West of England Medical Journal

Formerly Bristol Medico-Chirurgical Journal

The e-journal of the
Bristol Medico-Chirurgical Society

Personalised Respiratory Medicine in Bristol- The Hospital and the Community

WEMJ Volume 112 No 1 Article 1 March 2013

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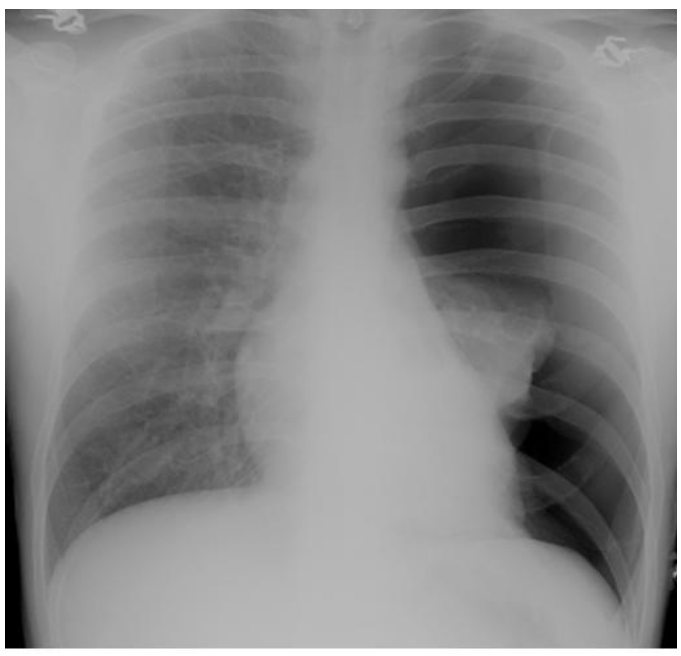

Figure 1: a. Large left sided pneumothorax.

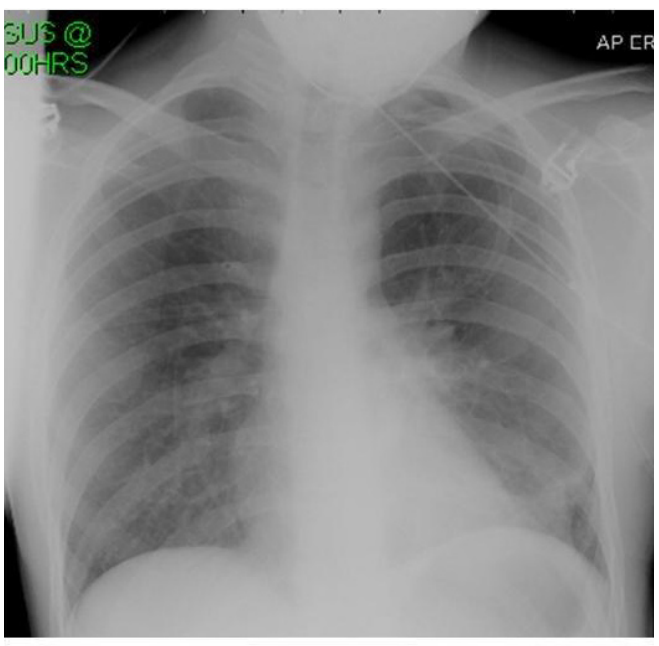

Figure 1b. Full lung expansion with a chest drain in situ

INTRODUCTION

The following three cases from Bristol Royal Infirmary outline three facets of modern hospital respiratory medicine.

The Saturday morning speciality ward round-

CASE 1: This is the case of a 32 year old previously fit man who presented with first left sided pneumothorax that responded to a standard chest drain insertion [figure 1]. As I was covering respiratory medicine, I was asked to see him by a consultant medicine for the elderly who was on acute take for that day.

In the ward round, the patient was given the standard recommendation not to undertake air flight for 6-12 weeks [1]. However, the patient was getting married the following month.

His honeymoon was planned to be in Rhodes (Greece). A great deal of planning for this honeymoon had been done over the previous 2 years. Cancellation or postponement would not be possible.

The only way forward was for him was to have a surgical pleurodesis after which the patients would be able to undertake safe air flight with no risk of recurrence of pneumothorax during the flight. Normally, this procedure would be indicated after recurrence of pneumothorax, but in this case, the thoracic surgeon agreed to make an exception.

The patient was discharged on the same day after removal of the drain, readmitted and was successfully operated on a week later and was discharged within 48 hours. The patient went on his honeymoon three weeks after surgery by aeroplane as planned.

The surgical intervention in this case was made against the standard guidelines for management of pneumothorax and was made for social rather than medical reasons. The case outlines the value of specialists managing acutely admitted patients from their own specialties out of hours.

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The urgent respiratory clinic– the HOT clinic 2

This is a daily run service during which patients with acute respiratory disease are seen within 24 hours of referral. Patients undergo chest radiographs, spirometry, basic blood tests and are seen by a specialist nurses and a senior respiratory specialist within two hours
CASE 2. A 32 year old computer analyst presented to his GP with one week history of cough, chest tightness and wheeze. He attributed the onset of his symptoms to a suspected peanut inhalation- a complaint that is much commoner in children than adults. On his physical examination there was bilateral expiratory wheeze audible more prominently at the right base compared to other lung field areas. His spirometry showed an obstructive defect [figure 2] and the chest radiograph was normal [figure 3].

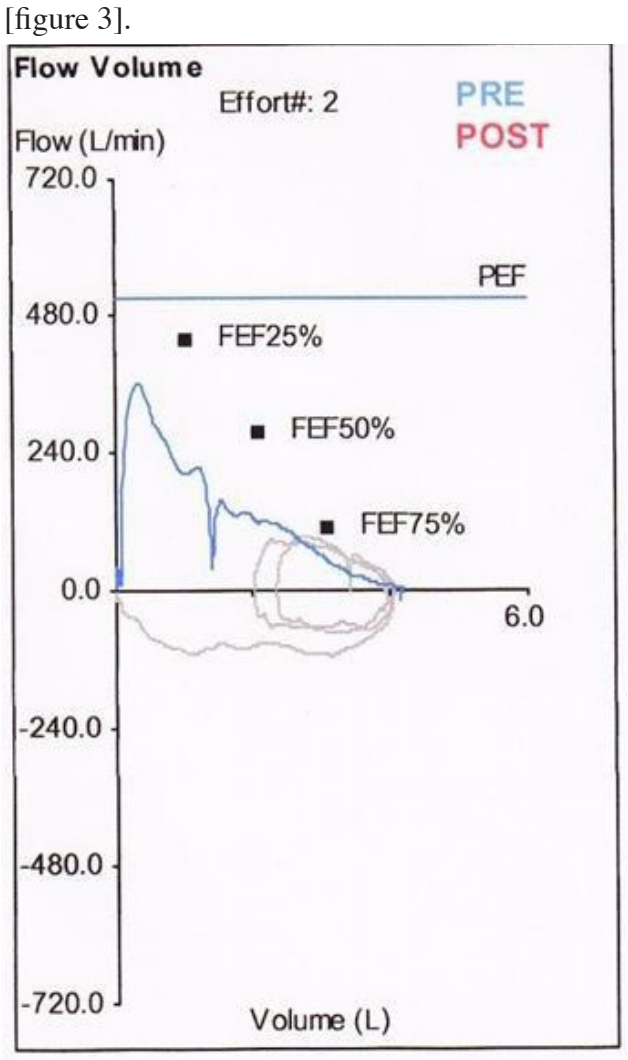


Figure 2: Flow volume loop showing an obstructive pattern.

A bronchoscopy (figure 4) was performed on the following day. This revealed a fragment of peanut lodged in the lateral segment of the right lower lobe with profound inflammatory reaction in the affected sub-segmental and adjacent bronchi. This is a known reaction to peanut oil.

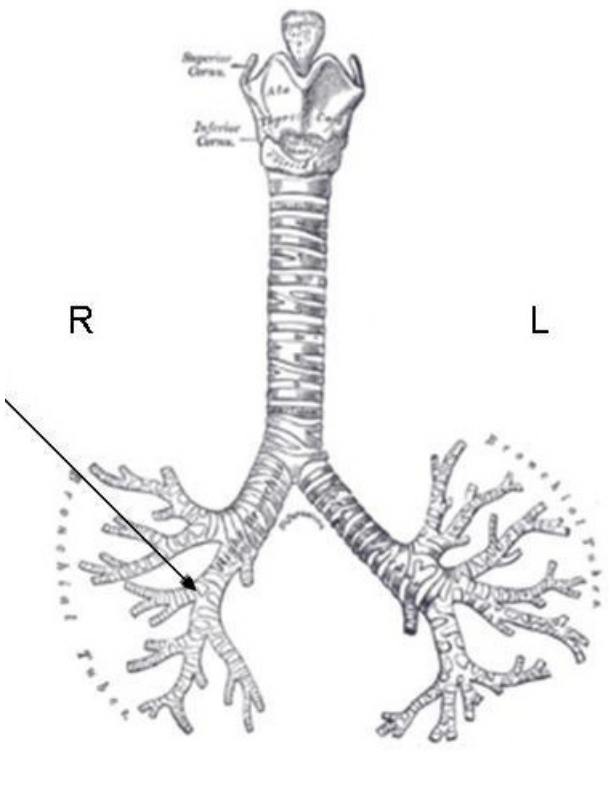
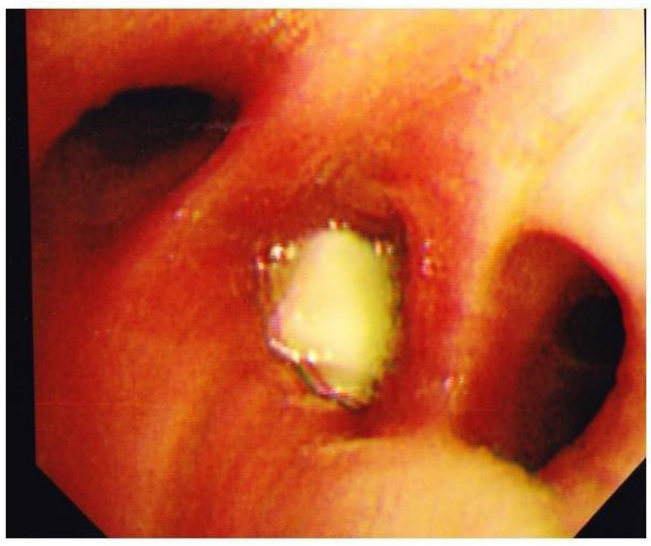


Figure 4: (a) A schematic drawing of the bronchial tree and the site of the peanut (black arrow).



(4b) The fragment of peanut shown on bronchoscopy.

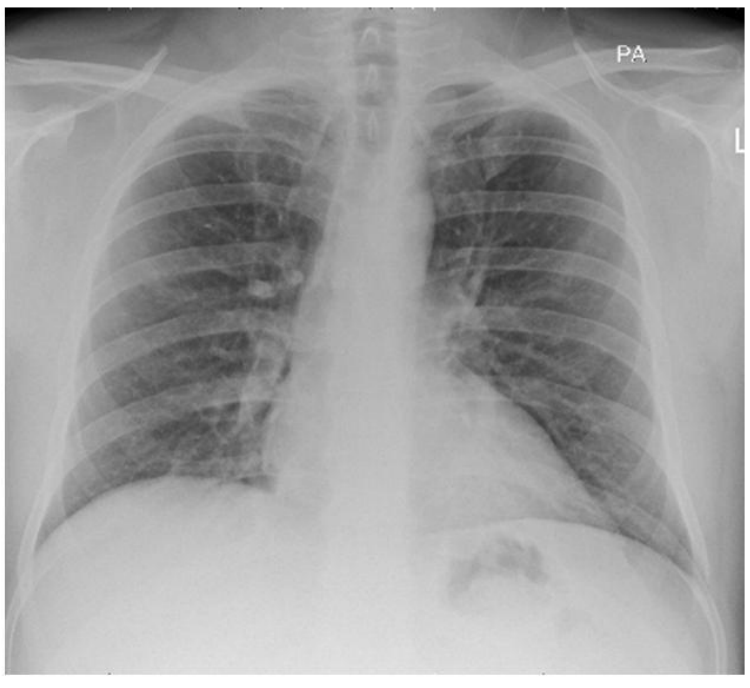
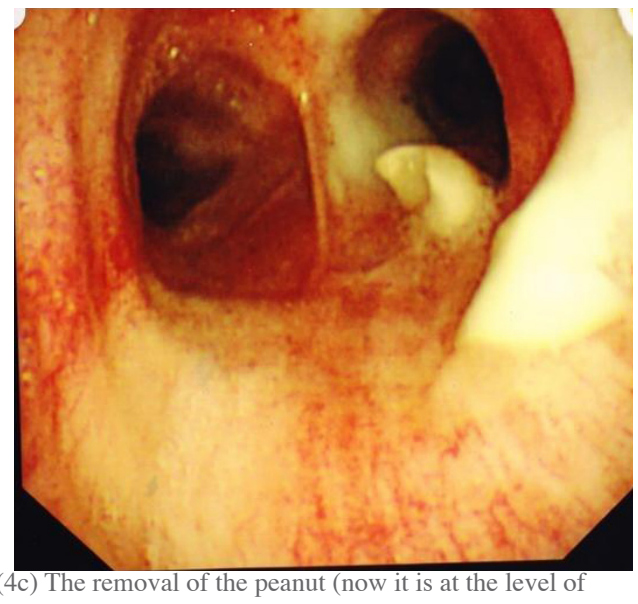
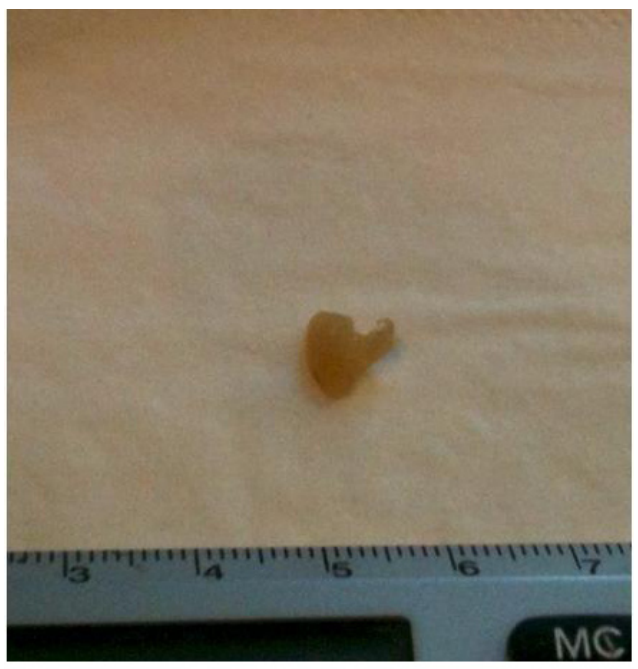


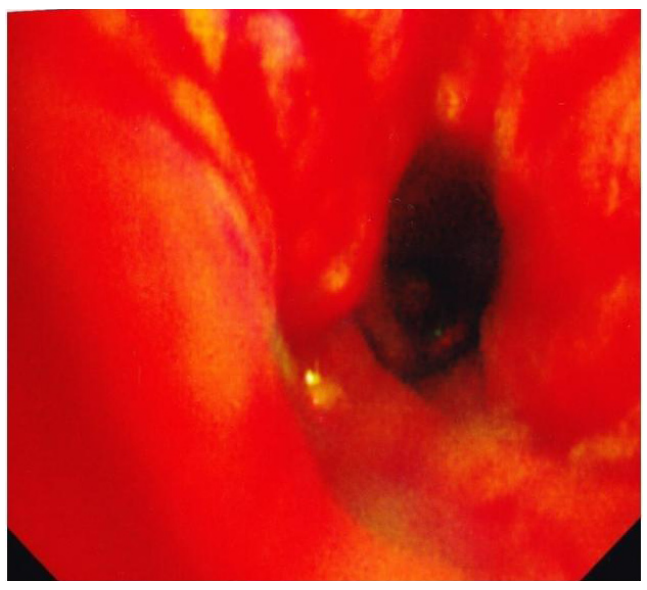
Figure 3: A normal chest radiograph



(4c) The removal of the peanut (now it is at the level of the carina with released retained creamy mucous behind the peanut)



(4d) The removed peanut



(4e) There is severe inflammation of the bronchial subsegment where the peanut was lodged.

The peanut was removed and the area was washed. The patient made a full recovery.

This case highlighted the value of an urgent daily specialist respiratory set up manned by a specialist team in a specialist set up.

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New technologies-

CASE 3: This is a case of an 85 year old lady who presented to her GP with cough a chest radiograph that was followed by a chest CT scan. These revealed a tumour in the right upper lobe [figure 5].

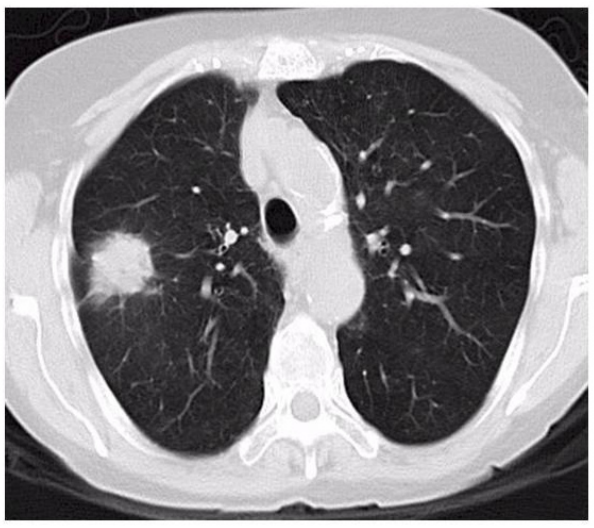
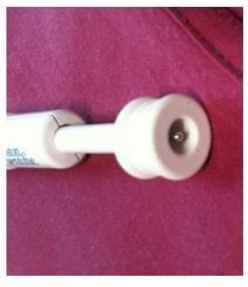


Figure 5: The lung cancer on CT thorax

The patient was reasonably fit, but was reluctant to have a surgical resection or radical radiotherapy. She was offered radiofrequency ablation, a minimally invasive treatment used in liver cancer, lung cancer and in ablation of abnormal cardiac conducting defects.
The figures below and to the right illustrate the radiofrequency generator, the needle and the patient receiving the treatment.

Figures 6a (above) and 6b, 6c and 6d (below) show respectively:
6a) Radiofrequency generator of alternating electrical current
6b) the needle
6c) the electrical probe site on the back of the needle
6d) the deployed fans through which the alternating electrical current will be transmitted to the tumour site.



The patient underwent this procedure under minimal sedation, basic monitoring and under CT scan guidance by a radiologist [Figures 6 and 7].

Figure 7(a) Basic monitoring of patients in the CT scanner room.

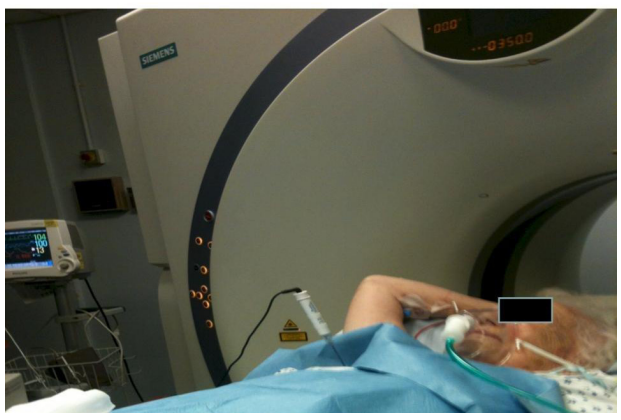


Figure 7(b) The patient during high frequency treatment with the needle and the electrical probe visible.

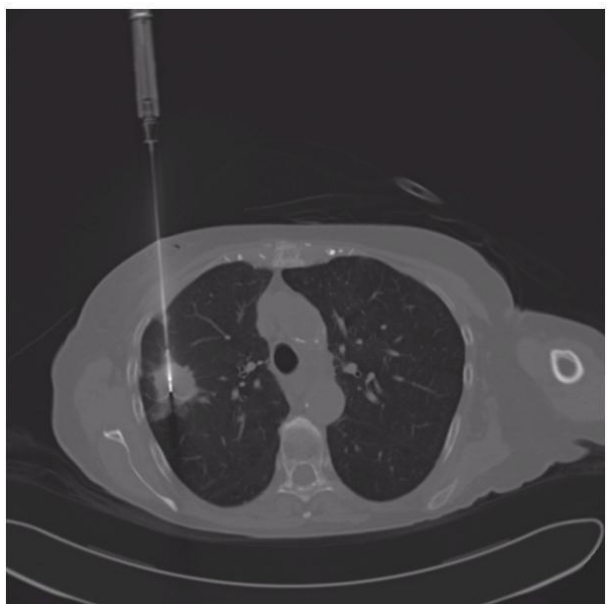


Figure 7c : CT scan images before treatment

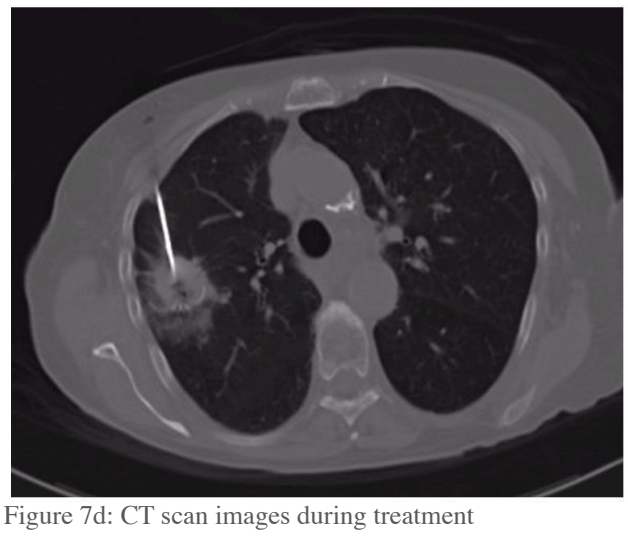


Figure 7d: CT scan images during treatment

As expected, the patient developed a pneumothorax that responded to a chest drain. The patient left the hospital four days later.

Management of limited lung cancer and single lung metastases using radiofrequency ablation has several advantages over radical radiotherapy and surgery. The procedure requires a single treatment (or multiple but not daily treatment). It is less taxing to patients and cheaper than radical radiotherapy which normally requires daily radiation for 2-4 weeks. Published survival data are also encouraging. Encouragingly, a review article has shown that 1, 2 year survival rate for non-small cell lung cancer is comparable to surgical interventionand to better than radical radiotherapy 3.

Respiratory Medicine-
from a palliative to personalised medicine

The large burden of respiratory disease in the UK is outlined in several documents including a notable report from the British Thoracic Society4 which was later summarised by Hubbard 5.

Respiratory medicine is an important part of acute and general medicine. It is estimated that 25-40% of acute admissions have respiratory disordered as the main cause of admission or as a main co-morbidity.

Respiratory conditions, mainly airway diseases (COPD-asthma and bronchiectasis) are a significant part of chronic conditions that exert a large burden of care on both primary and secondary care alike. Caring for patients in this group particularly for the elderly or those with added co-morbidity demands different ways of thinking.

In addition, in the breadth of respiratory medicine there are several specialised areas (table 1), in which super specialisation is often seen.

Compared to cardiology, diagnostic and therapeutic interventional procedures have been less progressive. More recently, this has changed with the advent of endo-bronchial ultrasound (EBUS) biopsies. Availability of low cost ultrasound machines has made diagnostic and therapeutic pleural procedures safer for malignant pleural effusions and empyema.

Furthermore, the emergence of more effective therapies for diseases that are traditionally viewed nihilistically has rejuvenated respiratory medicine. This includes intra-bronchial treatment for emphysema.

Table 1:
Service areas within respiratory medicine.

Asthma
COPD
Bronchiectasis
Occupational lung disease
Cystic Fibrosis
Sleep disordered breathing
Primary pulmonary hypertension
Long term non-invasive ventilation
Pleural diseases
Tuberculosis
Thoracic malignancies
Interstitial lung disease

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Personalised Respiratory Medicine:

Personalised medicine is *"an emerging practice of medicine that uses an individual's genetic profile to guide decisions on prevention, diagnosis and treatment of diseases"* 6.

This promising science is made possible due to the significant reduction in cost of genetic sequencing estimated to be the cost of an MRI scanner. Whole gene sequencing would predict diseases, allow foreseeing the probability of a disease responding to treatment (pharmaco-genetic) and is intended to reduce cost of medicine by providing a more targeted and cheap treatment.

The concept of personalised medicine has added to the excitement in managing respiratory conditions. Outlined below are four examples of modern intervention in three areas of respiratory medicine where promising restorative therapies have changed the natural history of lung diseases.

Personalised respiratory medicine is already re-shaping therapies for common and less common diseases. This article explains its role in cystic fibrosis, lung cancer and asthma.

Cystic fibrosis (CF):

No area in chest medicine has witnessed more successes in focussed care than that of Cystic Fibrosis (CF). Over the past 30 years, most CF patients reach adulthood, [figure 8] and the average age of CF patients has exponentially increased [figure 9].

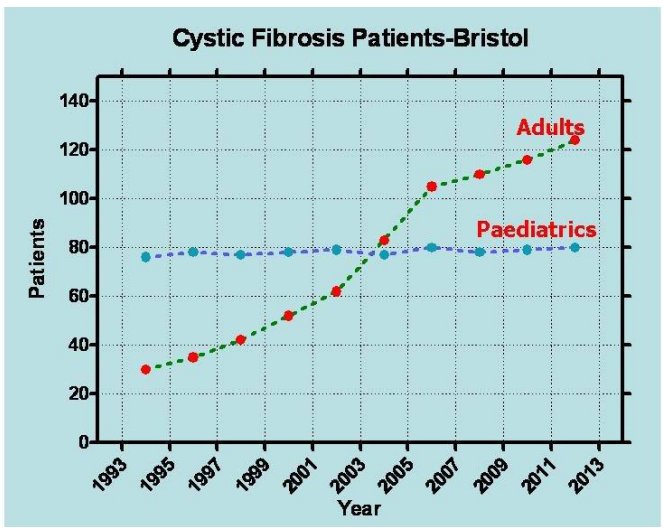

Figure 8: The numbers of paediatric and adult CF patients in Bristol over the past 20 years. Since 2003 the number of adult patients exceeded those of the paediatric group.

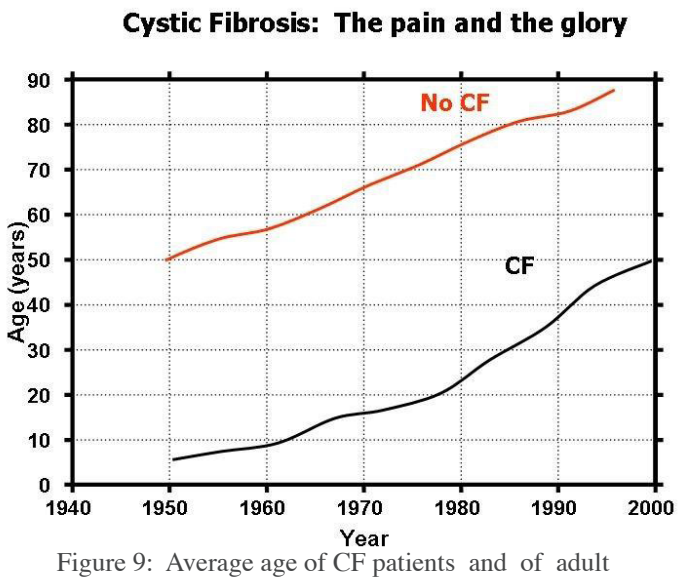

Figure 9: Average age of CF patients and of adult population in the UK over the past 70 years. Average life expectancy for CF patients has increased several fold but remains below people unaffected by CF.

The increased longevity is associated with improvement of quality of life. The remarkable improvement in CF natural history is mainly owing to the introduction of potent intravenous antimicrobial agents and the advent of pancreatic supplementation. In addition, the confinement of CF care to one team allowed researchers to understand the course of disease over time. The advent of the multidisciplinary approach has improved the understanding of microbiology, radiology and of CF complications such as CF-related diabetes and CF-liver disease.

Patients with CF demand high standard of care, excellence in research, independence from disease burden and friendship with eth CF team.

The improvement of care has meant that the disease is now mainly an adult disease. The number of adult patients is increasing [figure 8]. The demand on resources in adult medicine and on extra capacity to prevent cross-infection in clinics and wards has added to the already high burden of care in adult chest medicine.

Patients' care is expensive due to the high cost of intravenous and nebulised antibiotics, the cost of pancreatic enzymes and nebulised recombinant DNAse (pulmozyme) a useful but costly mucolytic agent. In addition, CF patients feel that they need to have a privileged access to health care.

One of the important consequences of good CF care is the increase in number of patients who are in full time education and employment and in those who live with partners and or those who are married.

To help with independence, self administration of IV antibiotics [figure 10] and remote tele-monitoring [figure 11] have been introduced in Bristol.

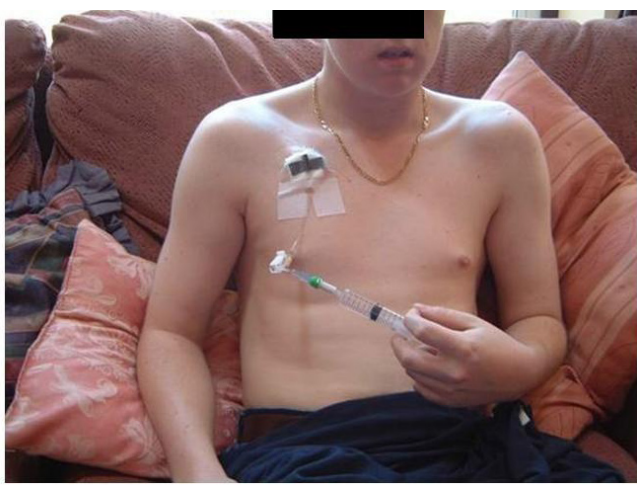

Figure 10: A Cystic Fibrosis patient self-administers his own antibiotics through a permanent central intravenous catheter (port-a-cath).

To accede to patients' quest for local research, critical appraisal of the outcome of tele-monitoring 7,8 and of examining the values and shortcomings of home IV treatment as well as the value of extending the course of IV antibiotics have all been evaluated 9,10. Factors affecting the common symptom of fatigue in adult CF patients, including poor sleep quality and poor perception of health by patients have been explored 11.

The fertility rate in CF females is reduced whilst almost all male patients with CF are infertile due to the absence of vas deferens during uterine years or early life.

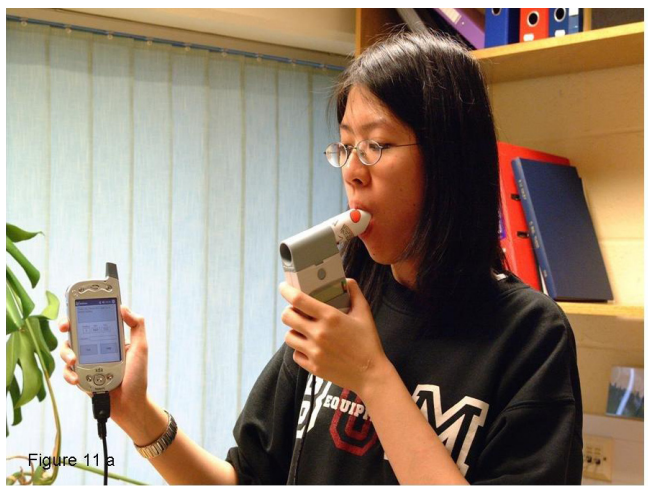

Figure 11(a): The telemonitoring kit consisting of a mobile phone that sends real time data consisting of a simple questionnaire and spirometry data.

Figure 11(b): A Bristol CF patient using the device at home – [From the BBC archive 2006].

Improvement of longevity and of quality of life has resulted in increasing number of patients seeking treatment for infertility with a high success rate. Genetic counselling and careful clinical and psychological assessment are often needed by both the CF team and the obstetric team who, as a consequence, forged a successful relationship.

Male fertility has become possible by intra-cytoplasmic sperm injection (ICSI); a technology in which healthy sperms are extracted from the testicles of a CF male and injected it into the cytoplasm of harvested eggs of his partner. The fertilised eggs are injected back into the uterus. The success rate is considerable.

The improvement in outcome of CF care has been achieved despite the fact that the cause of disease has not been addressed. The main genetic defect in CF is in a cell surface protein called the CF Trans-membrane Regulator (CFTR). This protein is a chloride channel that regulates the transfer of chloride from intra cellular to extracellular space. Physiologically, chloride binds to a sodium anion. The defect in chloride channel results in sodium being retained inside the cells – the devastating consequence of this that water does not reach the surface resulting in under-hydrated secretions which is the hallmark feature of CF.

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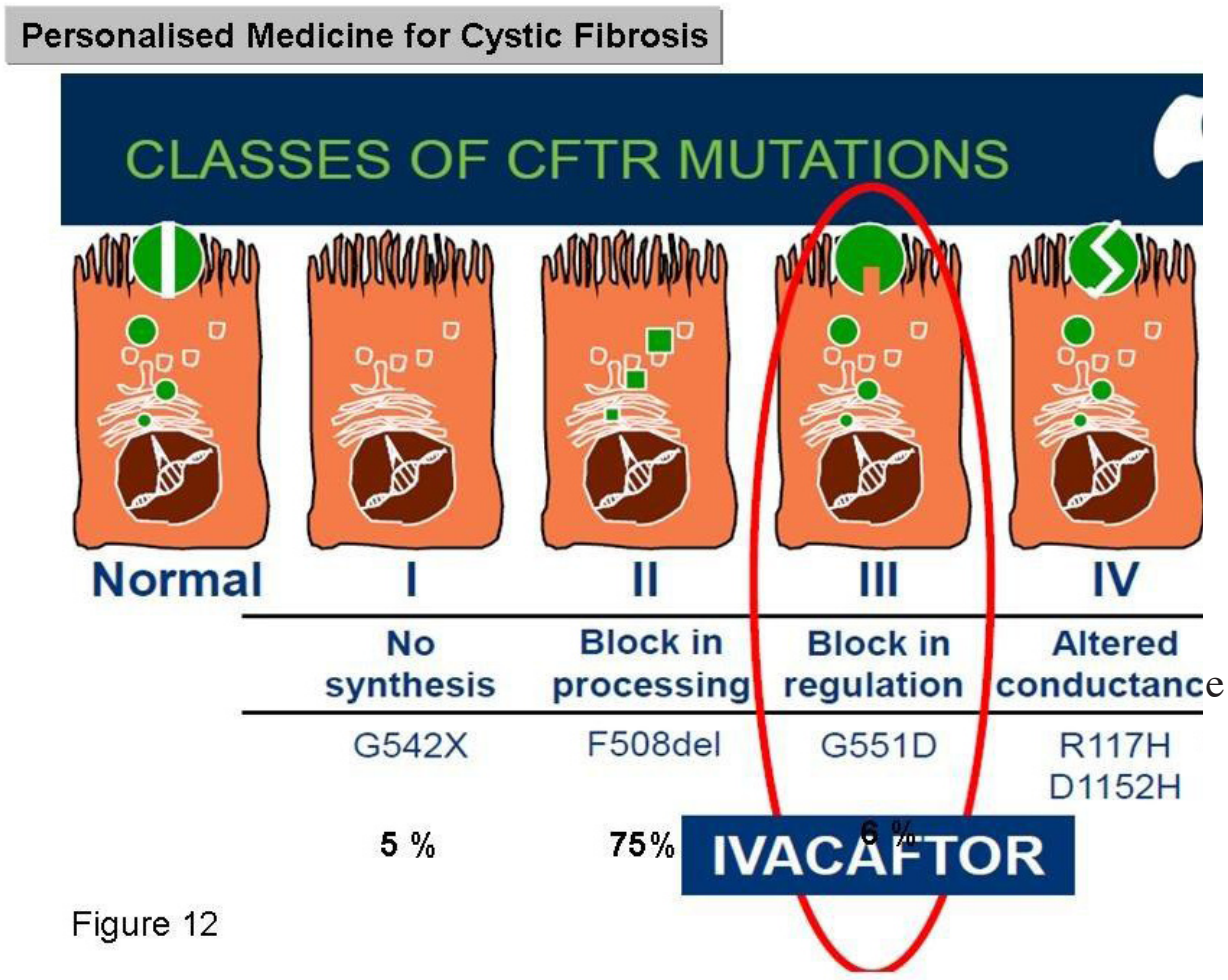

Figure 12

Figure 12: Types of genetic defects in CF corresponding to the fate of CFTR protein. The highlighted G551D is seen in approximately 5% of all CF patients

Over the past 25 years, several patterns of defects in the CFTR protein were found in patients with CF [figure 12]. The majority of CF patients carry the homozygote Delta F 508 mutation (F508del) where the protein is formed but not trafficked to the cell surface. However in the 5% of CF patients who carry the G551D mutation, the protein reaches the surface of the cells but does not function properly.

Over the past 3 years clinical trials on Ivacaftor in those carrying the G551D gene found impressive improvement in many out-come measures in CF starting 2 weeks after commencing the treatment [12] [Figure 13]. Ivacaftor epitomises the value of personalised medicine to create modalities for treatment that targets defected proteins due to specific gene mutations. The drawback has been in the cost of this drug that amounts to nearly £ 220,000 per year per patient for life. The dilemma created by the high cost of this drug is highlighted by an argument by Bush and Simmonds [13] who estimated that the treatment for 5% of patients who carry the G551D gene may amount to the 50% of the cost of the entire CF budget.

Figure 13 (below): The effect of Ivacaftor on FEV1 in patients with the G551D mutation.

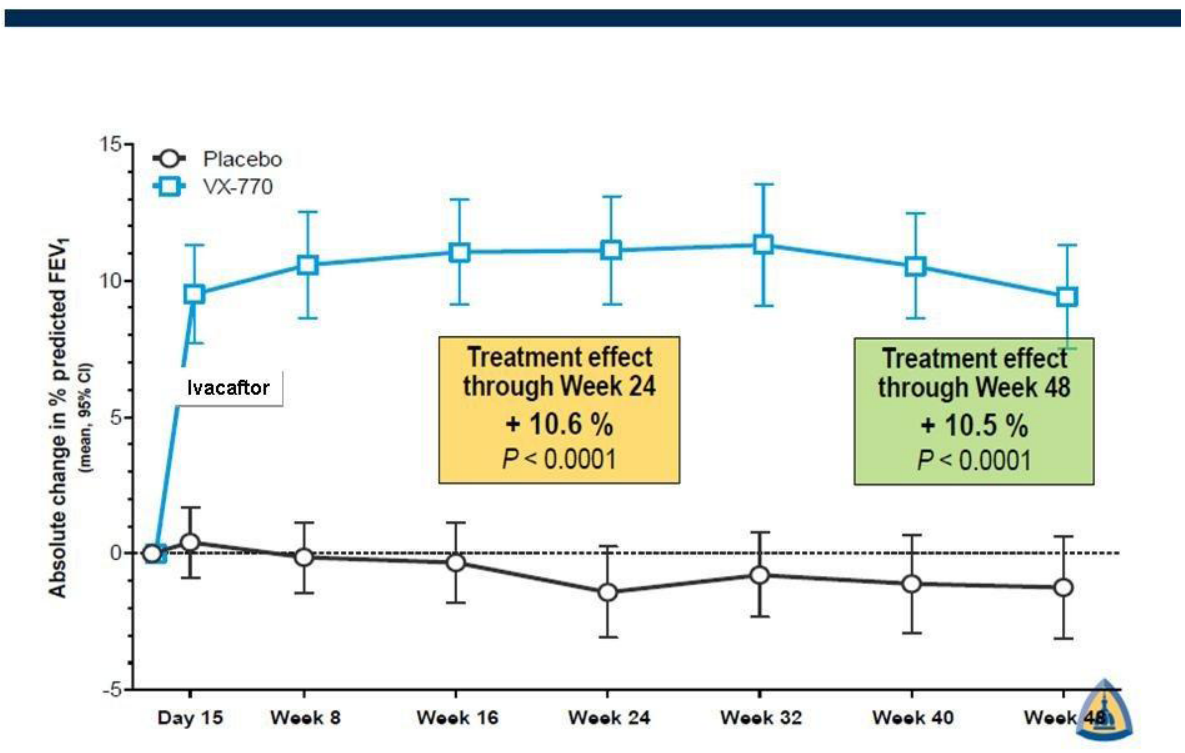

Figure 13

Lung cancer:

Over the past decade the surface of cancer cells has been mapped in order to identify specific receptors with the view of using them as therapeutic targets.

Out of many receptors described on the surface of cancer cells, the most notable and relevant for treatment was the Epidermal Growth Factor Receptor (EGFR) identified in about 5% of lung adenocarcinoma. The significance of EGFR positive adenocarcinoma is of their high response rate to gefitinib; a monoclonal antibody. An added advantage is that gefitinib can be provided orally or intravenously. Some of the anecdotal examples highlighted in figures 14 and 15 were remarkable enough to draw the attention of the respiratory and the cancer community to these agents. Looking for the EGFR mutation has become a routine part of the work of lung pathologists.

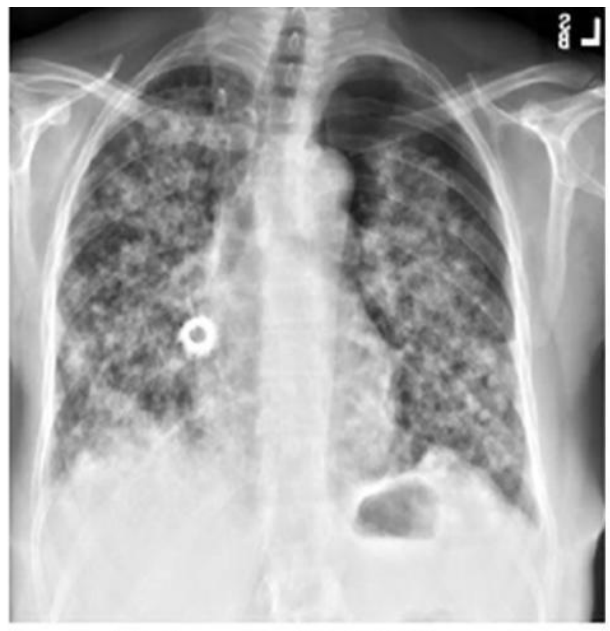

Figure 14(a)

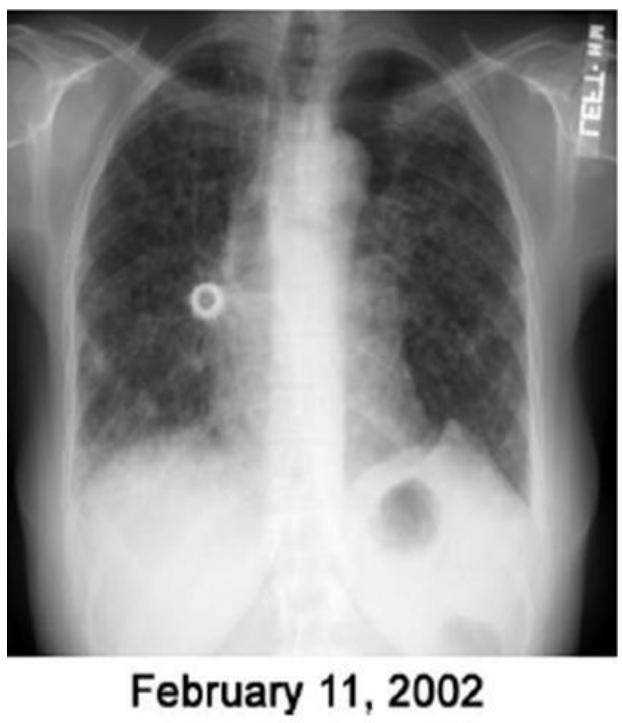

Figure 14(b)

Figure 14: Adenocarcinoma with EGFR surface marker before (a) and 5 days after IV gefitinib (b). There is a left sided pneumothorax and a port a cath in situ for drug delivery. Gefitinib is now available as an oral agent.

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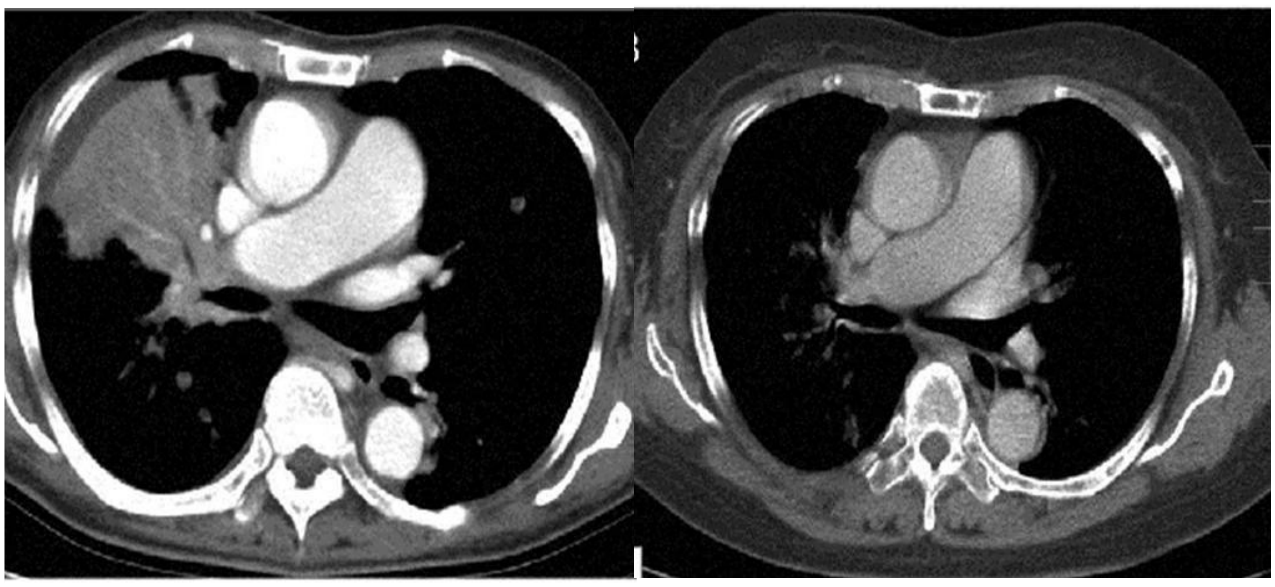


Figure 15a

Figure 15b

Figure 15: Adenocarcinoma with EGFR markers in the right upper lobe with Intra pulmonary metastasis in the left upper lobe (a) before and 90 days after treatment with gefitinib (b)

Clinical trials have supported the good efficacy of gefitinib in EGFR +ve adenocarcinoma. These have been reviewed by Gredilli et al[14] who observed several fold increase in tumour response rate to gefitinib for EGFR positive cells compared to conventional chemotherapy [table 2].

	Gefitinib Trial a	Gefitinib Trial b	IVChemotherapy Trial a	IVChemotherapy Trial b	Odds ratio for Gefitinib Trial a	Odds ratio for Gefitinib Trial b
EGFR +ve	71%	84%	37%	47%	2.8	9.1
EGFR -ve	1%	7%	23%	51%	0.04	0.32

Table 2: Two clinical trials (a and b) comparing the response rate for adenocarcinoma for gefitinib. Both trials showed superior outcome in disease response for tumours carrying the EGFR mutation. Please also see text.

Asthma:

Asthma is defined as a disease characterised by fluctuating symptoms of wheezing, cough, breathlessness and chest tightness[15]. Up to 3% of all the UK population suffer from asthma or are treated by asthma drugs. The impact and the severity of asthma are greatest in childhood and old age. The burden of disease on patients is considerable. The management of asthma normally follows an escalating pattern that is often referred to as step wise of management. Asthma steps are achieved by addition of drugs [figure 16 a] with increasing cost [figure 16 b] and side effects. In contrast, de-escalation of drugs in asthma when symptoms improve does not often happen.

Figure 16: (a)
Steps of escalation in asthma management

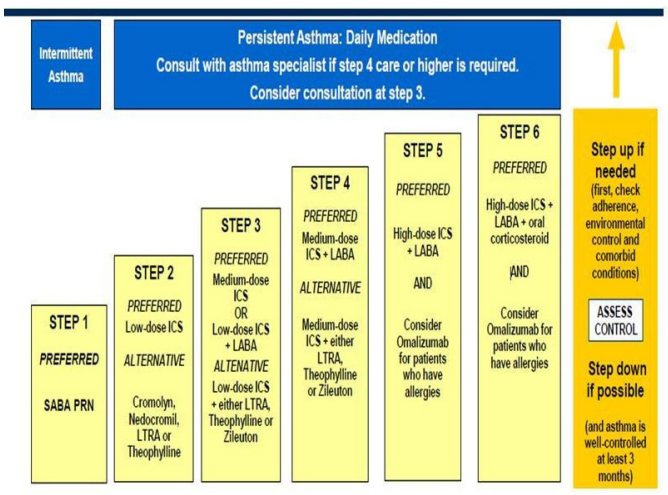


Figure 16 (b) The increase in drug cost of asthma drugs with every step.

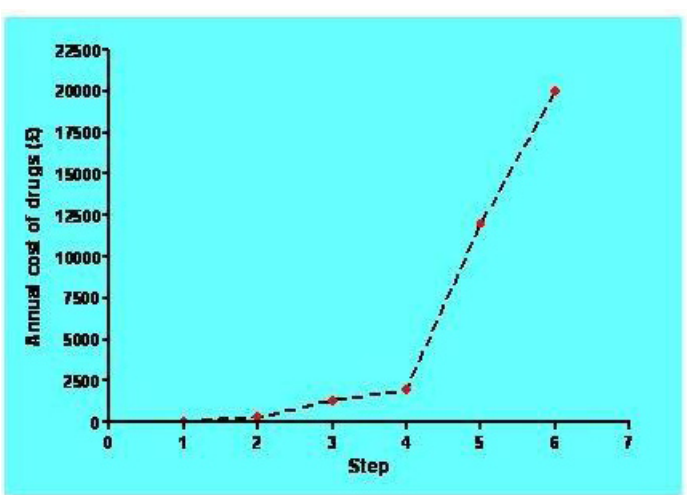
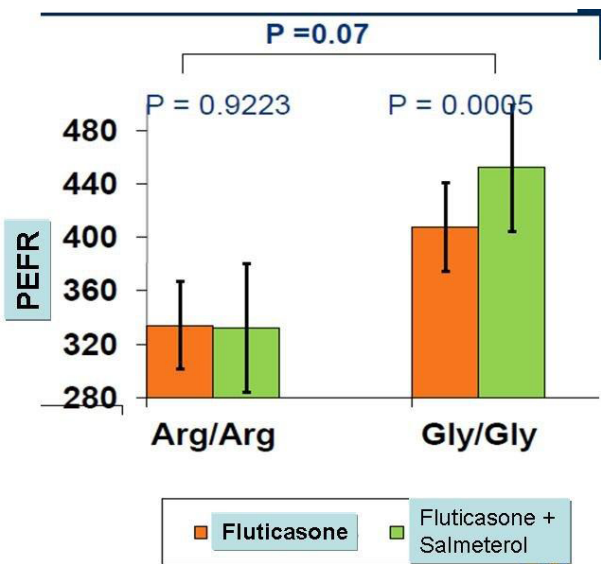


Figure 18a

Figure 18: Change in AM and PM PEFR salbutamol (a) and to inhaled corticosteroids (ICS) with and without long-acting beta2 agonists (LABA) (b) in asthmatics differs according to the gene mutation- adapted from references 17 and 18.

Figure 18b



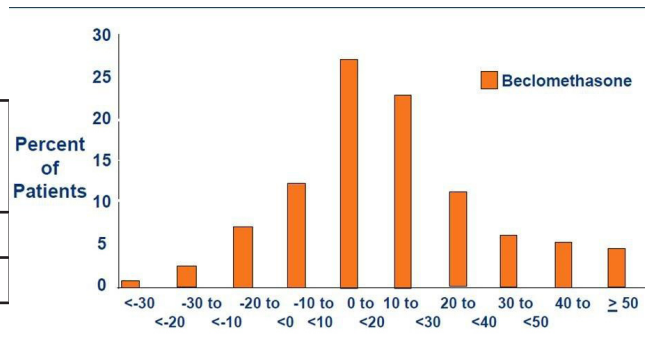


Figure 17: FEV1 change from baseline after prescribing beclomethasone. Note that up to 45% of all asthmatics do not show any response or even decrease after prescribing beclomethasone. From Malmstrom et al [16].

In a careful prospective study, Israel et al found that possessing certain genetic mutations is associated with different response to common asthma drugs. Those who were homozygots to the arginine genes (Arg/Arg gene) were resistant to improvement in morning peak expiratory flow rate (PEFR) to inhaled beta2 agonist alberterol (salbutamol) when compared to patient carrying the glysin gene (gly/gly). [Figure 18 a). In a similar work, Wechsler et al, found a reduced response of AM and PM PEFR to long acting Beta 2 agonists alone and with inhaled corticosteroids in African American carrying the Arg/Arg gene compared to those carrying the Gly/Gly gene (figure 18 b). More recently Tantisira enforced the genetic basis of response to therapy in a study where he found variation in response of asthmatics to inhaled corticosteroids [19]. These three studies would suggest that gene mapping might help to direct asthma treatment to best candidate responders and underpin the importance of future personalised respiratory medicine and its application in geno-phrmacology.

Another facet of response to treatment is found in asthmatics with predominant blood and sputum eosinophels. Eosinophil-predominant asthma is probably genetically driven. This group has been found to markedly respond to medications acting against interleukin 5 (IL5 inhibitors) – mepolizumab. IL5 is an important cytokine that recruit eosinophils and increases their numbers in circulation and bronchial mucosa.

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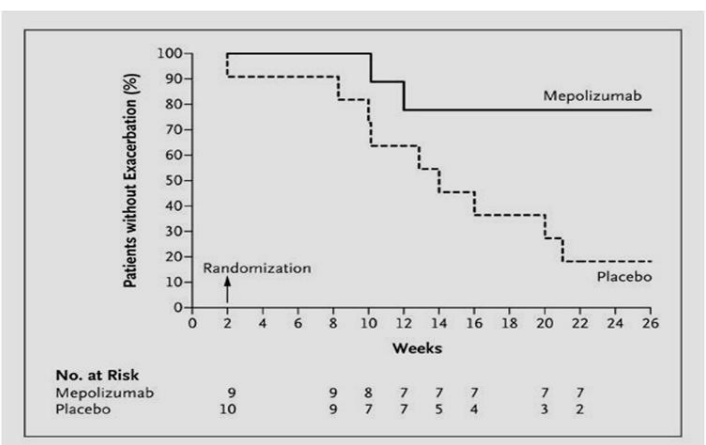


Figure 19: Reduced exacerbations in a small number of eosinophelic asthmatics (from reference 20)

A preliminary work by Nair [20] et al [figures 19] found that intravenous mepolizumab in patients with eoinophelic asthma resulted in a significant degree of reduced exacerbations. This research was confirmed by a larger placebo controlled study of 3 doses of mepolizumab where a marked difference was found in prevention of asthma exacerbations as well as night and early morning symptoms and AM and PM PEFR values [21] [figure 20].

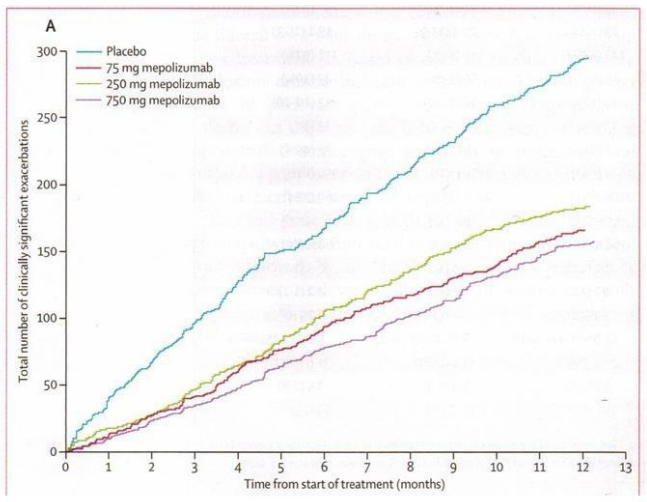


Figure 20: Three doses of mepolizumab were found to be effective in preventing asthma exacerbations compared to placebo in asthmatic with raised blood or sputum eosinophils.

Respiratory Medicine in the frail and the elderly:

The predicted rise in the number of elderly population [21] with consequences of increasing demands on primary and secondary care poses a significant and unique set of problems. So far, this challenge has not been matched with corresponding change in clinical practice and resource redirection to accommodate their needs.

Respiratory Medicine in old age [22] is different in many ways to respiratory medicine in younger population. Respiratory infections increase with old age [23] with clinical manifestations of both respiratory and non-specific respiratory symptoms.

COPD, asthma and infections due to aspiration increase with old age [24, 25, 26]. Aging increases the frequency and the severity of COPD exacerbations as well as the length of hospitalisation and mortality due to COPD exacerbation [27,28,29].

Social isolation, difficulty in mobilisation and the presence of co-morbidity [30, 31] including cardiac failure and joint disease with reduction of mobility and tendency for syncope increases with old age [figure 21].

Figure 21a: An elderly COPD patient who lives alone and uses ambulatory cylinders of oxygen

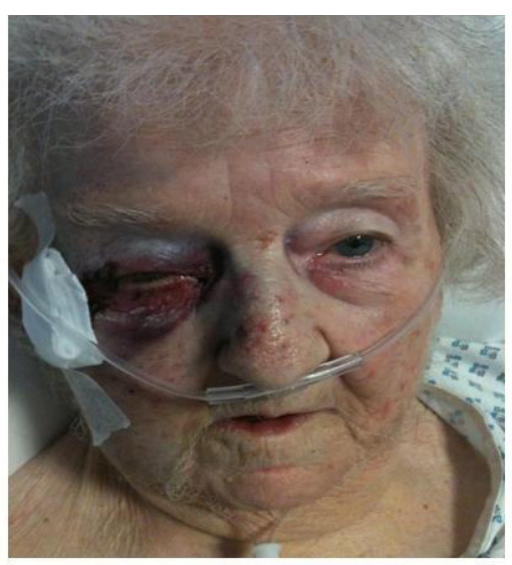


Figure 21b: An elderly lady with COPD on long term oxygen therapy who was found by her cleaner on the floor by an episode of syncope induced by hypoxia.

The added rise in depression and cognitive problems necessitates establishing different goals for management of chronic respiratory diseases in the elderly. Improvement of lung function tests is not the most relevant aim. Rather, improvement of quality of life and enablement of old persons to gain independence are better aim of any intervention.

To cope with the challenges of old age and to achieve these aims require multi-dimensional assessment and multi-modality intervention [32]. In Bristol, the set up of admission avoidance clinic (the HOT clinics) has gained instant approval from patients [33], clinical professionals and administrative staff alike. Over the past 3 years, the demand on the HOT clinic increased [Figure 22 a] and the constant ability of this service to reduce admission have been a constant feature [figure 22 b].

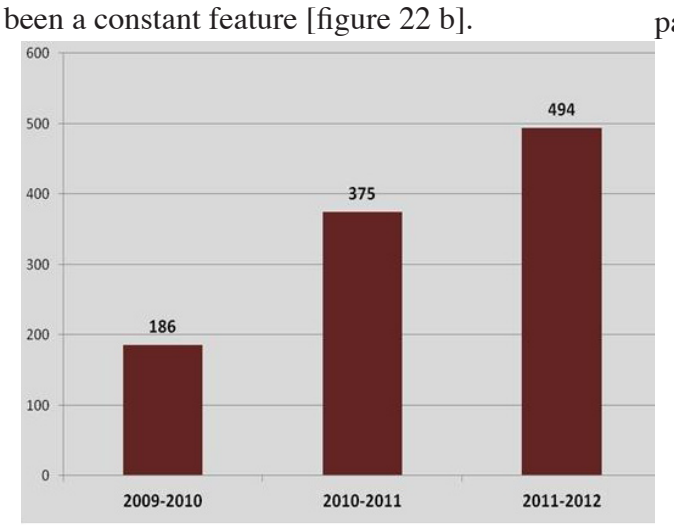
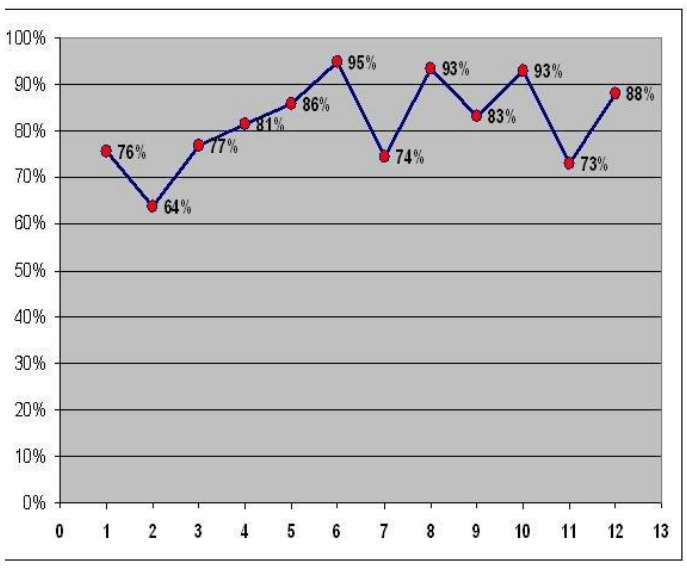


Figure 22: The HOT clinic service at Bristol Royal Infirmary. Graph a (above) shows the number of patients seen annually over 3 years. Graph b (below) shows the rate of admission avoidance for every month in 2012 where 1 on the X axis is January and 12 is December.



The cost of setting up the clinic is modest and patient satisfaction is high [figure 23].

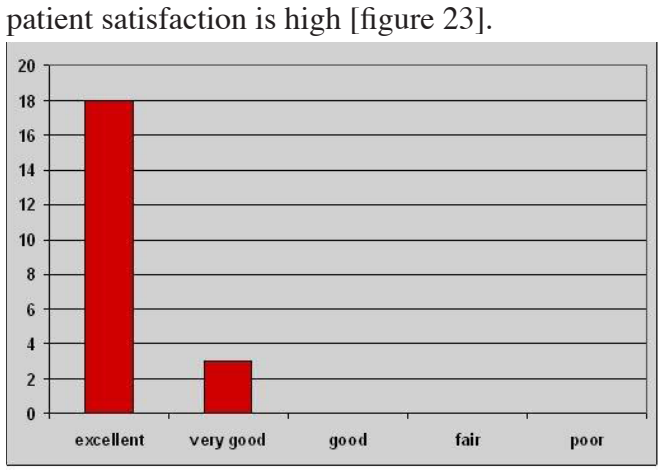


Figure 23: Rate of patients' satisfaction in a nurse-led survey for patients seen in the HOT clinic (see also reference 32).

Tracking the whereabouts of newly admitted patients by specialist respiratory nurses within the hospital has become the norm. This has the advantage of patients seen by specialist nurses with the input from respiratory physicians whether they were admitted to respiratory or non-respiratory wards.

NICE recommendations indicate that early follow-up of hospitalised COPD patients is associated with decrease in hospital admission and decreased 90-day mortality after hospital discharge. Accordingly an early follow-up clinic for hospitalised patients with COPD exacerbations has been instigated in a respiratory clinic based in a community hospital. The community hospital is situated in the most densely populated and most deprived part of the city of Bristol [Figure 24].

The clinic gained high satisfaction by patients with minimum non-attendance rate compared to clinics run in the main hospital.

Figure 24: South Bristol Community Hospital where the community respiratory clinic is held.

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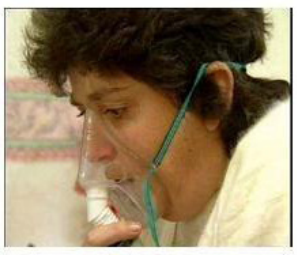

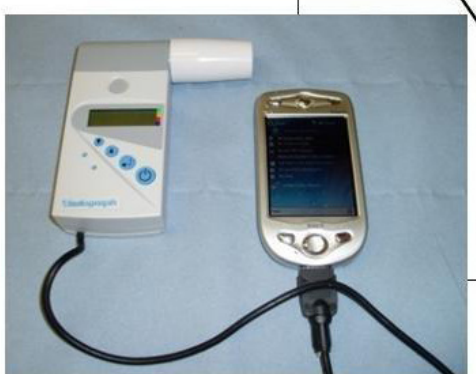

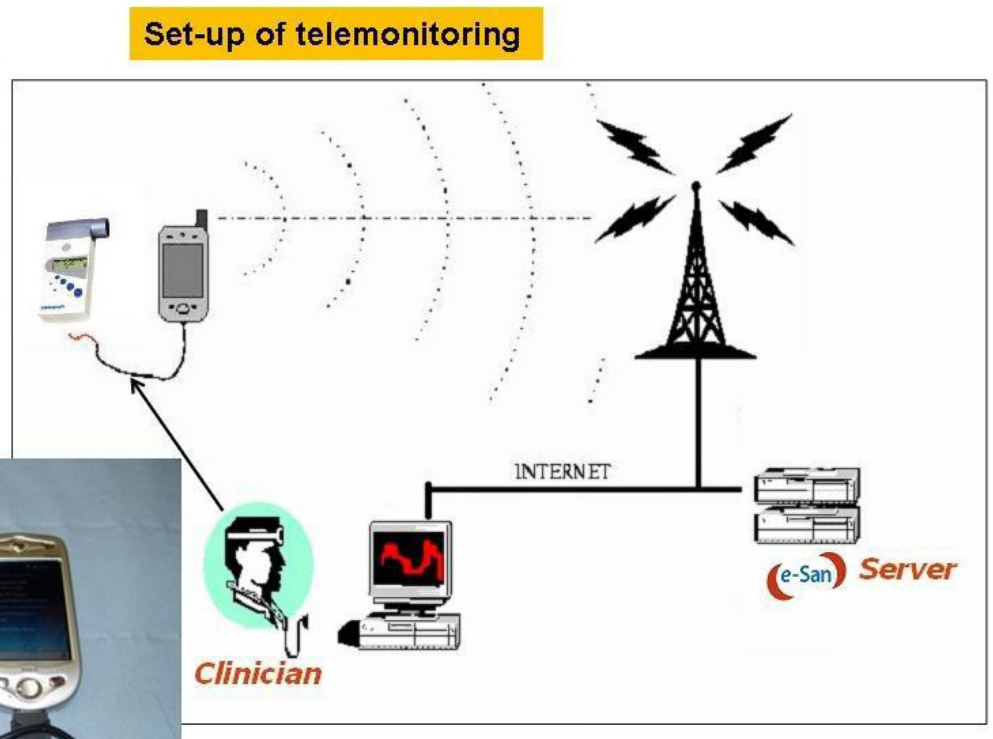

Figure 25: Electronic daily monitoring of symptoms and spirometry with real time transmission of data to a clinician.

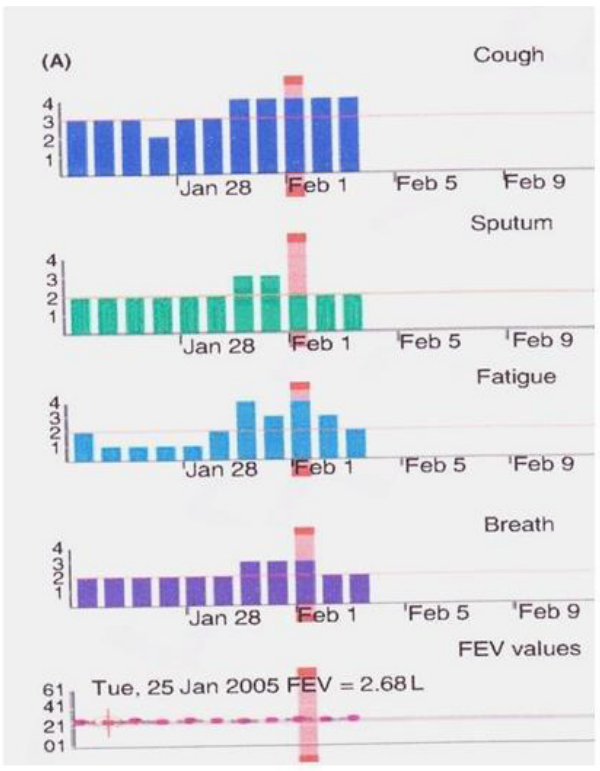

Figure 26: daily score of common symptoms and spirometry. Exacerbation is defined with increase in symptoms for 3 successive days (red line). Upon starting treatment, symptoms resolved with 72 hours

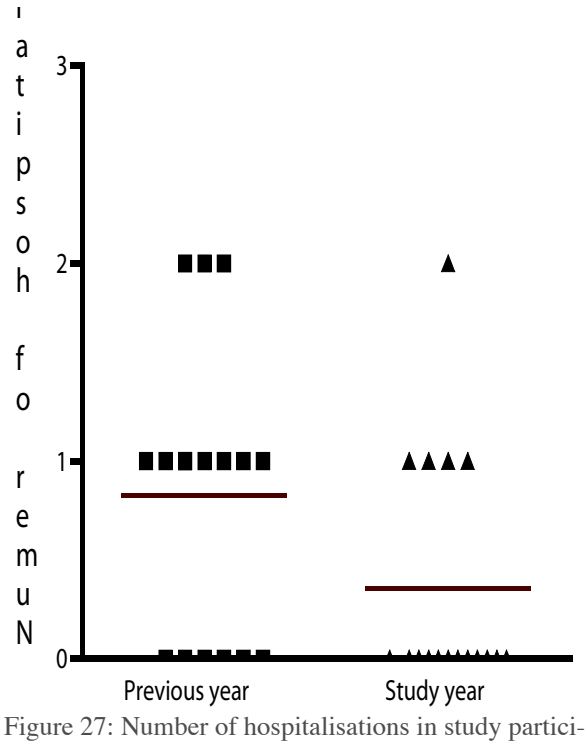

Figure 27: Number of hospitalisations in study participants are halved compared to the previous year (reference 34).

Finally, setting up tele-monitoring [Figure 25] with daily monitoring of symptoms and timely intervention during exacerbations [Figure 26] has resulted in reduced hospitalisation for COPD and reduced length of stay [34] [Figure 27].

CONCLUSION:

Respiratory medicine is emerging from the nihilistic phase where the emphasis of treatment was on symptom control and reducing progression of disease and is becoming more effective and personalised. In Bristol increased specialist input in acute medicine and establishing a responsive daily acute clinic has resulted in improvement of care of respiratory diseases.

There is a further opportunity of Bristol to take a leading role in many specialist areas. However, the large burden of the disease remains in the frail and the elderly where hospitals and community need to work seamlessly to care for a population that are increasing in number and in disease complexity.

The Bristol Medico chirurgical society is in a position to set up collaboration between primary and secondary care to improve communication between health professionals and to ensure a timely contact between the two sectors – an issue which has been poor in the UK National Health Service.

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