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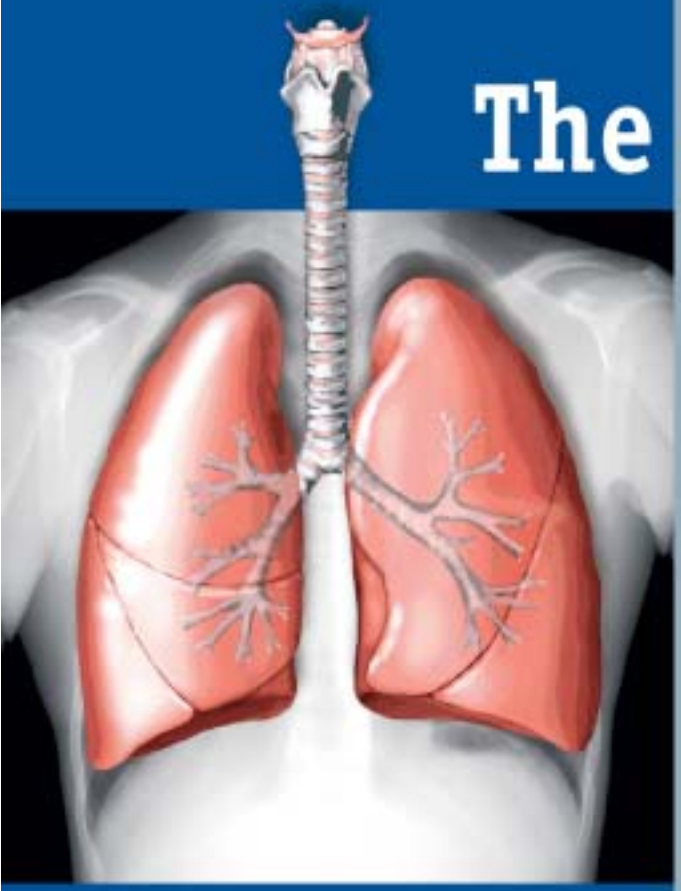
The Chronic*ill



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The burden of respiratory disease

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Respiratory diseases are a leading cause of morbidity and mortality world wide. The World Health Organisation attributes 18.7% of the total number of deaths to respiratory disease, whilst in Europe respiratory diseases rank as the second cause of death after cardiovascular disease. In economic terms, respiratory diseases place a burden of approximately €102 billion on Europe. A total of €48.3 billion, being due to days lost from work with the leading cause (62.4%) being chronic obstructive pulmonary disease, followed by asthma (21.4%) and pneumonia (7.6%). In terms of pharmaceuticals, Europe spends €3.6 billion on anti-asthma drugs and €2.7 billion on drugs to treat COPD (European White Lung Book).

Health care systems are more oriented towards treating acute problems. However, chronic disease management is more complex as it necessitates a more horizontal and integrated approach. Management of chronic disease is an ongoing lifetime task requiring a multidisciplinary team of health care professionals together with the patient and also with the involvement of the patient's family. This approach is more difficult in practice and may be criticised as being unrealistic. Evidence has however shown us that it provides better clinical outcomes and improved quality of life.

While the spectrum of drugs to treat respiratory disease continues to increase and more knowledge is gained regarding pathophysiology, there are an unacceptably high percentage of patients who are not receiving the

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appropriate treatment resulting in a negative impact on their lives and that of their families. It may seem obvious that the appropriate diagnosis must be made and the correct treatment for the patient with the disease (as opposed to just treating the disease) is selected, the patient then needs to be monitored and therapy adjusted accordingly. Surprisingly this is not done in a large number of patients.

If we had to consider asthma and COPD, we encounter a number of common pitfalls. Very often an appropriate differential diagnosis between asthma and COPD, which necessitates spirometry, is not performed. In COPD patients, treatment all too often includes an inhaled glucocorticoid, a $ß_2$ agonist and an anticholinergic agent. While at times this treatment is indicated, since a proportion of patients present with both asthma and COPD, in those patients who only present with COPD, inhaled glucocorticods are not useful, unless the condition is severe (FEV_1 <50% predicted) and should only be used if there is a significant symptomatic and lung function response or if there are repeated exacerbations (eg, 3 in the last 3 years). On the other hand, withdrawing inhaled glucocorticoids may lead to exacerbations in some patients. Prescribing an additional inhaler when not absolutely necessary will only tend to confuse the patient and possibly decrease adherence to medication which is of some use and also contributes to increased drug costs.

Asthma may be under diagnosed and under treated. With the exception of intermittent asthma, inhaled glucocorticoids are indicated as first line therapy. Failure to prescribe these drugs in the appropriate dose will lead to deterioration in lung function, increased symptoms and exacerbations and eventual need of a higher dose of glucocorticoids to achieve control of the condition. Patients may need emergency room visits and possibly hospital stays. These factors, accompanied by days lost from work, lead to a decrease in the quality of life of the patient and impose a substantial financial burden to the health care system. These undesirable events may also occur due to inappropriate monitoring of the condition. Although prescribed the appropriate therapy, patients may either not be taking their therapy altogether or they may be using their inhaler inappropriately.

Over treatment with inhaled glucocorticoids may also be a problem. High doses are necessary to achieve control as fast as possible, however, patients need to be reviewed on a regular basis and stepped down accordingly. While the safety profile of inhaled glucocorticoids is clearly better than that of oral glucocorticoids, evidence shows that long term treatment with inhaled glucorticoids leads to a number of systemic side effects. Emergence of systemic side effects increase morbidity and treatment costs.

This publication is aimed at sensitising pharmacists and doctors to common respiratory conditions with the aim of improving patient care. While appropriate therapy is available, suboptimal therapeutic management is often encountered.

Emphasis has been placed on asthma and COPD, however, antibiotic use also allows for vast room for improvement. Antibiotic dosing for the future is aimed at individualised dosing. This would assure better clinical and bacteriological efficacy and lead to minimisation of development of resistance, adverse effects and potentially costs.

Improved pharmacotherapeutic management leads to better patient outcomes, increased professional satisfaction and makes better use of the financial resources available.

Guest Editorial

A breath of fresh air

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Symptoms of pulmonary disorder are one of the major reasons why patients seek advice from their doctor or pharmacist. They usually follow a seasonal pattern and are much more common during wintertime. Most symptoms follow common viral infections and are of a transient and self-limiting nature: very often the only therapy necessary is rest and simple symptomatic relief. Upper respiratory tract infections are rarely lethal, but they cause much morbidity and account for the loss of countless workdays, and school absenteeism.

The spectrum of respiratory disease fluctuates over time and reflects changing milieux and life-styles. The practice of pulmonary (or chest) medicine around a hundred years ago was mostly concerned with the diagnosis and treatment of infection and its consequences. Then, the tools were rudimentary and there was, of necessity, complete reliance upon accurate physical examination. This issue of Chronic*ill features a paper by Ellul Micallef that not only affords insight into the medical scene prevailing many years ago but also details the pioneering work of Auenbrugger and Laënnec in the field of physical examination of the chest. Their methods of rigorous direct observation are as valid today as they were then.

A hundred years ago, the use of X-rays to aid diagnosis was in its early infancy and the work of Robert Koch in the field of bacteriology was still being questioned and debated. Over the years, radiology and bacteriology became an integral part of the practice of chest medicine. The specialty is currently going through a phase of critical reappraisal and not only is there close cooperation with radiologists and microbiologists, but also with pharmacists, public health specialists, physiotherapists, nurse-practitioners and immunologists. The paper discussing pharmacogenetics of asthma therapeutics by Fenech and Ellul Micallef is a prime example of such collaboration and is evidence of a healthy blurring of demarcation lines between scientific disciplines.

The pattern of respiratory tract infection has changed significantly over the years and one now has to consider both the resurgence of "old" diseases such as tuberculosis as well as the emergence of "new" diseases, such as infection with Legionella and SARS. Indeed, the impact of widespread and frequent travel overseas has also had an effect on the epidemiology of respiratory communicable disease.

The rise in incidence of tuberculosis is multifactorial and the World Health Organisation predicts an increase of 57% in the EU and 10% in USA and Australia. Co-infection with TB and HIV only partly explains this rise and other factors are changes in patterns of human migration and in healthcare funding. In addition, the emergence of resistant TB strains poses a great challenge both to healthcare systems themselves, as well as to public health.

A hundred years ago, Sir William Osler referred to pneumonia as 'captain of the men of death'. Mortality from

this disease is no longer high; however in today's practice one often encounters difficulties in treating hospital-acquired pneumonia and lung infections in patients with compromised immunity. Treatment options today are incomparable with those available to Osler, while the antibiotic armamentarium at the disposal of physician and pharmacist is extensive, and one that is rapidly evolving to keep ahead of emerging resistance.

In developed countries, a sizeable portion of the workload of specialist respiratory teams consists of care of patients with non-communicable lung disease. Asthma has a rising incidence among all age groups in the Maltese community and the impact of this disease is felt at many levels, amongst them the increasing demands and costs for the provision of care. At an individual level, patients are rightly concerned about their quality of life and Cordina's paper in this Journal addresses this issue together with the need for adequate and sustained control.

COPD is common among the middle-aged and elderly population and because of former patterns of cigarette smoking in Malta, it is much more prevalent among men. Epidemiological patterns taken from other EU states suggest a future increase in incidence in Malta, given the high prevalence of smoking among young women. Malta forms part of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and a paper in this Journal highlights the need to increase awareness of COPD, not only at an individual level, but also as a public health problem on a countrywide scale.

Evidence-based medical practice is here to stay, and guidelines for management are often used as standards of care. Locally, in the field of respiratory medicine there are two published sets of guidelines for management (Asthma and COPD) and another two are in the pipeline (Oxygen Therapy and Pulmonary Thromboembolic Disease).

The underlying methodology of these four sets of guidelines has been development by multidisciplinary groups and their basis upon systematic review of scientific evidence.

Cigarette smoking contributes to much morbidity and mortality among our community. Cancer of the lung, causally related to smoking, is the most common form of cancer among Maltese men and a forecast of increasing incidence among women mirrors the current gender-specific smoking pattern.

The year 2004 was a landmark for public health in Malta, in that significant anti-smoking legislation was implemented in the face of much opposition from many quarters. The restrictions on smoking in public places were long-awaited by the health care professions, but more importantly they were eagerly welcomed by the multitudes in our population who feel that it is their right to breathe clean air.

Auenbrugger and Laënnec

Two pioneers who have demarcated the development of Western thoracic medicine

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With the publications in 1761 of Giovan Battista Morgagni's (1682-1771) 'De sedibus et causis morborum' (On the Sites and Causes of Diseases),[1,2] pathological anatomy became a science in its own right. Morgagni's aim was to try and correlate the symptoms of a disease as it developed with findings at post mortem.[3] Although this found immediate application in surgical disorders, where lesions were often visible and palpable, it was not thought to be equally useful in cases of internal ailments as long as physicians were unable to explore what was happening to internal organs during life.[4] This was made possible with the clinical diagnostic procedures pioneered by Leopold Auenbrugger (1722-1809) and by René Théophile Hyacinthe Laënnec (1781-1826).

Auenbrugger, (Figure 1) senior physician to the hospital of the Holy Trinity and the Spanish Military Hospital at Vienna, introduced percussion of the chest as a diagnostic tool. It is said that this son of an Austrian innkeeper from Graz first latched on to the diagnostic potential of percussion after he had observed his father tapping wine barrels in his cellar. Leopold studied medicine in Vienna during the time that the medical school there was being reformed along the lines of the Leyden school by the Dutchman Gerhard van Swieten (1700-1772). Auenbrugger was blessed with a musical ear and this undoubtedly helped him unravel the dullness and resonances which he elicited through the percussion of the chest and correlate them to underlying pathological processes. He published his findings in 1761,[5] as a modest little volume of 75 pages, 'Inventum novum in percussione thoracis ut signo abstrusos interim pectoris morbis detegendi thoracis'. (Figure 2)

Figure 1:
Leopold Auenbrugger

Auenbrugger established that by percussing the chest wall a careful clinician could obtain almost as much information about underlying pathology as if he were looking through the chest. It was thus possible to diagnose abscesses, areas of collapse, consolidation of the lung, air in the pleural cavity, pleural effusion and different kinds of enlargements of the heart.[6,7]

He was also an accomplished musician and at the Emperor's request wrote the libretto for a comic opera, Der Rauchfangskehrer (The Chimney Sweep) for the court composer Salieri. Its first performance was reported to have been 'ein Kolossales Succes'! Although he was ennobled in 1784 his new method of clinical examination was not immediately widely accepted. Indeed it is said to have been given


LEOPOLDI AUENBRUGGER

INVENTUM NOVUM

EX

PERCUSSIONE THORACIS HUMANI

UT SIGNO

ABSTRUSOS INTERNI

PECTORIS MORBOS

Figure 2:
Auenbrugger's Monograph on percussion

only a muted reception by his contemporary, Anton de Haen (1704-1706), one of Herman Boerhaave's (1668-1738) star pupils, who as Professor of Medicine in Vienna did a lot to introduce thermometry. Auenbrugger was well aware that it was not easy for innovations to be accepted by one's professional colleagues, for in the introduction to his book he wrote: '... it has always been the fate of those who tried to improve their arts or sciences to be beset by envy, malice, hatred, detraction and calumny'.[8] He was being perhaps a little paranoid but not totally so.

The importance of percussion as a bedside skill in the clinical examination of a patient was however fully appreciated by Jean Nicolas Corvisart (1775-1821), Napoleon's personal physician. As the first professor of medicine at the Hôpital de la Charitè he had plenty of opportunity to introduce this clinical method of examination to his many students among whom was Laënnec.[9] In 1808 he published an annotated translation in French, 'Nouvelle Méthode pour reconnaitre les maladies internales de la poitrine' of Auenbrugger's monograph in which he gave full credit to the Austrian physician. The first English translation by Sir John Forbes (1787-1861), 'A new invention for Percussing the Human Chest to Detect Hidden Signs of Disease' had to wait for a further 16 years before being published.[6] Auenbrugger's method was further improved upon by Pierre Adolphe Piorry (1794-1879)[10] and Josef Skoda (1805-1881).[11,12]

Both Auenbrugger and Corvisart are considered to be important forerunners of the greatest medical revolutionary of the nineteenth century, Laënnec (Figure 3). The latter was born in Quimper, in Brittany, and lost his mother when he was only five years old. René spent his later childhood first with an uncle, a curé, who had to flee to England from the Revolution and subsequently with another uncle, a medical practitioner at Nantes who subsequently became Rector of the University.[13] Laënnec's name is forever linked with the invention of a simple diagnostic aid, the stethoscope.[14] The word, a combination of two Greek words, 'chest' and 'to view' is curiously a misnomer because whilst it aids in the auscultation of sounds emanating from inside the chest it certainly does not permit the viewing of any thoracic organs.

Laënnec described what led to his invention during the examination of a somewhat buxom patient, Mlle de Surenne, in 1818: 'As I realised that both percussion and direct auscultation were almost useless through the layer of fat, I recalled from boyhood a familiar fact of acoustics, namely that if one places one's ear at the end of a piece of timber one can hear very distinctly the scratch of a pin at the other end ... I therefore took a paper notebook, rolled it up tightly, applied one end to the precardiac region and listened at the other. I was as surprised as I was pleased to hear the heartbeats much more clearly and

Figure 3:
René Théophile Hyacinthe Laënnec

distinctly'.[15] As with Auenbrugger, a simple boyhood observation led Laënnec to a discovery that was to deeply affect the practice of medicine.

Laënnec performed a number of experiments to establish the best material to use and to determine the right length, the correct internal measurements and most convenient shape. He produced a hollow wooden tube about 30cm long and 5cm in diameter, widening into a funnel at one end and fitting into the doctor's ear at the other (Figure 4). His observations, reported to the Paris Académie des Sciences, were at first met with disbelief. Within a few years however the use of the stethoscope had become widespread not only in France but also

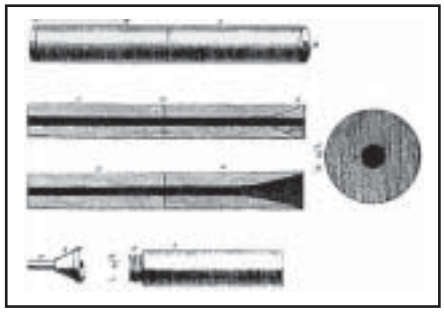

Figure 4:
Laënnec's own design for a stethoscope

in a number of other European countries. Forbes, who had earlier translated Auenbrugger's work, became an admirer of Laënnec. He translated into English his work, first published in Paris in 1819 as 'De l'auscultation médiate, ou traité du pronostic des maladies des poumons et du coeur'.[16] Forbes was however sceptical as to whether this 'ingenious instrument' would ever 'come into general use' in England 'because its beneficial application requires a good deal of trouble and skill but also because its whole character is utterly foreign'. In addition Forbes felt that 'To Englishmen there will always be something ludicrous in the image of a grave physician listening to a chest through a long wooden tube as if the disease were a living thing in communication with him ....' This Scottish physician had something even more damning to say about English clinicians: 'there is in this method', Forbes wrote, 'a sort of bold faith in the physical examination of patients wholly alien to English medicine, more accustomed to calm cautious philosophical musings'.[17] He could not have been more wrong!

Laënnec's medical and scientific achievements were many. Based on clinical and postmortem findings he described many respiratory ailments ranging from tuberculosis and asthma to bronchiectasis, a condition he called 'bronchorrhées purulentes'. He was eventually appointed to the Chair of Medicine at the Collège de France in succession to Corvisart. Laënnec died of tuberculosis almost certainly picked up in the post mortem room.[18]

Percussion and auscultation helped the physician obtain an objective view into a patient's illness. It may well be worth quoting here what one of Laënnec's students, Jean Baptiste Bouillaud (1797-1881) had to say in his book 'Essai sur la philosophie médicale et sur les généralites de la clinique médicale' published in Paris in 1836: 'C'est ainsi, par exemple, que dans les maladies de poumon et du coeur, l'oreille, s'il m'est permis de parler de la sorte, voyant et touchant ces organes, receuille, au moyen d'un examen attentif, des signes qui, comme l'a dit Laënnec, rendent le diagnostic de la plupart des maladies dont il s'agit aussi sûr que celui de certaines maladies chirurgicales, telles que les fracturis et les luxations entre autres'. (... in diseases of the heart and lungs, the ear, if I may so express myself, 'seeing' and 'touching' these organs, by means of an attentive examination picks up signs which, as Laënnec said, render the diagnosis of most of the ailments in question as certain as that of certain surgical conditions such as fractures and dislocations).[19]

Decades would have to pass before radiography would make the next significant contribution to the diagnosis and follow up of diseases.[20] It was in fact on the night of November 11th 1895 that Wilhelm Conrad Röntgen (1845-1923), professor of Physics at the University of Würzburg in Bavaria, while investigating the passage of an electric current through a vacuum tube, discovered X-rays.[21] Chest X-rays were to transform the diagnosis of pulmonary diseases especially tuberculosis, but Auenbrugger's and Laënnec's introductions still form an integral part of every clinical examination.

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Drug-induced respiratory disease

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Drug-induced lung disease is a relatively common condition caused by an adverse reaction to medication and it is often impossible to predict who will develop lung disease resulting from a drug.[1]

Introduction

Drug-induced lung disease may occur via various mechanisms:

- *Direct toxicity*: This usually takes time before it manifests clinically. The toxic effect is usually dose related, though other factors such as age and renal function can enhance toxicity.
- *Hypersensitivity reaction*: This is not dose related and requires prior sensitization to the drug. It is a result of interactions between the drug and humeral antibodies or sensitized lymphocytes.
- *Pulmonary oedema*: This can occur with various drugs. Pulmonary oedema typically occurs within hours of administration of the drug.
- *Pulmonary haemorrhage*: This is most commonly a complication of anticoagulant therapy or drug-induced thrombocytaemia.
- *Pulmonary granulomas*: These are composed of macrophages reacting to various drugs.[2]

Cardiovascular Drugs

Angiotensin-converting enzyme inhibitors

Angiotensin converting enzyme inhibitors (ACEIs) are rightly so prescribed for the treatment of hypertension, especially in the presence of left ventricular dysfunction and congestive heart failure. In these patients ACEIs decrease morbidity and mortality. Yet, some patients may experience a tedious dry cough which affects their compliance. Cough is the most common adverse effect with this class of drugs and it occurs about five times more often than with placebo. Cough is more common in women and older patients.[3] Approximately 0.1 to 0.2% of patients receiving ACEIs experience more serious adverse effects which can vary from a mild swelling of the face to swelling of the tongue and supraglottic area leading to respiratory compromise.[4] The etiology of ACEI-related side-effects is not completely understood, however, the accumulation of bradykinin is thought to be one explanation. Bradykinin causes vasodilation and capillary leakage leading to side effects. Adverse effects might be seen in some patients and not others due to a possible genetic deficiency of bradykinin-metabolizing enzymes in some patients.[4]

Beta-Blockers

Beta-blockers are frequently prescribed in hypertensive patients or ischaemic heart disease sufferers without taking into consideration whether the patient suffers from asthma. Beta-blockers are contra-indicated in asthma as they can cause bronchospasm. Being competitive inhibitors of beta-adrenoceptors, even small doses of beta-blockers can cause bronchospasm, with manifesting symptoms such as shortness of breath and wheezing.[3] The severity of the bronchoconstrictor response to a given beta blocker is not predictable, and occurs mainly in patients with reversible bronchial obstruction.[5] This can also be extended to topical beta-blockers, such as eye drops. Systemic absorption and thus side-effects can be encountered even with these preparations.

Amiodarone

Atrial fibrillation is a common dysrhythmia frequently treated with antiarrhythmic drug therapy, such as amiodarone. Long-term use of amiodarone may cause pulmonary complications, including pneumonitis

and acute respiratory distress syndrome (ARDS), in up to 10% of patients receiving this drug. However, most of the published cases have been in patients receiving more than 200mg per day of amiodarone (usually 400mg/d or more). Low dose amiodarone poses fewer problems though the Canadian Myocardial Infarction Amiodarone Trial showed that even low-dose amiodarone increased pulmonary toxicity compared to placebo (3.89% vs. 1.2%). Therefore, the clinician must keep in mind that even low-dose amiodarone is associated with some risk for pulmonary toxicity.[6]

Anti-inflammatory agents

Aspirin and NSAIDs

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for a variety of medical conditions. Patients commonly take NSAIDs for any type of pain they experience, without even consulting a doctor or a pharmacist. Aspirin and NSAIDs may precipitate asthmatic attacks in approximately 8 per cent of asthma sufferers and these attacks can occasionally proceed to be potentially fatal. Patients with chronic rhinitis and nasal polyps are at greatest risk. Persons with aspirin-induced asthma are usually not previously sensitive to aspirin and this usually appears in the third to fourth decade.[7] After aspirin ingestion, patients who are sensitive to aspirin may present with various symptoms such as rhinorrhea, dyspnoea and cough. These symptoms usually occur over a period of 20 minutes to three hours after ingestion of the drug and can lead to bronchospasm and angioedema. The overproduction of leukotrienes may be implicated in this asthmatic reaction.[8]

Methotrexate

Methotrexate is used in the treatment of rheumatoid arthritis and other connective tissue disorders, as well as in cancer chemotherapy. Pulmonary complications seen in patients who are on anti-inflammatory doses of methotrexate include opportunistic infections, acute interstitial pneumonitis, interstitial fibrosis, and asthma.[7]

Infliximab

Infliximab is used in patients with rheumatoid arthritis and Crohn's disease. It can cause infusion reactions which can occur during or 1-2 hours after infusion. These reactions can cause symptoms such as fever, chills as well as dyspnoea and cough.[9]

Chemotherapeutic drugs

Bleomycin

Bleomycin is deposited in the skin and lungs; hence the most serious adverse effects are seen in these organs.[7] Chronic lung damage secondary to the use of bleomycin is rare though it can progress to pulmonary fibrosis and death in a minority of patients.[10] The role of Interleukin-4 in the development of lung fibrosis is as yet unclear.[11] Risk factors for bleomycin toxicity include total dose of bleomycin given, exposure to high oxygen concentrations, thoracic radiation, decreased renal function, older age and smoking. With doses of bleomycin less than 300mg, the incidence of pneumonitis is 3-5% whilst with doses higher than 500mg the incidence is 20%. Bleomycin-induced pneumonitis usually occurs gradually in the first few months of therapy. Pulmonary function tests should be monitored in order to detect the onset of bleomycin-induced pneumonitis.[10]

Mitomycin-C

Incidence of pulmonary toxicity with Mitomycin-C is about 5% and this includes bronchospasm, acute pneumonitis, haemolytic-uremic-like syndrome, acute lung injury, chronic interstitial pneumonitis, and pleural disease.[7]

Hypnotics and Anxiolytics and Barbiturates

Benzodiazepines

Benzodiazepines are widely prescribed in general practice to relieve anxiety and facilitate sleep. There is still much debate regarding the over use of this class of drugs, especially since benzodiazepines can easily cause dependence the over use of this class of drugs.

Benzodiazepines are also weak respiratory depressants. When administered as monotherapy, respiratory depression with diazepam may be detectable at doses of 0.2mg/kg (14mg dose for a 70kg person). The resulting increase in CO_2 is slight, clinically insignificant, and may be attributable to decreased tidal volume. However, respiratory depression with benzodiazepines can be clinically significant when used in combination with other respiratory depressants or if allowed to accumulate to toxic levels. Elderly patients are at particular risk from longer acting agents such as flurazepam and diazepam. This should be of concern to clinicians when considering the high amount of prescriptions issued for diazepam, especially to the elderly. Often benzodiazepines may be prescribed concomitantly. Lorazepam and temazepam are eliminated primarily by glucuronidation, which is less dependent on microsomal enzymes, and are unlikely to be influenced by hepatic dysfunction or increasing age. Moreover, they do not have active metabolites and have a shorter half-life (15 hours). As a result, they are safer than the other benzodiazepines.[12]

Barbiturates

Barbiturates are still sometimes prescribed for patients suffering from epilepsy. These are strongly associated with drug-induced respiratory depression and are, therefore, contra-indicated in patients with severe respiratory disease. Barbiturates are thought to induce respiratory depression by desensitization of the medulla to hypercapnia and these agents inhibit the respiratory rate and affect the depth and volume of inspiration. Phenobarbitone should be therefore prescribed with great caution.[12]

Antimicrobial drugs

Nitrofurantoin

Nitrofurantoin, commonly prescribed for urinary tract infections, may cause pulmonary disease with eosinophilia. Initially the patient presents with fever, dyspnoea, cough and pulmonary infiltrates, and there is often marked

peripheral blood eosinophilia. There may be an acute presentation, developing hours to days after initiation of treatment and complications usually resolve within 15 days of discontinuation of nitrofurantoin. Long term therapy with nitrofurantoin may eventually cause pulmonary fibrosis. This may occur from two months to five years after initiation of therapy and the patient will present with exertional dyspnoea and a non-productive cough and fatigue. This chronic form represents direct tissue damage from oxidants.[7,13]

Sulphonamides and sulpha containing drugs

Sulphonamides, commonly used to treat urinary tract infections as a combination in co-trimoxazole, are known to cause pulmonary eosinophilia which tends to occur 10-14 days after exposure. The patient presents with fever, blood eosinophilia and new pulmonary opacities.[13] Sulfasalazine, indicated for ulcerative colitis, Crohn's disease and rheumatoid arthritis, can cause lung complications such as eosinophilia and fibrosing alveolitis.

Tetracyclines

Minocycline can cause pulmonary eosinophilia, which is characterised by pulmonary infiltrates on the chest X-ray, chest symptoms such as dyspnoea, and eosinophilia in blood and bronchoalveolar lavage fluids. These symptoms may be severe enough to lead to transient respiratory failure.[13]

Illicit drugs

Cannabis, the most widely used illicit drug, contains carcinogens similar to those found in tobacco smoke, and hence chronic heavy marijuana use may predispose people to chronic obstructive lung disease.[14] Heroin is a derivative of morphine and can cause slow breathing by stimulation of mu receptors. Heroin reduces the brain's responsiveness to changes in PCO_2 and with high doses, it can also depress the brain's response to hypoxia. This results in severe respiratory depression progressing to apnoea. Therefore, fatal heroin overdose is nearly always caused by respiratory arrest.[15] Cocaine may cause wheezing which occurs from exacerbated asthma or hypersensitivity pneumonitis. Cocaine use may also lead to non-cardiogenic pulmonary oedema or to diffuse alveolar hemorrhage. Long-term users of crack, a chemical derivative of cocaine, can suffer from bronchitis and other breathing problems.[16]

Miscellaneous Drugs

Several other drugs can affect the respiratory system. Bromocriptine, a stimulant of dopamine receptors, can cause pulmonary fibrosis and pleural disease[7] as well as nasal congestion.[17] Antidepressant and antipsychotic agents have been associated with pulmonary oedema.[7] Venlafaxine, a serotonin and noradrenaline reuptake inhibitor, may potentially cause pneumonitis.[18] Some propellants found in inhalers which are intended to relieve respiratory problems, may actually cause cough. Doxazosin, an alpha-adrenoceptor blocking drug, may cause rhinitis and a potential side-effect of candersartan, an angiotensin-II receptor antagonist, is upper respiratory-tract and influenza-like symptoms including rhinitis and pharyngitis.[19]

Conclusion

This paper has only reviewed the more commonly used medications and illicit drugs. However, currently there are at least 150 agents which have the potential to cause pulmonary disease. Early diagnosis is important since stopping the drug usually reverses toxicity, whereas unrecognized toxicity can be progressive and even fatal. Therefore, both doctors and pharmacists in the clinical settings should be on the alert for possible associations between medication and lung related symptoms.

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Respiratory infections in childhood

To use antibiotics or not?

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Respiratory tract infections are the most common infections of childhood but are, in the main, caused by common viruses and result in a relatively benign course. The great majority can be managed by simple, supportive measures. Recourse to antibiotics is often unnecessary and, indeed, encourages antibiotic resistance that is fast becoming the greatest microbiological challenge of the 21st century. This article will outline the key features of common childhood respiratory infections and indicate the appropriateness, or otherwise, of antibiotics for each individual infection.

Introduction

Respiratory tract infections constitute the greatest 'illness burden' in childhood, virtually affecting all age groups but especially infants and pre-school children. They account for up to 30% of general practice consultations [1] and, worldwide, they result in 15 million deaths per annum in those below the age of five years. [2] Although most children will have between 2-4 upper respiratory tract infections per year, the vast majority of these will have a viral aetiology and are self-limiting. Nevertheless, they constitute a significant workload in primary practice and have important implications for pharmaco-prescribing. Others such as otitis media and pustular tonsillitis, though generally benign, may lead to secondary complications and, finally, a small minority such as epiglottitis and pneumonia may be serious from the outset. The crux of good medical practice is to differentiate between the benign and the potentially problematic, and intervene appropriately. In practice, this will translate into simple supportive measures in the great majority and aggressive intervention, including antibiotics, in just a few. This article will attempt to outline the clinical and identifying features of the more common respiratory infections affecting children beyond the neonatal period, and will provide simple guidelines for their management.

Respiratory infections

Types of respiratory infections

Respiratory infections can be conveniently divided into upper and lower infections, and may be caused by viral, bacterial and other organisms as shown in Table 1.

Upper respiratory tract infections

Nasopharyngitis

This constitutes the common cold, presenting with the coryzal syndrome of snuffles (rhinorrhoea), sneezing, cough and a low-grade fever. Involvement of the glottic area results in 'laryngitis' with pain and a hoarse voice. The vast majority (>75%) of infections are viral and self-limiting after 3-5 days. [3] Simple measures including paracetamol for temperature control and attention to regular fluid intake are indicated (Table 2). Oral decongestants/ antitussive medications with or without nasal decongestant drops are of doubtful value though they commonly result in behavioural problems. Antibiotics are grossly over prescribed in this setting, in Malta and elsewhere, and are only indicated if: (i) symptoms persist beyond 5-7 days; (ii) there is a marked purulent nasal discharge (may imply secondary streptococcal infection), and (iii) with signs of systemic deterioration with or without complications (e.g. otitis media or pneumonia).

Sinusitis

Sinusitis is uncommon in preschool children when the facial sinuses are

Table 1: Causes of respiratory tract infections		
Respiratory infections	**Upper tract**	**Lower tract**
Viral causes	rhinoviruses adenoviruses influenza A+B parainfluenza respiratory syncytial virus Ebstein-Barr virus coxsackie A+B echoviruses	influenza A+B respiratory syncytial virus cytomegalovirus human immuno- deficency virus measles virus* varicella*
Bacterial causes	streptococci spp. *S. pneumoniae* *H. influenzae* staphylococci spp.	*S. pneumoniae* streptococci spp. staphylococci spp. *H. influenzae* *B. pertussis* klebsiella spp.** pseudomonas spp.**
Other causes	mycoplasma	mycoplasma *P. carinii** fungal spp.*

* especially in the immunosuppressed patient.
** especially with underlying respiratory disease (e.g. cystic fibrosis).

still relatively underdeveloped. Children with sinusitis generally present with fever, headache, local tenderness, nasal stuffiness and catarrh that may be purulent. The majority are viral but secondary bacterial infection occurs in about 2-5%.[4] The latter include pneumococci, streptococci, Haemophilus and sometimes staphylococci. In the latter situations, antibiotics (beta lactam ± clavulanic acid, or a cephalosporin or macrolide[4]) are also indicated, together with analgesics, antipyretics and general supportive measures (Table 2).

Tonsillitis

Acute tonsillitis is very common, generally resulting in more systemic upset than nasopharyngitis with pain, higher fever, catarrh and cough, usually associated with cervical lymphadenopathy. Most are due to viruses but around 30-40% may be bacterial (usually streptococcal), when a pustular or exudative appearance may be more marked. The latter is, however, not diagnostic for bacterial versus viral tonsillitis and it is therefore reasonable to prescribe antibiotics for 5-7 days if the child is systemically unwell with pus on the tonsils. Conversely, the absence of pus does not exclude some bacterial infections and, again if systemic upset is present, antibiotics such as beta lactams, cephalosporins or, if allergic, a macrolide could be used (Table 2).

Otitis

Otitis externa presents with a sero-purulent discharge and erythema of the external canal with little in the way of systemic upset. In the majority, local cleansing and topical antibiotic drops will suffice.

Otitis media commonly complicates acute tonsillitis or nasopharnygitis and results in acute pain, high fever, nausea and vomiting and general irritability. Ear pulling or rubbing is not a particularly reliable sign, especially in toddlers. Inspection of the tympanic membrane during otostopy is resisted due to pain but will demonstrate dullness/redness of the

Table 2: Respiratory tract infections in childhood: aetiology and need for intervention				
Infection	**Incidence**	**Aetiology**	**Morbidity**	**Intervention**
Upper				
Nasopharyngitis	very common	V>>B	minimal	supportive ±Ab**
Sinusitis	very common	V>>>B	mild	supportive±Ab
Tonsillitis	common	V>>B	mild	supportive±Ab
Otitis externa	common	V=B	minimal	supportive±Ab
Otitis media	common	V=B	moderate	supportive+Ab
Laryngobronchitis	common	V>B	moderate/severe	supportive/intensive
Epiglottitis	very rare	B	severe	intensive+Ab
Lower				
Tracheitis	uncommon	B>V	moderate/severe	supportive/intensive+Ab
Pneumonia (lobar)	less common	B>>V	moderate/severe	supportive/intensive+Ab
Bronchopneumonia*	less common	B=V	moderate/severe	supportive/intensive+Ab
Empyema	rare	B	severe	intensive+Ab

Ab=antibiotics; V=viral; B=bacterial (including mycoplasma).
*includes RSV bronchiolitis.
**Supportive measures include paracetamol for temperature, attention to regular fluid intake, oral decongestants/antitussives ± nasal decongestant drops.

drum sometimes with vesicles. Fluid and air bubbles may be visible behind the drum that may perforate spontaneously to release pus.
Up to 50% of cases are caused by *S. pneumoniae* and other bacteria which infect the upper airway (Table 1). Supportive measures, adequate analgesia and a short 5-day course of antibiotics (beta lactam or macrolide) are indicated (Table 2), although reports of antibiotic resistance are increasing.[5]

Laryngotracheobronchitis

Commonly known as '**croup**', larnygotracheobronchitis is a common condition affecting children between the ages of 6 months to 4 years and is usually caused by parainfluenza, influenza and RSV viruses. A mildly febrile, coryzal prodrome of 1-3 days is followed by a deterioration with a barking/hacking cough, hoarseness and stridor. Significant airway swelling may lead to obstruction with hypoxia causing irritability, distress and eventually exhaustion. Most cases resolve before reaching this stage and may be treated with paracetamol and fluids. A short 3-day course of oral or rectal steroids may help to reduce the upper airway oedema.[6] Simple decongestants/antitussives may offer some relief but humidifiers and humidification tents have not been shown to be effective. Those with signs of respiratory embarrassment should be referred to hospital with urgency where nebulised adrenaline may buy time until the airway can be secured (Table 2).

Epiglottitis

This serious infection, caused by *H. influenzae,* is now extremely rare since the advent of the Hib vaccine. Children would present with a short, rapidly deteriorating history with general 'toxicity', fever, stridor and increasing respiratory compromise. The ill looking stridulous child, drooling at the mouth and assuming a position with forward neck extension should raise alarm bells and prompt urgent referral to hospital. Nebulised adrenaline and oxygen are the mainstay of initial therapy pending intubation (by the most experienced operator available), followed by intravenous fluids and a third generation cephalosporin (Table 2).

Lower respiratory tract infections

Lower respiratory tract infections (LRTIs) are less common but more likely to result in serious complications when compared with URTIs (Table 3). Furthermore, they are more likely to be caused by bacterial agents and the indication for adding antibiotics to the treatment regimen is clearly greater.

Tracheitis

Severe tracheitis is a rare, serious infection involving the main airway in childhood that results in generalised debility, copious pus in the trachea and airway compromise. Staphylococci are often to blame and treatment entails respiratory support, intravenous fluids and anti-staph antibiotics (flucloxacillin, aminoglycosides).

Pneumonia

A **lobar pneumonia** complicating an URTI should be suspected when the symptoms do not subside after a week or so, particularly in those with persistent lethargy, high, swinging fevers and a productive cough. Clinical focal signs may be difficult to illicit, especially in young children and, whenever there is any doubt, this would be an indication for a 'screening' chest X-ray. Most are due to *S. pneumoniae*, followed by mycoplasma and other bacteria (streptococci, staphylococci, Haemophilus, etc). It is difficult to differentiate between bacterial pneumonias and 'atypicals' due to mycoplasma and, for this reason, current guidelines dictate that all cases where either agent may be responsible are treated with dual antibiotics including a beta lactam or cephalosporin and a macrolide for at least 10 days, half of which is administered intravenously. [7] Physiotherapy, fluids and antipyretics complete the treatment regimen. Staphylococcal and streptococcal pneumonias may be complicated by lung abscesses, air leaks, effusions, empyemas or pneumatocoeles and may require surgical drainage. Recurrent, refractory or unusual pneumonias may indicate an underlying disorder affecting the respiratory tract such as cystic fibrosis, immune or congenital defect.

Bronchopneumonia presents with a similar clinical picture but produces diffuse crepitations throughout both lung fields, confirmed by patchy non-focal changes on X-ray. Infecting causes include bacterial and atypical organisms (as per lobar pneumonias), as well as opportunistic organisms such as fungal species, certain viruses (measles and varicella) and pneumocystis carinii. The latter are almost invariably seen in children with an immune defect or those undergoing immunosuppressive therapy (e.g. cancer chemotherapy).

Table 3: Complications of URTI and LRTIs

Complication	URTI	LRTI
General	Fever, debility, poor feeding	Fever, debility, poor feeding
Secondary infection	Otitis media *Mastoiditis* *Retropharyngeal abscess* *Meningitis* *Septicaemia*	Lung abscess Septicaemia *Empyema*
Others	Febrile convulsions Chronic otitis media *Airway compromise* *Glomerulonephritis* *Rheumatic fever*	Febrile convulsions Pleural effusions Air leaks *Pneumatocoeles* *Bronchiectasis*

Complications in italics are rare.

Table 4: Recommendations for antibiotic usage in URTI and LRTIs		
Infection	**Most common organism**	**First line antibiotic**
Upper		
Nasopharyngitis	75% viral;	Nil
	20% Gp A strep	Penicillin V or clarithromycin
Sinusitis	95% viral;	Nil
	2% *S. pneumoniae, H. influenzae*	Amoxycillin & clavulanic acid; macrolide; cephalosporin
Tonsillitis	60% viral	Nil
	40% *S. pneumoniae*, streptococci, *H. influenzae*	Beta lactam, cephalosporin, macrolide
Otitis media	50% viral;	Nil
	50% *S. pneumoniae*, streptococci, *H. influenzae*	Beta lactam, cephalosporin, macrolide
Laryngobronchitis	parainfluenza, influenza, RSV	Nil
Epiglottitis	95% *H. influenzae*	3rd generation cephalosporin
Lower		
Tracheitis	*S. aureus,* streptococci	Flucloxacillin, vancomycin, aminoglycoside
Pneumonia	*S. pneumoniae*, mycoplasma	Beta lactam or cephalosprin + macrolide
Bronchiolitis	RSV	Nil
Pertussis	*B. pertussis*	Macrolide

Bronchiolitis is a specific, generalised bronchopneumonia usually due to RSV infection in 70% of cases, which affects infants and pre-school children particularly during late autumn to early spring. Children present with a minimal fever but have a 'spluttering' cough, copious catarrh and increasing respiratory distress often with widespread wheezing. Oxygen and ventilatory support is required in those with significant respiratory compromise - the majority may benefit from bronchodilatation therapy, as well as supportive measures, with or without simple decongestants. Steroids have been shown to confer some benefit in those who are severely ill and require ventilation, whereas antibiotics are only indicated for secondary bacterial super-infection. [8]

Pertussis

Concerns with pertussis vaccines in the 1970s led to inadequate uptake of this vaccine and suboptimal herd immunity. As a result, pertussis is still prevalent and may cause a severe generalised pneumonia, especially in young infants yet to be immunised. Apart from general supportive measures, antibiotics effective against Bordetella pertussis such as macrolides are prescribed since they may shorten the period of excretion and risk to others. [9] There is little evidence that they alter the course of the primary illness.

Empyema

This arises when a pleural effusion, generally associated with an underlying lobar pneumonia, becomes secondarily infected to form a large collection of pus between the lung and chest wall. The empyema may become loculated and will require prolonged anti-staph. and anti-strep. intravenous antibiotics, plus repeated chest drains and/or surgical interventions before resolution.

Conclusion

In summary, most URTIs are viral in origin and simply require supportive therapy without antibiotics. Indeed, widespread inappropriate prescribing in this situation has contributed significantly to the development of antibiotic resistance and is irresponsible. When antibiotics are indicated, they should be used in accordance with guidelines that are evidence-based. Guidelines for antibiotic usage should target the most likely pathogen, take into account current resistance patterns and the results of well-conducted clinical trials, as well as the safety profile, ease of administration and patient tolerance of the antibiotic in question. On this basis, Table 4 outlines the current recommendations for the use of antibiotics in the more common respiratory tract infections of childhood.

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Cough: a defence mechanism and a symptom

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Keywords: cough, smoking, post-nasal drip, asthma, gastro-oesophagela reflux, diagnostic protocol

Cough is a very frequent reason why patients consult their family doctor and seek advice from the community pharmacist. Together with breathlessness, it is one of the commonest symptoms of lung disease.[1] Cough is not only a symptom, but also a very rapid defence mechanism that both protects and clears the airways. Coughing may also be looked upon as a means of spreading infection via droplets and contamination of objects.

Coughing may be voluntary but it is usually an involuntary reaction to stimulation of cough receptors in the airways. The cough centre in the medulla oblongata reacts to stimuli arising from receptors in the nose, nasopharynx, tracheobronchial tree, and the pleura. The slightest inhalation of minute amounts of foreign matter is enough to trigger the cough reflex.

The physiology of coughing involves quite a complex sequence. There is first deep inhalation, and a closed glottis seals the air within the lungs. The abdominal and other respiratory muscles contract forcefully, raising pressure within the lungs to over 100mmHg. The vocal cords and epiglottis suddenly open, releasing the air in the lungs at exhalation velocities of over 100km/h.

Complications of coughing are infrequent and are usually mild, such as hoarseness and headaches. Recurrent severe bouts may however lead to such complications as urinary incontinence, disruption of surgical wounds, subconjunctival haemorrhages and rib fractures. Chronic coughing often causes persons to be self-conscious and may affect the quality of life significantly.[2]

The most common cause of acute cough is the common cold and usually subsides without the need for any treatment; other causes are acute sinusitis, pertussis and asthma.[3] Occasionally, acute cough is a symptom of serious disease such as congestive heart failure, pulmonary embolism, pneumonia or inhalation of a foreign body.

Chronic cough may be defined as a cough of more than eight weeks' duration.[4,5] Cigarette smoking is a leading cause of chronic cough and the symptom is directly related to the number of cigarettes smoked per day.[6] About 25% of those who smoke half a packet per day report a chronic cough, and this figure rises to over 50% among those who smoke more than two packets daily. Many smokers accept coughing as normal and may not seek medical attention for a cough that persists. Cough is also an important symptom of lung cancer, a disease predominantly prevalent among smokers. Indeed, a change in the character or pattern of coughing in a smoker should always be thoroughly investigated.

The four most common causes of chronic cough among non-smokers are post-nasal drip, asthma, gastro-oesophageal reflux and post-infectious bronchial infection. Patients with post-nasal drip syndrome also complain of a sensation of something dripping into the throat, a tickle in the throat, hoarseness, nasal congestion and/or discharge. If sinusitis is the cause of post-nasal drip, combined treatment with antibiotics, intranasal corticosteroids and decongestants may

be necessary.[7]

Asthma may cause chronic cough across all age groups and must be considered in the differential diagnosis of most patients presenting with this symptom. When cough is the only symptom of this condition, the term cough-variant asthma is used. Treatment for this form of asthma is the same as for asthma presenting with other symptoms: anti-inflammatory treatment being the mainstay of therapy, and use of bronchodilators for rapid relief.[8]

Gastro-oesophageal reflux (GOR) occurs when acidic stomach contents leak into the oesophagus or higher up. The most likely pathogenesis is stimulation of vagally mediated receptors in the oesophagus, and the actual aspiration of stomach contents causing cough is uncommon. Patients with GOR may complain of chest discomfort and heartburn; however chronic cough may be the only symptom present. Diagnosis of GOR-related cough can be made with certainty when the symptoms respond to anti-reflux therapy.[9]

Chronic inflammation of the airways is an important trigger of persistent cough, and chronic bronchitis due to exposure to tobacco smoke or other respiratory irritants is the commonest cause in this respect; other causes include bronchiectasis. Coughing may persist following acute respiratory tract infection and is due to ongoing inflammation. This cough eventually resolves, however treatment is often necessary to ease discomfort.

Occasionally, cough occurs as a side-effect of medication and the class of drugs most commonly implicated is angiotensin converting enzyme (ACE) inhibitors. A review of the literature suggests that around 10% of patients treated with an ACE inhibitor may have cough as a side-effect, rapidly resolving when the drug is withdrawn.[10] Treatment with beta-blockers may cause increased airway resistance and consequent provocation of coughing especially among patients suffering from asthma and COPD.

Psychogenic cough occurs more frequently in children; however it has lower rates of resolution among adults. Emotional and psychological problems are the likely causes and this diagnosis can only be made after all other possibilities have been ruled out. Most patients with psychogenic cough neither have this symptom during sleep nor during enjoyable distraction. In some patients, coughing is a nervous tic, occurring only when they become upset or self-conscious. [11]

When coughing is transient, and of a trivial nature, investigations are not necessary and only symptomatic relief is warranted. When the cough becomes chronic, evaluation should begin with a detailed history and a physical examination initially focusing on the nose, the nasopharynx and the lungs. Easily identifiable causes, such as ACE inhibitor use and exposure to irritant fumes, should be addressed. A chest X-ray should be considered very early in the evaluation process, and more specific tests considered should this be abnormal or if the cough persists. Algorithms for evaluating cough have been drawn by a Consensus Panel of the American College of Chest Physicians and the European Respiratory Society Task Force[5], and suggest a sequential approach both for immunocompetent and for immunologically-incompetent adults.

When pharmacologic treatment of cough becomes necessary, distinction between anti-tussive therapy and pro-tussive therapy is important.[1] Non-specific cough suppressants such as codeine and dextromethorphan are directed at the symptom and not at the cause. They are indicated when specific therapy cannot be given or when this has not yet treated the cause.[12] They are also given when specific therapy cannot work, as in advanced and inoperable lung cancer.

Coughing is necessary for mucus clearance and this may be facilitated by agents that increase cough effectiveness, often by making expectoration easier. In practice, however, evidence of clinical utility of these agents is not clear.

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Controlling asthma and improving quality of life

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Asthma is a common chronic condition which usually presents with the symptoms of wheeze, cough, shortness of breath and chest tightness due to the underlying inflammation and bronchoconstriction present in the lungs. This condition causes considerable distress to the patient and negatively affects other members of the family. To date we cannot cure asthma, but we can aim to achieve optimum control as recommended by international guidelines.

Current therapeutic options offer the possibility of enabling the patient to lead as normal a life as possible with minimal interference from the condition. Successful outcomes for asthma control necessitate health care professionals to understand the experiences, expectations and needs of male and female asthma patients of all ages.

Introduction

International asthma management guidelines state that the aim of therapy is to achieve control of asthma (Table1).[1] Inadequate control of asthma contributes to increased morbidity and mortality and places considerable restrictions on the physical, emotional and social aspects of persons with asthma. These restrictions have a substantial negative impact on the quality of life of asthma sufferers and their carers.

Effect of asthma on quality of life

The limitations placed on physical activities, such as getting around the house, shopping, gardening, exercising and engaging in sports are significantly more of a burden on asthma suffers than on patients with other chronic conditions, such as diabetes, and are even more pronounced in young women with asthma. [2,3] The emotional impact of asthma is felt across all age groups, however it is particularly evident in children, who experience feelings of anger, frustration, sadness and guilt because of their condition.[4] Persons with asthma often choose to refrain from engaging in social activities or do so with reluctance and possibly trepidation due to fear of experiencing an exacerbation.[5]

Inadequate control, leads to increased asthma symptoms, decreased quality of life and could promote a lack of confidence in the medical care being given. The lack of perceived benefit from therapy decreases adherence to prescribed medication and in some cases also stimulates patients to substitute medication with alternative therapies, which are not validated by conventional standards, potentially leading to detrimental effects on health. It is therefore essential to provide patients with therapy which is safe, effective at the physiological level, provides adequate symptom control and allows them to live a normal life i.e. patients need to be provided with medication that works and that they perceive is working.

The use of guidelines in the management of asthma

While guidelines are well accepted as being an effective tool in the management of asthma, studies show that the desired degree of control is still not being achieved.[6] Various reasons have been cited for this, the main ones being inappropriate implementation of guidelines, under treatment of asthma and inefficient communication between health care provider and patient.[7] Evidence shows that appropriate management according to guidelines, close monitoring and increased access to health care professionals i.e. delivery of pharmaceutical care, improves therapeutic outcomes and patient

Table 1: GINA defined asthma control[1]

- Minimal (ideally no) cough, wheeze, chest tightness, breathlessness including nocturnal symptoms
- Minimal (infrequent) exacerbations
- No emergency room visits
- Minimal (ideally no) use of prn short acting $ß_2$ agonist
- No limitations on activities, including exercise
- Peak expiratory flow (PEF) circadian variation of less than 20%
- (Near) normal PEF
- Minimal or no adverse effects from medication

satisfaction.[8] The close monitoring of the patients permits adaptation of treatment to the current severity of the disease, addressing the variable and dynamic nature of this chronic condition.

Achieving and maintaining control of asthma in daily clinical practice, in the real world as opposed to clinical trials, is challenging. It is therefore essential for health care professional to be equipped with the necessary skills which include appropriate diagnostic tools and the ability to select the appropriate therapy according to the patient's needs. The selection of the correct medication/s-dose, dosing frequency and a delivery system which is appropriate and acceptable to the patient is of primary importance. The ability to listen to and address the patients' concerns is paramount if successful outcomes are desired. It is important for the health care professional to enquire what the expectations of the patient are and to try and fulfil them adequately. A study conducted with school children demonstrated the feeling of anger experienced by adolescents with asthma who felt ignored by their doctors as the latter choose to address their parents when determining the degree of asthma control.[4] Such evidence indicates vast room for improvement and the need for health care professionals to have better training in communication skills.

The stepwise approach to management in asthma (Table 2) is ideal as it is flexible and therapy is initiated at the relevant step of asthma severity and stepped up when control is not achieved. A clear indication of inadequate control is the use of reliever medication more than 4 times a day. The patient is stepped up only after inhaler technique and degree of adherence to therapy have been assessed.

Pharmacotherapy

Control of asthma is achieved by using controller medications daily on a long term basis. Inhaled glucocorticoids are, to date, the most effective controller, anti-inflammatory medications available.

Table 2: Medication by severity (Adults)[1]

Severity	Daily Controller Medication
Step 1: Intermittent Asthma	None
Step 2: Mild Persistent	Inhaled Beclomethasone dipropionate ≤500µg
Step 3: Moderate Persistent	Inhaled Beclomethasone dipropionate 200-1000µg + LA $ß_2$ agonist
Step 4: Severe Persistent	Inhaled Beclomethasone dipropionate >1000µg + LA $ß_2$ agonist + oral prednisolone
Short acting $ß_2$ agonist prn not more than 3-4 times daily	

Inhaled glucocorticoids are indicated for all levels of asthma severity except when asthma is intermittent. A patient's asthma is classified as intermittent only if (i) symptoms are experienced less than once a week over a period of 3 months and are brief, (ii) nocturnal symptoms are experienced no more than twice a month and (iii) lung function between episodes is normal. If, however, rapid acting $ß_2$ agonists are needed more than once a week over a 3 month period, therapy should be stepped up and inhaled glucocorticiods introduced.[1]

A dose of 500µg of beclomethasone dipropionate daily (or equivalent - Table 3) controls most adult asthma. In general, at this dose or less, systemic side-effects are not a problem in adults, although this may vary on a patient to patient basis. Should a dose of 500µg of beclomethasone dipropionate, prove to be insufficient to control asthma it is preferable to add on another class of controller medication, such as a long-acting (LA) $ß_2$ agonist, rather than increase the dose of inhaled glucocorticoids.[9] Other alternative add-on controller medications include anti-leukotrienes and sustained release theophylline. Control should be maintained at the lowest dose of inhaled glucocorticoid possible. It is recommended that the patient is reviewed on a regular basis, ideally every 3 months. If a patient is well controlled and stable, a gradual reduction in dose by 25-50% is suggested. When stepping down, the factors to be taken into account include severity of asthma, side-effects/beneficial effects of treatment and patient preference.[1,10,11] It should however be emphasised that the selection of the appropriate dose of inhaled glucocorticoid and additional controller medication for a patient requires clinical judgement. Some patients may benefit from high doses of inhaled glucocorticoids, as this would permit control without the use of oral glucocorticoids, whose side-effect profile is by far more pronounced.[12,13]

There is a significant body of evidence which suggests that the combination of a long acting $ß_2$ agonist such as salmeterol/formoterol and an inhaled glucocorticoid is the most effective means of controlling asthma in the majority of patients. There is a strong scientific rational for the combination of these two types of controller medication since they each target different and complimentary aspects of the inflammatory process.[14] $ß_2$ agonists and glucocorticoids interact in a beneficial way. Glucocorticoids prevent the development of tolerance to $ß_2$ agonists, while the latter probably potentiate the local anti-inflammatory action of glucocoticoids.[15] This evidence has led to the development of fixed combination inhalers of fluticasone/salmeterol (Seretide®) and budesonide/formoterol (Symbicort®) in one inhaler device.[16,17] Various clinical trials have

Table 3: Estimated equipotent doses of inhaled glucocorticoids in adults[1]

Drug	Low Dose	Medium Dose	High Dose
Beclomethasone dipropionate	200-500µg	500-1000µg	>1000µg
Budesonide	200-400µg	400-800µg	>800µg
Fluticasone	100-250µg	250-500µg	>500µg

demonstrated the effectiveness of combination therapy in controlling asthma.[18,19,20] Since combination therapy achieves better control of asthma than doubling the dose of inhaled glucocorticoids it has a very important steroid-sparing role, thus enabling attainment and maintenance of control at the lowest possible dose of inhaled glucocorticoid.[21,22] Recently published evidence has shown that combination therapy can achieve guideline defined asthma control (Table1).[23] Combination therapy is now regarded as the new 'gold standard' of asthma therapy.[24]

In practice combination therapy offers the advantage of controlling asthma using two complementary controller medications delivered through one inhaler device, with a convenient twice daily dosage increasing the possibility of adherence to therapy. It is delivered as a dry power inhaler offering the advantage of increased ease of use.

Adherence to therapy

Adherence to therapy plays a major role in asthma control. Adherence is influenced by dosage regimen, beliefs regarding effectiveness, recall of dosing times and access to therapy.[25] Data pertaining to the local situation indicates that, while access to medication is not a problem, 55% of patients studied were unable to mention their asthma drugs and/or did not follow their regimen, while 97% had barriers to adherence due to recall, indicating 'sporadic non-adherence' which can be addressed by adjusting and simplifying the regimen. Interestingly, 60% of patients had negative beliefs regarding the effectiveness of their medication, stating that they did not believe their asthma medicine worked well and/or that their prescribed therapy bothered them.[26] It is therefore imperative for prescribers to identify and take into account potential barriers to adherence in order to achieve better outcomes.

Conclusion

Attaining and maintaining control in asthma is complex. It entails more than appropriate drug selection. Unless the healthcare provider is willing to understand the patient's perspective of asthma control, listen to the patient's concerns and address any issues causing anxiety to the patient, control is bound to be lost. In this day and age we are also sufficiently aware that there is a relationship between gender and health and it is necessary to take into consideration sex and gender differences when treating a male or a female patient with asthma.[27] Health care professionals need to work with the patient and adopt a holistic approach to improve all aspects of asthma control thus enhancing the quality of life of the individual.

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Pharmacogenetics of asthma therapeutics

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Asthma is recognised to arise from complex interactions between environmental exposure and disease-susceptibility genetic contributions.[1] Pharmacological management of the condition aims to relieve symptoms, decrease airway hyperresponsiveness, and optimize the quality of life in patients. Inter-patient variability in the clinical responses to anti-asthma drugs is a recognized factor that may confound therapeutic outcome.

Introduction

Estimates show that as much as 60.6% of interindividual statistical variance to salbutamol response may be attributable to genetic factors, while with inhaled glucocorticoids, the figure may be as high as 86.1%.[2] This strongly suggests that genetic factors may significantly contribute to the clinical outcomes of pharmacological treatment. It is the challenge of pharmacogeneticists to identify these genetic determinants and study their roles.

Pharmacogenetics and pharmacogenomics

The term *pharmacogenetics* was originally coined by Friedrich Vogel in 1959[3], who used it to describe the influence of genetic factors on the response to drugs. A second term, *pharmacogenomics*, has relatively recently found its way into the literature, and although it has often been used interchangeably with the former, pharmacogenomics is better used to describe the study of the genome and its products as they relate to drug responses, such as the examination of whole genomes in order to identify putative drug targets or to study large scale differences in gene expression in response to drugs.[4,5]

Pharmacogenetic variation

The Human Genome Sequencing project has provided us with the sequence of the three billion base pairs that make up our DNA, of which is estimated that only 2% to 5% actually consists of the coding regions that are responsible for 25,000 – 32,000 genes. Background DNA variation is present throughout the whole genome, but tends to occur at a higher frequency in non-coding compared to coding regions. The most common variation consists of single base substitutions (single nucleotide polymorphisms, SNPs), of which nearly 1.8 million have been identified to date.[6] Other types of DNA variation include deletions or insertions of one or more bases, and variable repeats of specific sequences. Pharmacogenetically-relevant DNA variation would be expected to be mainly located in coding sequences or in regulatory regions of genes which code for proteins involved in pharmacological responses. Such genes may include those responsible for drug receptors (e.g. $ß_2$-adrenoceptor, muscarinic receptors, glucocorticoid receptor) or proteins involved in drug receptor signalling (e.g. G_s) as well as genes which code for drug-metabolizing enzymes (e.g. cytochrome P450 group).

Pharmacogenetic variation relevant to asthma therapeutics

$ß_2$-adrenoceptors

$ß_2$-adrenoceptors are primarily expressed on airway smooth muscle cells[7], and are the target of the $ß_2$-agonist drugs used in asthma. Nine SNPs have been identified in the

ß$_2$-adrenoceptor coding region, of which 4 result in amino acid substitutions at the protein level. Three of these have demonstrable functional effects.[8,9]

A DNA base change of adenine to guanine at position 46 of the ß$_2$-adrenoceptor gene (46A→G), results in a receptor protein for which the sixteenth amino acid is glycine instead of arginine (Arg16→Gly). In cultured cells, the Gly16 receptor variant downregulates faster than Arg16 in the presence of agonists[10,11], while patient studies have shown homozygous Gly16 adult asthmatics to exhibit a greater degree of tolerance (described by a higher loss in positive FEV_1 or FEF_{25-75} responses) to formoterol treatment (24µg b.d. for 4 weeks) compared to Arg16 homozygotes.[12] Arg16 adult homozygotes have been shown to demonstrate a higher and more rapid salbutamol-evoked FEV_1 response[13] while Arg16 asthmatic children are 5.3 fold more likely to exhibit positive clinical responses to salbutamol treatment than Gly16 homozygotes.[14] Gly16 asthmatic patients are 6 times more likely to suffer from nocturnal asthma symptoms[15] and they demonstrate a higher degree of airway reactivity to histamine.[16]

A second polymorphism (Gln27→Glu, 76C→G) confers on the receptor a strong resistance towards agonist-promoted *desensitization* and *downregulation.* In primary cultures of human airway smooth muscle cells, approximately 60-fold greater concentrations of isoprenaline were required to desensitize the homozygous Glu27 variant to the same extent as the homozygous Gln27 form[11], while homozygous Glu27 patients have four-fold lower methacholine reactivity than their Gln27 counterparts.[17]

Work on Gly16/Glu27 double mutant receptors, showed the Gly16 effects to be dominant over Glu27 in cell culture.[10] The highly downregulating Gly16/Gln27 variant has a higher prevalance in moderate than mild asthmatics[18] and is associated with a higher degree of bronchial hyperresponsiveness.[19]

A third identified polymorphism (Thr164→Ile, 491C→T) is rare and population studies are lacking. *In vitro* work has identified the Ile164 variant to bind isoprenaline, adrenaline and noradrenaline with 4-fold lower affinity than the wild type Thr164 form[20], and also to possess a reduced ability to mediate agonist-independent basal activation of adenylate cyclase, implying the existence of a second mechanism by which this variant transduces signal less efficiently.[21]

Various SNPs are present in the 1470bp DNA region upstream of the ß$_2$-adrenoceptor gene which is involved in transcriptional control of the gene. Cell culture studies have revealed that the most commonly occurring mutant haplotype (-20C, -47C, -367C, -468G) exerts a small but significant decrease in promoter activity compared to the wild type sequence[22] and this may result in decreased ß$_2$-adrenenoceptor expression in patients carrying this variant.

Muscarinic receptors

Polymorphic variation within muscarinic M_2 and M_3 receptors could potentially alter treatment responses to anticholinergic agents, such as ipratropium bromide. Mutation screening of the M_2 receptor gene in Maltese asthmatic individuals identified two degenerate polymorphisms in the coding region (1197T→C, Thr→Thr and 976A→C, Arg→Arg) and a common SNP in the 3' non-coding region (1696T→A), none of which are likely to be functionally relevant, while no variation could be identified in the M_3 coding sequence.[23] A third M_2 coding region degenerate polymorphism (1050A→G) was identified in the Japanese population while a rare degenerate M_3 substitution (261C→T) was identified in the M_3 coding region in the same population.[24] A recently identified variable CA tandem repeat in the human muscarinic M_2 gene promoter has been shown to significantly influence gene transcription in cultured cells[25] and ongoing work by our group strongly suggests that this variation may be contributory to the development of asthma symptoms in patients. It is suggested that these promoter variants may contribute to inter-individual variability in response to muscarinic antagonists (such as ipratropium bromide) due to their influence on muscarinic M_2 receptor expression.

Anti-leukotriene drugs

Cysteinyl leukotrienes are released into the airways by pro-inflammatory cells including eosinophils, neutrophils and mast cells, and bind to specific receptors (primarily $CysLT_1$) exerting effects which include airway smooth muscle contraction, plasma extravasation and mucus hypersecretion.[26-28] The products are derived from arachidonic acid, via an enzymatic pathway in which 5-lipoxygenase (5-LOX) and leukotriene C_4 synthase (LTC_4S) exert primary roles.[29] Drugs which inhibit 5-LOX, (e.g. zileuton) or block receptors to which cysteinyl leukotrienes bind (e.g. zafirlukast, montelukast, pranlukast) are the latest addition to the available anti-asthma drugs, and they have a proven clinical efficacy in relieving symptoms.[30] The genes for the cysteinyl leukotriene receptors have only been recently cloned, and studies concerning genetic variation are currently underway.

The 5-LOX gene (ALOX5) is located on chromosome 10q11.12 [31], and the upstream flanking region has promoter activity and contains consensus sequences for several transcription factors, including Sp1, Sp3, Egr-1, Egr-2, NF-κB, GATA, Myb and AP family members[32], including a series of 5 tandem binding motifs for Sp1/Egr-1($[GGGCGG]_5$).[33] Thirty five percent of the population carries an ALOX5 promoter with either one or two Sp1/Egr-1 sequences deleted ($[GGGCGG]_4$, $[GGGCGG]_3$) or the insertion of an extra one ($[GGGCGG]_6$). All 3 variants show decreased promoter activity in cell culture, compared to wild type $[GGGCGG]_5$. A study using ABT-761, a 5-LOX inhibitor derivative of zileuton, in 114 asthmatic patients, at a dose of 300mg/day for 84 days, showed the highest degree of improvement in FEV_1 to occur in patients who are heterozygous or homozygous for the wild type allele at the promoter locus, while patients who are homozygous mutant did not benefit from anti-5-LOX treatment.[33-35]

The gene for LTC_4 synthase (LTC_4S) is located on chromosome 5q35. Sanak, *et al*., (1997) identified an A→C substitution in a regulatory region, 444 bases upstream of the coding sequence

which resulted in an additional motif for transcription factor AP-2 (CCCG). The polymorphism shows an association with aspirin induced asthma and could potentially contribute to increased LTC_4 in the airway.[36] It could also be a potential risk factor for adverse reactions to nonsteroidal analgesics in asthma, since it may alter the expression pattern of the enzyme.

Glucocorticoid receptor

Glucocorticoids (GCs) act by binding to a cytoplasmic receptor (GR), which subsequently enters the nucleus and through various mechanisms acts as a positive or negative transcriptional regulator. In this way, the transcription of various pro-inflammatory proteins is decreased, while there is transcriptional upregulation of anti-inflammatory molecules, such as lipocortins.[37,38] Two isoforms of the human glucocorticoid receptor (hGR) exist, hGRα and hGRß, of which only hGRα can bind ligand. There is evidence to suggest that one role of hGRß is to dimerize with hGRα, creating a heterodimer that has less transcriptional regulatory activity than a normal hGRα homodimer[39], although some authors disagree on this.[40] Although the ligand-binding isoform is the better studied in the literature, polymorphic variation in either hGRα or hGRß may potentially exert an influence on glucocorticoid-mediated transcriptional regulation.

Notwithstanding the proven efficacy of GCs, there remain a subset of asthmatic patients who are GC-resistant.[41] GRs in corticosteroid resistant asthmatics exhibit a lower interaction with activator protein-1 (AP-1), and this effect is accompanied by raised levels of AP-1.[42]

While various glucocorticoid receptor abnormalities have been reported to contribute to generalized inherited glucocorticoid resistance (GIGR), a rare disorder characterized by high cortisol levels with no Cushingoid features[43], studies identifying defined contributions of hGR variants to steroid resistance in asthma are currently lacking.[44] Examples of identified hGR variants include a Val641→Asp substitution which results in a three-fold lower binding affinity for dexamethasone in COS-7 cells[45], a Val729→Ile substitution which results in a four fold decrease in dexamethasone activity[46] and a Asn363→Ser substitution which results in a higher sensitivity to exogenously administered glucocorticoids in healthy elderly individuals, with respect to cortisol suppression. Subjects carrying this polymorphism tend to have a higher body mass index and a lower bone mineral density compared to wild type individuals.[47] A recent variant identified in leukaemic cells (Cys643→Arg) has been found to decrease steroid-binding affinity and transcriptional activity[48], while an Asn363→Ser variant has been correlated with increased glucocorticoid sensitivity, lowered bone mineral density and increased body mass index.[49] Although it may be expected that asthmatic patients carrying the Val641→Asp, Cys643→Arg or Val729→Ile GR variants may exhibit a decreased clinical response to glucocorticoid administration than the respective wild-type individuals, current evidence suggests that glucocorticoid resistance in asthmatics may be associated with variation in genes coding for other proteins involved in glucocorticoid-mediated pathways such as histone deactylases.[50]

Phosphodiesterase

At least 7 different phosphodiesterase enzyme families are expressed in humans, of which type 4 (PDE_4) represents the predominant cAMP hydrolyzing activity in human airway smooth muscle.[51] Augmentation of PDE_4 activity might be expected to decrease $ß_2$-agonist response, by degrading $ß_2$-adrenoceptor mediated *de novo* cAMP. Variations in enzyme activity might also alter the response to theophylline, although it is not yet clear whether the *in vitro* phosphodiesterase inhibitory action of theophylline also occurs *in vivo.*[52,53] Indeed, the development of 'second generation theophyllines' which specifically inhibit PDE_4 enzymes *in vivo*, is underway with phase III clinical trials of PDE_4 selective inhibitors currently in progress.[54]

Database searches suggest that phosphodiesterase genes contain a number of polymorphisms; however there are currently no available data on the mutation screening of phosphodiesterase genes in asthmatics.

Applications

One of the major aims of pharmacogenetic research is to develop DNA testing procedures that will predict how a particular patient will respond to a given drug, in terms of efficacy as well as adverse effects. On a clinical level, this will enable a more patient-focused prescribing, and will help to ensure that patients will receive the drugs that will benefit them most, at the dose which will provide the required clinical response. Pharmacogenetic tests may be used to stratify individuals participating in clinical trials, into pharmacogenetically homogeneous groups and this may lead to more robust scientific findings regarding the group of patients who might eventually be prescribed the medicine.[55] Pharmacogenetic knowledge may also help to develop drugs that will provide efficacy in a wider spectrum of patients, or promote the development of new drugs specifically designed for pharmacogenetically compromised patients.

Ethical considerations

The present status suggests that pharmacogenetic testing for specific drugs may be available sooner rather than later, and this oncoming is not devoid of ethical dilemmas. Pharmacogenetic testing may discourage pharmaceutical companies from developing medicines that would only provide benefit for a minority of patients. If pharmacogenetic testing is incorporated into the licensing conditions for specific drugs, this increased expense might adversely affect the cost-benefit equilibrium, thus potentially depriving patients who would particularly benefit from these drugs. A pharmacogenetic test might reveal more knowledge than is specifically intended. For example, a patient who is a rapid metabolizer for a particular drug, is likely to also rapidly metabolize other pharmacologically

unrelated drugs which share the same metabolic pathways. Should such additional information be disclosed to the patient? In the clinical setting, a patient might be expected to provide informed consent for a pharmacogenetic test to be carried out. The implications of such a test should be clearly explained, and the result should be accompanied by professional advice. Ethnicity may bear an influence on the validity of a pharmacogenetic test, since specific genotypes may only be present in particular populations. Will test developers take this into account, or will particular populations be sidelined due to marketing or financial considerations? Pharmacogenetic information may be requested by insurance companies, to aid in the computation of health insurance premiums, thus potentially dissuading patients from consenting to such tests for fear of having to pay higher premiums or being unable to obtain insurance. It is applaudable that the UK has currently imposed a moratorium on the use of genetic and pharmacogenetic data for setting insurance premiums. This moratorium however expires in 2006.[55,56]

Conclusion

Functional pharmacogenetic variation is often initially demonstrated using cell culture models. Although results obtained from such systems provide accurate descriptions of cell-based responses, this data cannot be automatically extrapolated to patients. Only after having studied genetic variants in clinical studies, can one obtain concrete evidence of the actual relevance to phenotype.

The discovery of a novel pharmacogenetic variant of high allelic frequency, may warrant modifications of standard treatment protocols in order to optimize management in a greater number of patients. On the other hand, identification of a rare pharmacogenetic variant, which poses serious therapeutic implications, would allow for better management of selected patients who might otherwise be classified as difficult to treat. At present, the currently available data regarding asthma pharmacogenetics may not be sufficient to justify routine genotyping of all patients prior to treatment. However, as new data becomes available, and novel therapies are developed, the knowledge of patients' genotypes will be a necessary requisite in order to enable pharmaceutical companies and prescribers to optimize management of the disease. Further clinical and molecular work is needed in order to consolidate and expand current knowledge.[57-59]

The importance of this area of research has been accented by the recent UK Department of Health announcement of a commitment of £4 million over 3 years to be granted to pharmacogenetic research.[60]

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COPD
A public health problem requiring attention

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Chronic obstructive pulmonary disease (COPD) is currently a major cause of morbidity and mortality throughout the world. The disease responsible for an estimated 2.75 million deaths each year, ranking it as the fourth leading cause of death. Recent data published from the Burden of Obstructive Lung Disease Study estimates that at least 10% of the world's population over 40 years of age may be suffering from COPD.

Data also indicates that COPD is three times more common than previously estimated. COPD therefore poses a significant public health problem. While other chronic diseases, such as cardiovascular disease, are on the decrease, COPD is on the increase.

The Global Initiative for Chronic Obstructive Lung Disease, GOLD, of which Malta forms a part, is conducted in collaboration with the US National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organisation (WHO). The overall aim of GOLD is to increase awareness of COPD and to decrease morbidity and mortality from this disease.

Diagnosing COPD

Chronic obstructive pulmonary disease is characterised by airflow limitation that is not completely reversible. This airflow obstruction is progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases such as cigarette smoke, occupational dusts and chemicals, environmental tobacco smoke and indoor/outdoor air pollution. Most patients present with cough, which either precedes the onset of breathlessness or appears concurrently with it. Chronic cough and sputum production can precede development of airflow limitation by many years, although not all individuals with cough and sputum production go on to develop COPD. Other symptoms may include wheezing, chest tightness, haemoptysis and, at an advanced stage, anorexia and weight loss.

Spirometry is necessary for definitive and accurate diagnosis of COPD. Spirometry is the gold standard as it is the most reproducible, standardised and objective way of measuring airflow limitation. A finding of FEV_1 of less than 80% of the predicted value after bronchodilation and a FEV_1/FVC ratio below 70% predicted confirms the presence of airflow limitation that is not fully reversible. Serial measurements of FEV_1 are essential to monitor disease progression, and a fall of more than 50ml/l per year implies accelerated decline. GOLD recommends that health care professionals involved in the diagnosis and management of COPD patients should have access to spirometry.

Targeting COPD in primary health care

Due to low symptom awareness, COPD is not usually diagnosed before it is at a moderately advanced stage and significantly affecting a person's quality of life. Early diagnosis enables initiation of appropriate prevention and treatment strategies. Diagnosing COPD in primary health care is an effective means of helping people at an early stage. For this reason GOLD has developed the 'Could it be COPD?' questionnaire (Table 1). This questionnaire consists of 5 simple questions about COPD symptoms. It is mainly a self-assessment questionnaire which can be conducted by the individual in just over 30 seconds. If the person has answered yes to 3 or more questions he/she is encouraged to

Table 1: Could it be COPD?

1. Do you cough several times most days?	Yes ☐	No ☐
2. Do you bring up phlegm or mucus most days?	Yes ☐	No ☐
3. Do you get out of breath more easily than others your age?	Yes ☐	No ☐
4. Are you older than 40 years?	Yes ☐	No ☐
5. Are you are current or an ex-smoker?	Yes ☐	No ☐

If you have answered yes to three or more questions, ask your doctor if you might have COPD and should have a simple breathing test.

Table 2: Therapy at each stage of COPD	
Mild	Short-acting bronchodilator prn
Moderate	Short-acting bronchodilator prn, Regular treatment with one or more long-acting bronchodilators Rehabilitation
Severe	Short-acting bronchodilator prn, Regular treatment with one or more long-acting bronchodilators Inhaled glucocorticoids if there is significant symptomatic and lung function response or repeated exacerbations Rehabilitation
Very Severe	Short-acting bronchodilator prn, Regular treatment with one or more long-acting bronchodilators Inhaled glucocorticoids if there is significant symptomatic and lung function response or repeated exacerbations Treatment of complications Rehabilitation Long term oxygen therapy if there is chronic respiratory failure.

ask the doctor to investigate the possibility of COPD by having a simple breathing test done. The questionnaire in Table 1 can be very easily reproduced by health care professionals. It can be made available at the waiting area of a doctor's clinic. It can also be made available through community pharmacies. Pharmacists can identify at risk patient as those who regularly ask for cough preparations, or whom they know to be smokers/ex-smokers or who complain of being short of breath. These could be encouraged to take the questionnaire and if appropriate referred to a doctor for further investigation. The questionnaire may also have a poster format which may be placed in a doctor's clinic or a pharmacy. This is an effective means of increasing awareness among health care professionals and the general public.

Prevention and treatment of COPD

Since cigarette smoking is the major cause of development of COPD, smoking cessation is the single most effective way to arrest its progression. Every contact between health care professionals and smokers should be used to reinforce advice about smoking cessation. This message is strengthened by linking smoking to signs and symptoms of the disease. Pharmacotherapy, such as nicotine replacement and bupropion, should be appropriately prescribed in the absence of any other contraindications. Healthcare professionals should maintain contact with persons attempting smoking cessation and offer ongoing support. Follow up of these persons on a regular basis enhances the chance of a sustained successful outcome.

Therapeutic management of COPD should be characterised by a stepwise increase in the treatment depending on severity of the disease. Table 2 provides an overview of the therapy at each stage of COPD.

Bronchodilators are central to the symptomatic treatment of COPD. Depending on the severity, inhaled bronchodilators may be given on a regular basis to prevent and control symptoms or on a prn basis for relief. Inhaled bronchodilators used in COPD are $ß_2$ agonists, which may be short acting (eg salbutamol, terbutaline) or long acting (salmeterol, formoterol) and anticholinergics which may also be short-acting (ipratropium) or long acting (tiotropium). The use of methylxanthines are restricted due to side effects and narrow therapeutic window.

Inhaled glucocorticoids are of limited use among patients with COPD, except in those presenting with repeated exacerbations. In such cases inhaled glucocorticoids have been shown to reduce the frequency of exacerbations and improve quality of life. Recent evidence has shown that inhaled glucocortcoids combined with long acting $ß_2$ agonists are more effective than the individual components.

Oxygen therapy is the principal component of treatment for patients with very severe COPD. Long term oxygen given at this stage has been shown to increase life expectancy.

Conclusion

In 2002, under the auspices of GOLD and the academic sponsorship of the University of Malta, the Department of Health, the Malta College of Pharmacy Practice and the Malta College of Family Doctors, *The Malta Guidelines for the Management of Chronic Obstructive Pulmonary Disease* were published and distributed to health care professionals. This was a first step towards sensitising health care professionals to the problem of COPD. The fight against COPD, however, needs a continuous concerted effort by health care professionals, policy makers and public health officials. It is also necessary to increase awareness among the general public.

Further Reading

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Mycoplasma pneumoniae in community acquired pneumonias

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***Mycoplasma pneumoniae* is best thought of as a bacterium without a cell wall, a property that has important therapeutic considerations. It is an exclusively human pathogen. As most cases of human infection are either sub clinical or result in a relatively mild infection of the respiratory tract, infections with this organism are much more common in the community than people generally realize.[1]**

Epidemiology

An organism of worldwide prevalence, *M. pneumoniae* tends to cause sporadic illness throughout the year. In addition, in most countries, it has been noted that the infection rates tend to peak every 3 to 5 years as an epidemic.[2]

As these epidemics tended to involve schoolchildren and military recruits, the trend has been to associate this organism with these younger age groups. However, endemic illness (occasionally even epidemics) does occur at ALL ages. In particular, the incidence of mycoplasma pneumonia in the under fives seems to be increasing in most developed countries, possibly because of the increasing use of day care centers for the very young. In the elderly, it is second only to *S. pneumoniae* as a cause of community acquired pneumonia.[3,4]

The disease is transmitted person to person, by droplet infection. While patients with active disease are the ones most likely to transmit the illness, the organism may persist in the respiratory tract of asymptomatic carriers for long periods of time, even when these would have been active cases treated with antibiotics.[1] It is thought that such persons serve as a reservoir or carrier from which the disease is maintained within the human population. Re infection readily occurs.

The clinical illness

Apart from pneumonia, the organism is capable of causing upper respiratory tract infections, such as pharyngitis. Once again, as an etiological agent of sore throats, it is probably a much more common cause than it is usually given credit for. While mycoplasma infections may trigger off bronchospasm in chronic asthmatics, more recent evidence is suggesting that the organism can be a primary cause in the development of this chronic lung disease. In the future, it shall be interesting to see if the incidence of asthma goes up as children are exposed to the organism at ever-younger ages, for reasons explained above.

The pneumonic illness is typically a mild one, and sometimes referred to as the "walking pneumonia". Certainly, compared to the classical pneumococcal pneumonia, the onset is more gradual. Many adult patients will have little or no symptoms, yet physical and X-ray examination will show very definite signs of a chest infection. The disease tends to be more marked in children, possibly since, on their first encounter with the organism they would have no form of acquired immunity to give them at least partial protection against the disease.[5]

When symptoms are severe, these would usually be ascribed to an aggressive immune response to the infection, rather than the organism itself, which, with rare exceptions, does not spread beyond the mucosal epithelial surface.

Laboratory diagnosis

As the illness, both clinically and radiologically, is very non-specific, microbiological tests are essential to confirm the diagnosis. Over the years, various such tests have been developed:

1. Mycoplasma culture - apart from being laborious and expensive, and relatively insensitive[6] compared to DNA amplification techniques, there is also the problem of the organism persisting in the patient's respiratory tract for (in some cases) weeks or months after the acute episode. With all these drawbacks, it is not surprising to learn that most microbiological labs would never attempt to culture mycoplasma.
2. Antigen detection techniques - this has been tried using many different laboratory methodologies. Two examples would be direct immunofluorescence[7] and antigen capture enzyme immunoassay. In these cases, the already discussed problem of detecting a presence of the organism in a human carrier is compounded by the tendency of such tests to cross react with other non pathogenic mycoplasma which are normally present in the human respiratory tract. This low specificity, together with a low sensitivity means that they cannot really be recommended for use, especially now that superior molecular diagnostic techniques are available.

3. Molecular identification techniques - Labeled probes that target the non-amplified mycoplasma DNA, have been supplanted by the superior amplified technologies, and specifically PCR (polymerase chain reaction).[6] Its advantages include a high specificity (but beware the mycoplasma human carrier!), the ability to detect the organism's DNA or RNA (depending on the kit used) in preserved tissue, as well as the short turnaround time for completing the test and the fact that, at least theoretically, it should give a quicker result than an antibody test in a positive case.

On the other hand, the PCR test may turn negative very soon after the start of antibiotic treatment (in some cases, within 24 hours) while the antibody test will remain positive for a considerably longer period of time. Thus, the result of a PCR specimen taken after the start of antibiotic therapy has to be interpreted with caution. There have also been problems with false negative results, probably from the presence of reaction inhibitors present in the patient's upper respiratory tract.

At this stage, the mycoplasma PCR tests available are still in use as a research tool, rather than as a routine diagnostic method. Together with cost, this renders this technique not quite ready for widespread use.

In the light of all of the limitations mentioned above, it is not surprising that antibody testing is still the most commonly performed microbiological test to confirm suspected mycoplasma pneumonia.

4. Serology - Antibodies to *M. pneumoniae* would be expected to reach their maximum serum concentration 3 to 6 weeks after exposure. Bearing in mind that most cases of the illness would be associated with a relatively long incubation period (1 - 3 weeks), it can be expected that by the time most patients present to their doctor, an antibody response can usually be demonstrated.

In a primary infection (most likely in peadiatric age group), the specific IgM antibodies would start to appear within one week of the infection. IgG antibodies would typically show up two weeks later. Where reinfection occurs (most adult cases) the patient may show up only IgG immunoglobulins, without ever exhibiting an IgM response.[8] On the other hand an IgM response has occasionally been shown to persist for months or even years following the primary infection! This sometimes makes the proper interpretation of the patient's IgM + IgG response to a mycoplasma infection, and specifically when it comes to distinguishing a past from a recent infection difficult.

In the future, one other possible diagnostic tool is the detection of a specific IgA response, which preliminary studies suggest might be the most reliable indicator of a recent mycoplasma infection than both IgG and IgM antibodies.

In view of the above, it would appear prudent to test suspected cases both of IgG and IgM antibodies simultaneously, and then repeat the tests 2 to 3 weeks later to detect any changes in titre.

Treatment

The organism is exquisitely sensitive to the macrolides and related compounds (azalides and ketolides), as well as the newer respiratory quinolones. As such, it is no surprise to find these antibiotics forming the mainstay of treatment.

Treatment duration varies according to the agent selected: in most cases it would hover around the 10-day mark. However, there are those who would insist that cases of mycoplasma pneumonia should be treated for at least 2 to 3 weeks.

Over the years, various antibiotics have been successfully used to treat mycoplasma pneumonia in the published literature. However, one should point out that in some of these studies, the number of patients involved where quite small.

These have included:

- Clarithromycin and Erythromycin for 10 or 14 days[9]
- Telithromycin for 7 to 10 days[10]
- Azithromycin for 3 or 5 days[11]
- Moxifloxacin for 7 to 14 days[12]
- Levofloxacin for 7 to 14 days[13]

This is not a comprehensive list of all studies done on the subject. In fact, one would expect all macrolides and fluoroquinolones to be effective against *M. pneumoniae.* Furthermore, tetracyclines should also work against this organism.[14]

Curiously, in one small comparator study, co-amoxiclav, together with various other beta lactam antibiotics[12,13] appeared to achieve a very good clinical cure rate after 7 to 14 days of treatment, despite the fact that this antibiotic is definitely inactive against *M. pneumoniae.* As described above, most of these "walking pneumonias" are usually mild and self-limited, and the majority of patients can be expected to make a full recovery even in the absence of antibiotic treatment.

Vaccine research

Attempts to develop a *M. pneumoniae* vaccine have been going on for many years, unfortunately without success. In a way this is not surprising, considering that some individuals who succumb to the infection, and develop an immune response to the organism may still get reinfected later on in their lives. After a number of failures with different experimental vaccines, interest in the subject appears to be low at the moment.

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