, both clinically and biochemically is needed to determine the most appropriate drug supplementation dosages for a particular patient. Patient information is a key component of the management of these patients in order to ensure drug treatment compliance and minimise potential problems.

References

The extemporaneous compounding of paediatric medicines at Mater Dei Hospital

Antonella Aquilina  B. Pharm (Hons), MSc Clin (Aberdeen)
Pharmacist, Compounding Section, Pharmacy Department
Mater Dei Hospital, Msida MSD 2090, Malta
Email: antonella.a.aquilina@gov.mt

Educational aims

• To gain further knowledge about extemporaneous compounding of medicines
• To highlight the importance of extemporaneous preparations in paediatric use
• To appreciate the need for the extemporaneous compounding of medicines locally
• To showcase the extemporaneous preparatory service provided at Mater Dei Hospital

Key words
extemporaneous, compounding, off-licence preparation

Extemporaneous compounding is defined as the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient.1 The lack of commercially available formulations for patients with specific needs poses a challenge to making medicines available to what are considered to be the most vulnerable patients.2 This qualifies as off-license use of a medicine, whereby a licensed medicine is reformulated into a preparation that is acceptable/appropriate for the patient.

Introduction

Children, especially the younger age groups, may require age-appropriate formulations allowing both safe and accurate dose administration.3 Lack of appropriate studies preclude most medications from being labelled for use in paediatric patients.4 In order to improve the health of children in Europe without subjecting children to unnecessary trials, or delaying the authorisation of medicinal products for use in adults, the European Union’s Paediatric Regulation came into force in 2007.5

Since licensed medicines represent the ‘gold standard’ for quality, safety and efficacy, the underlying general rule is that a licensed preparation is always preferable to a compounded one. Medicines are given a license, now called a marketing authorisation, if the pharmaceutical company has demonstrated the quality, efficacy and safety of the medicine as recommended in the Summary of Product Characteristics (SmPC) when given in the dose and for the disease and age group recommended. The Standing Committee on Medicines has stated that in paediatric practice, the informed use of some unlicensed medicines or licensed medicines for unlicensed applications is necessary.6

There are circumstances in which there is no licensed product or alternative which fully meets the clinical needs of a particular patient and therefore it becomes necessary to extemporaneously prepare a limited quantity of a custom-made product for an individual patient.7 Between 15 and 80% of all medicines used in hospitalised children have either not been licensed at all (‘unlicensed’) or are used outside the specification terms of the product license (‘off-license’).8

Extemporaneous compounding of medicines carries significant risk, as the risks of using unlicensed medicines are combined with inherent risks associated with the pharmaceutical compounding process.7 The risk for the patient is that total accuracy and uniformity of the dose can never be assured and the risk for the operator is that he/she is being exposed to the chemicals whilst reconstituting a preparation. Extemporaneous compounding is defined as the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient.1 At Mater Dei Hospital, the extemporaneous compounding service caters for both children and adults, to both in- and out-patients and liaises with clinicians, pharmacists and nursing stuff to...
ensure seamless care. Since the majority of medicines are prepared for paediatric patients, this article will focus on this category of patients.

Extemporaneous medicines can range from oral formulations such as suspensions and solutions, sachets, mouthwashes to topical formulations such as creams and ointments. Examples range from captopril suspension for cardiovascular disease to controlled medicines such as clobazam sachets, both for use in paediatric patients. Oral liquid medicines are commonly prepared extemporaneously because of a relative lack of licensed formulations for children who are unable to swallow tablets or capsules, or for whom the required dose is less than a single tablet or capsule. A large proportion of extemporaneous compounding lies in converting capsules and tablets to oral liquids or powders. Others are made from the bulk active ingredient, such as oseltamivir powder to prepare oseltamivir phosphate solution.

It can be noted that most medications are marketed without adequate studies and availability of appropriate dosages for infants and children. Even medications such as phenobarbital and spirinolactone, which have been approved for use in paediatric patients, are not available in an appropriate dosage form for this category of patients. One of the aims of extemporaneous compounding is making medicines available to paediatric patients.

**Legal considerations**

Extemporaneous compounding of medicines is usually not covered by the manufacturer in the product’s SmPC. An off-license form must be filled in by the prescriber every time there is a new request for an extemporaneous formulation, wherein the prescriber takes full responsibility for the clinical use of the preparation. This should accompany every new prescription. At MDH, off-license forms can either be departmental (e.g. caffeine citrate oral liquid is used by Neonatal and Paediatric Intensive Care Unit (NPICU) in neonates for respiratory distress syndrome) or patient-specific (e.g. sildenafil suspension for pulmonary hypertension in paediatrics) and are downloadable from the hospital intranet via the following link: http://www.kura.gov.mt/infolcentre/forms/result.asp?keys=off-license&SearchMonth=&SearchYear=. A database of off-license medicinal products is kept by Quality Assurance (QA) section within the Pharmacy Department.

The role of QA is to ensure that services and medicinal products provided/supplied by the Pharmacy Department are of the quality required for their intended use.

**Key points for consideration prior to compounding**

The following alternatives should be considered before extemporaneous compounding is undertaken:

1. Soluble or dispersible tablets may be a useful and convenient alternative to the preparation of liquid extemporaneous products. Some tablets can be dispersed or crushed and information on this aspect can be obtained from the Medicines Information Section within MDH. In this case, the dose should be prepared and administered immediately. In general compressed tablets or tablets which are scored or just film coated can be crushed whereas modified release tablets cannot.

2. If a particular medicine is not available as a liquid formulation, another medicine from the same therapeutic classification may well be used, such as the use of a less potent steroid rather than diluting a potent one.

3. Using a suitable preparation intended for a different route of administration, for example, using an injectable solution orally.

4. Use of a ‘specials’ preparation manufactured in licensed premises (Specials are medicines made in larger volumes by a licensed manufacturer).

**Stability**

When evaluating the stability of a formulation, its chemical, physical and microbiological stability must be considered. It is highly important that the storage conditions stated on the label are adhered to. Even where a given formulation has been shown to achieve suitable physical, chemical and microbiological stability, the bioavailability and palatability of the preparation may be unproven.

Very few extemporaneous preparations are supported by any data to demonstrate a suitable absorption profile and/or bioequivalence with a licensed preparation. Other issues include concerns about inadequate access to equipment and materials needed to provide a safe extemporaneous dispensing service and the highest possible quality products.

In order to limit degradation and spoilage, products are given a maximum shelf-life of 28 days, unless the product is not chemically stable, whereby the shelf-life is then given according to the stability of the respective product. Stability studies for extemporaneous preparations are usually conducted over small periods of time. Lack of stability data limits many medicines from being made available for use in paediatrics. The armamentarium of formulations available for extemporaneous compounding relies heavily on the availability of stability data and the ingredients required for compounding.

A systematic approach to compounding at Mater Dei Hospital

- Non - sterile extemporaneous preparations must always be compounded upon receipt of a prescription i.e. on demand.
- If a worksheet for the formulation requested is not available and a licensed product or alternative cannot be found, an appropriate formulation must be researched. The details of the new formulation are presented to the prescriber who endorses it.
- A new worksheet and label must then be prepared. The master worksheets are then approved by the Quality Assurance section and endorsed by the Head of Pharmacy. A request for inclusion of the new extemporaneous formulation in the hospital formulary should also be filled in. The original master work sheets are stored by Quality Assurance section which is also responsible for uploading a secured electronic version on the intranet. A separate set of worksheets and labels are drawn up for every preparation compounded (i.e. patient-specific).
- All pharmacists and pharmacy technicians receive training which is certified by Quality Assurance prior to starting duties within the Compounding Section. All the compounding steps are double-checked by a pharmacist before a preparation is released for use.

**Premises**

At MDH, extemporaneous medicines are prepared in a clean controlled environment containing equipment required for extemporaneous compounding such as a fume cupboard and a powder-containment cabinet for personnel protection from fumes and aerosols generated during compounding. Personnel must don the prescribed garments.
before entering the clean area i.e. mob hat, gloves, overshoes, plastic overcoat and a facial mask for males.

**Final comment**
The pharmaceutical industry is expected to develop and market dosage forms which are suitable for children, hence relieving the hospital pharmacy from the burden of preparing extemporaneous preparations. However, it remains to be discussed whether this is a realistic expectation. Manufacturers would have to produce formulations that have a limited shelf life, since many existing medicines are intrinsically unstable in any aqueous vehicle, which is possibly the only acceptable formulation for paediatric oral administration. The manufacturer would be placed at a financial disadvantage, considering the small size of the paediatric healthcare market and the economic push for group purchasing and cost reduction, in order to solve the compounding problems of hospital pharmacies.10

**Conclusion**
The aim of extemporaneous compounding is that of meeting the therapeutic needs of vulnerable patients, especially the paediatric population, as a last resort in the absence of a marketed licensed preparation. Prescribers are encouraged to use their clinical judgment when recommending extemporaneous formulations to their patients, and should monitor for safety and efficacy throughout treatment. With the the resulting aim of preparing appropriate dosage forms for paediatric use, a significant responsibility in a pharmacists’ work remains the compounding of extemporaneous formulations.

**Acknowledgements**
The author would like to thank Mr Mario Barbara, Senior Pharmacist, Quality Assurance for reviewing the document.

**References**

Itraconazol Actavis

Itraconazole
100mg capsules
Triazole Antifungal

Targets Fungal Infection

For further information please refer to the full summary of product characteristics or to our website www.actavis.com.mt
PANADOL® ADVANCE

Disintegrates up to \(5^X\) Faster
than standard paracetamol tablets\(^1\)

PANADOL ADVANCE with Optizorb technology delivers significantly faster tablet disintegration, consistently better absorption, and significantly faster therapeutic levels.\(^1\)

PANADOL ADVANCE disintegrates significantly faster than standard paracetamol tablets.\(^{*}\)

Standard paracetamol  PANADOL ADVANCE

5 Min

The same trusted suitability of PANADOL in an advanced formulation.\(^{2,3}\)

Won’t harm the stomach.\(^4\)

\(^{*}\)Representation of actual gamma scintigraphy images of paracetamol in the gastrointestinal (GI) tract.

References