Expert Forum

New Zealand Lung Day 2016 – a focus on respiratory medicine

Making Education Easy 2016

In this review:

Welcome

to this review of the third New Zealand Lung Day, a multidisciplinary meeting held in Auckland on 18 March 2016. This review features summaries of presentations that covered a wide range of topics including under-treatment in COPD, circulating plasma DNA and T790M mutations in NSCLC, and the role of the gut and lung microbiome in lung diseases. The meeting featured local and international speakers and was attended by respiratory physicians, oncologists, pathologists, and nurse specialists, in addition to respiratory researchers, trial co-ordinators and study nurses.

This Scientific Symposium was organised and supported by AstraZeneca Limited. The agenda of this meeting was set-up by the steering committee – Prof. Lutz Beckert, Prof. Rob Young and Dr. Chris Lewis. The content is based on published studies and the speakers' clinical opinions. The views expressed are not necessarily those of AstraZeneca Limited.

SMOKEFREE NZ 2025

Professor Richard Edwards, University of Otago

In March 2011 the New Zealand Government responded to a recommendation of the Maori Affairs Select Committee and adopted a goal of New Zealand becoming smoke free by 2025, and became the first government in the world to introduce such an initiative.

What does Smokefree New Zealand 2025 mean? The Government committed to a goal of minimal tobacco use and availability. This is often interpreted as meaning:

- Our children and grandchildren will be free from exposure to tobacco and tobacco use
- The smoking prevalence across all populations will be less than 5%. The goal is not a ban on smoking.
- Tobacco will be difficult to sell and supply.

Progress and current status

A number of policy measures have been put in place to achieve Smokefree 2025; prisons became smoke free in 2011, point-of-sale displays were removed in 2012, duty-free tobacco allowances were reduced in 2014, and tobacco tax increases of 10% more than inflation have been introduced every year for the last five years.

Over recent years, there has been a steady decline in daily smoking rates, from almost 25% in 1996 to around 15% in 2014. In adolescents, huge reductions have been seen over the last 15 years to 5% in NZ Europeans, 8% in Pacific, and 15% in Maori. Increasing tobacco tax has probably been the single most important factor in reducing smoking rates. However, the current smoking prevalence of over 15%, and particularly of over 30% among Maori, is still far too high. Projections suggest that the 5% smoking prevalence goal will be missed, and will be missed by a wide margin for Maori.

The Maori Affairs Select Committee and many commentators have urged the Government to develop a clear strategy setting out how the Smokefree 2025 goal will be achieved. In 2012, the National Smokefree Working Group (an expert group of tobacco control specialists) devised its own action plan to achieve the Smokefree 2025 goal. **Figure 1** shows some of the key proposed action points on the left and the Government's progress in the coloured boxes on the right. Progress has been patchy at best, with the implementation of duty free

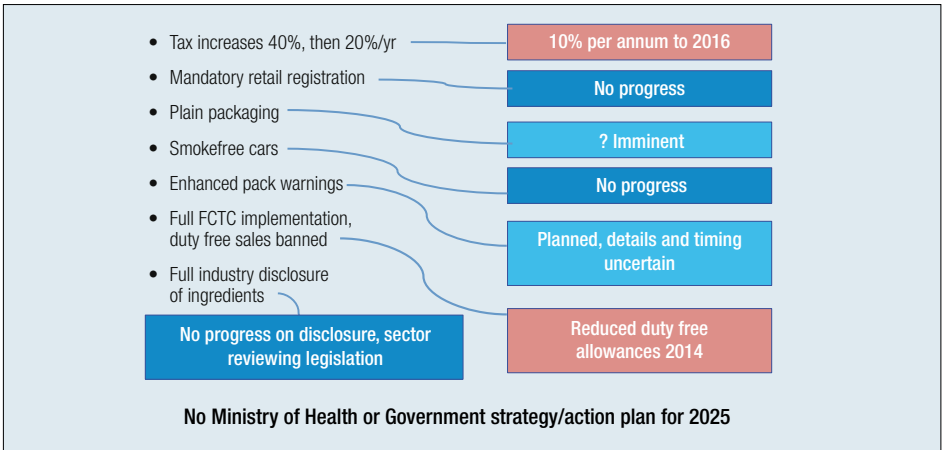

Figure 1. Smokefree 2025: current status

sales restrictions and moderate tax increases the most important advances. However, there is still no date set for introducing plain packaging, smoke-free cars have not been introduced, and there is no progress on retailer licensing or other measures to restrict supply. This contrasts with rapid progress on these issues in other jurisdictions like the UK, Australia and Ireland. Crucially, there remains no government plan or strategy for Smokefree 2025. Unfortunately, there is very little promotion of the Smokefree 2025 goal, and analysis of Government press releases and speeches shows that Health Ministers rarely mention the goal, suggesting a lack of a political imperative for action and lukewarm political support.

Achieving Smokefree 2025

In order to achieve Smokefree 2025, regular tax increases (10% p.a. or preferably greater) need to continue. Plain packaging and enhanced health warnings on packaging are important and should be implemented promptly. There needs to be greatly increased and sustained mass media interventions and enhanced smoking cessation promotion and support within key populations (particularly Maori and Pacific, and pregnant women). Other incremental intensification measures include smoke-free cars and other smoke-free policies and retail-based interventions (e.g. the introduction of licensing, and proximity/density restrictions for tobacco retailers).

In addition, one or more radical measures may be required to reduce smoking rates to as low as 5%. Possible initiatives include large and frequent tax increases of more than 20%, cigarette modification to include less nicotine and fewer additives, major reductions in retailer supply, and raising the age of purchase to 21 and then 25 years to achieve a 'tobacco-free generations' who will never be old enough to purchase tobacco.

What can healthcare professionals do?

There are many ways that healthcare professionals can support the achievement of Smokefree 2025. Health professionals are highly respected by their patients, the media and politicians, so can have real influence. At a very basic level health professionals can get informed about and engaged with Smokefree 2025. They can support initiatives in clinical settings e.g. support comprehensive smoke free policies and cessation support in your ward, clinic or surgery. Health professionals can also provide active support for Smokefree 2025 and hold the Government to account, for example through talking to their MPs, writing letters, through work in professional organisations and so on.

For more information, visit: http://smokefree.org.nz/smokefree-in-action/smokefree-aotearoa-2025

GETTING TO THE HEART OF COPD EXACERBATIONS – THE NZ β-BLOCKER STUDY

Dr Cat Chang, Waikato Hospital

The NZ β-blocker feasibility study evaluated the safety and tolerability of commencing a cardio-selective β-blocker in patients admitted to hospital with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Data were collected with the aim of designing a full-scale randomised controlled trial. The primary endpoints were the percentage of patients that could start metoprolol during an exacerbation and complete the 12-week protocol.

572 patients were screened from November 2014 to August 2015. Of these, 96% were excluded, recruiting only 23 patients. The main reasons for exclusion included already taking a β-blocker (n=115) and being discharged too quickly for test dose procedures (n=106). Only 16 patients completed the 12-week study. Twelve patients received 95 mg of metoprolol and four received 47.5 mg of metoprolol.

Results

Adding a β-blocker (metoprolol) did not alter lung function in these patients. Mean FEV_1 was 0.86 L at both baseline and at maximum β-blocker dose (p=0.77), mean percentage FEV_1/predicted FEV_1 was 33% and 32%, respectively (p=0.84) and mean percentage FEV_1/FVC was 39.5% and 37%, respectively (p=0.40). Mean heart rate changed from 91 at baseline to 71 at the maximum β-blocker dose (p<0.01). Blood pressure remained stable.

Most patients had at least one adverse event (AE). Not surprisingly, there were a large number of readmissions or ED presentations for COPD exacerbations (n=8). Two patients were admitted to hospital for heart failure. One patient died two weeks after discharge due to respiratory failure unrelated to the study drug. β-blocker-related AEs included postural hypotension/dizziness (n=4) and nonsymptomatic bradycardia (n=1). Possible β-blocker-related AEs included transient increase in dyspnoea (n=3) and lethargy (n=1).

Conclusions and future directions

In conclusion, it is not feasible to conduct a large scale randomised controlled trial starting β-blockers in patients with AECOPD using this study design, due to the large number of excluded patients. But it might be possible to conduct this study in patients with stable COPD. Can cardiac biomarkers help identify a subgroup of patients that may benefit from β-blockers? The 'frequent exacerbators' are most likely to benefit – can they be identified and treated between exacerbations? Another feasibility study is planned to answer these questions and has been submitted to the HRC for funding.

This research group is not alone in thinking that β-blockers may benefit patients with COPD. A US multicentre randomised controlled trial of metoprolol in stable COPD is due to start recruiting and a Trans-Tasman collaborative evaluating β-blockers in stable COPD has applied for funding.

Where else might this study lead? Most COPD exacerbations are low risk: can cardiac biomarkers help identify high risk patients and then be combined with other risk scores (e.g. CURB65, BAP65, DECAF). Can a group of patients that are safe to discharge be identified (the COAST study answering this question is in progress)? If it can be shown that treating cardiac dysfunction in COPD is beneficial, there is potentially a whole arsenal of existing treatments that can be used in COPD patients.

PATIENT PERCEPTIONS OF SEVERE COPD AND TRANSITIONS TOWARDS DEATH: IDENTIFYING MILESTONES AND DEVELOPING KEY OPPORTUNITIES

Professor Lutz Beckert, University of Otago

Patients with COPD often see their illness as a 'way of life', not as a life-threatening illness. The patients' story of COPD has no beginning, no entry point and, therefore, the thought of an exit point has no context. It is unclear how people with end-stage COPD prepare for end-of-life against the background of an unpredictable illness trajectory.[1] It has not yet been defined how a health system offers a palliative approach to these patients in an appropriate, timely and sustainable way.

The aim of this study was to explore the experience of patients with advanced COPD after a life-threatening event, particularly focusing on end-of-life issues.[2]

Qualitative methods were used to capture patient experiences. Patients admitted for noninvasive ventilation for COPD were recruited and interviewed following discharge. The interview explored the participants' understanding of their illness, concerns and plans, exploring end-of-life issues and perceptions of palliative care.

Results

A total of 15 participants were recruited. Six themes emerged from the interviews, which identified transition points and changes in care needs. These themes included loss of recreation, home environment, episodes of acute care, oxygen treatment, panic attacks and assistance with self-care. They appeared to accumulate over time and did not accumulate in any particular order.

Loss of the ability to participate in recreational activities was frequently mentioned. Discussions about planning for future place of care happened despite patients not recognising that they are close to death. Patients had mixed feelings about the need for acute care, however it was expected to be a part of their future needs. Long-term oxygen therapy featured strongly in the narratives. It is interesting that breathlessness was not mentioned as a trigger for concern about health status. However, when breathlessness induced panic, this was significant. Needing assistance with self-care signified the worrying possibility of lost dignity and of being a burden to others. Patients did not see

themselves as dying even with advanced disease, partially because of the unpredictable course of their chronic illness.

A new model of care is therefore proposed for patients with advanced COPD (**Figure 2**). The accumulation of these milestones could be used to identify patients with severe COPD who are deteriorating. The patients may use the terminology outlined by the milestones when discussing their current health status with a health professional they trust. It highlights to the health care team a key opportunity to initiate vital end-of-life discussions and a transition to the palliative approach.

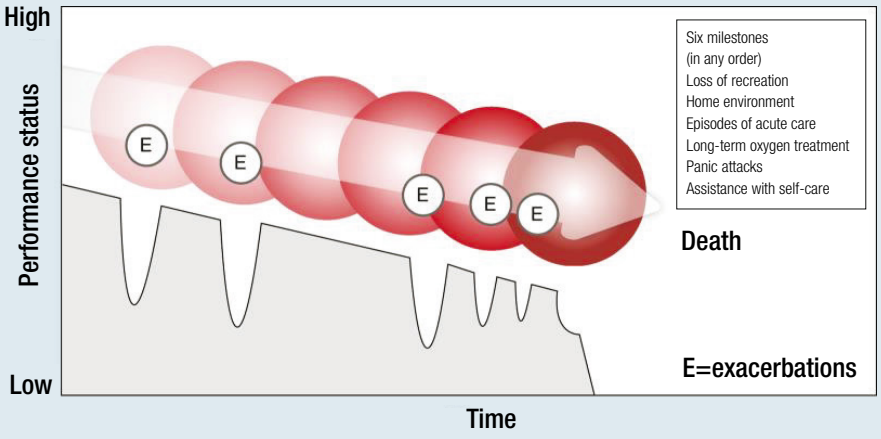

Figure 2. Trajectory of COPD

Conclusions

Even patients with severe COPD see themselves as living with, and not dying of, COPD. Therefore, offering palliative and end-of-life support is difficult to initiate. However, patients described six milestones illustrating multiple losses that may serve as stimuli for patients and health services to change focus. Health professionals can use these key opportunities to plan together for the future.

COPD: CAN WE ADD UNDER-TREATED TO UNDER-DIAGNOSED?

Professor Rob Young, University of Auckland

It is generally accepted in the literature that about 70% of patients with COPD don't know they have the disease. Alarmingly, of COPD patients categorised as GOLD I, more than 80% of patients remain undiagnosed.[3] Patients are typically diagnosed with COPD after they have presented with one or more exacerbations, but if spirometry was routinely performed in high-risk individuals, patients would be diagnosed at an earlier stage. The implication of under-diagnosis for mild or moderate COPD is under-treatment, and insidious exertional breathlessness worsens exercise capacity and QOL. As well as being under-diagnosed, COPD patients are also under-treated, not necessarily in terms of airways disease but in terms of cardiovascular disease (CVD).

Do statins benefit COPD patients?

There has been considerable interest in the idea that statins, through anti-inflammatory mechanisms, may benefit patients with COPD. Indeed, results from COPD observational studies of about 750,000 patients treated with statins show reductions (compared to patients not treated with statins) in all-cause mortality of 50%, respiratory mortality of 40-50%, respiratory hospitalisations of 30% and coronary artery disease (CAD)/MI mortality (high risk patients only) of 50%.[4] One of the concepts that has been proposed to explain this observation is the 'healthy user' effect, i.e. patients in observational studies that are taking a particular medication (in this case statins) that gain no clinically useful benefit but have better outcomes (such as less mortality). This implies that these medications are also providing something else that explains the observed benefits independently of the drug itself, termed a confounding effect or selection bias. In an evaluation of the observational studies, it was found that patient demographics of statin users versus non-users were very similar in terms of age, gender, smoking status, lung function and socio-economic status. Statin users actually had 1.5-2 fold greater prevalence of hypertension, diabetes, stroke, and CAD (as expected) but still had better outcomes than non-users. There was no evidence that statin users were doing anything different to account for these better outcomes (i.e. no "healthy user-effect" was evident).

However, STATCOPE, the only large randomised controlled trial that has evaluated statin use in COPD patients, found no difference in exacerbation rates in statins users versus non-users.[5] These data questioned the idea that statins may be useful in COPD. In their editorial in *Thorax*, Professor Young and colleagues examined the STATCOPE study data, particularly data of patients who were excluded.[6] They concluded that the negative result may be due to the selection of low-risk COPD patients. Unlike the observational studies which took ''all-comers" COPD patients, STATCOPE excluded an estimated 70-80% of COPD patients, including patients already on statins (who would have already had comorbid disease) and patients who were at risk for CAD. The remaining randomised patients were non-statin users with low risk for CV comorbidity. This raises controversy over the use of the STATCOPE study data – is it generalizable to the COPD population that are at risk of coronary complications or where occult coronary artery disease contributes to acute exacerbations?

COPD and the 'unhealthy nonuser'

The term 'unhealthy non-user' is derived from the observational studies of statins in COPD. It is based on the very poor outcomes in COPD patients with recognised CV morbidity that are not prescribed CV medications. As COPD patients are at high risk for CV-related death, undertreated patients do very poorly relative to those on life-preserving treatments. In fact, this hypothesis was suggested by the STATCOPE investigators to explain the discordant results between STATCOPE and the observational studies.

Audit of statin use in COPD – results from Auckland City Hospital

In an attempt to answer discrepancies between the observational studies and STATCOPE, Professor Young and colleagues conducted an audit into statin use in COPD at Auckland City Hospital. The audit identified COPD patients by ICD code admitted to the hospital from January 2014 to June 2015 (n=250). The aims of the audit were to establish the prevalence of comorbid CVD in patients with spirometry-confirmed COPD and to estimate the proportion of COPD patients who are on statin therapy or for whom it would be indicated.

Demographics were similar between statin users and non-users, except for comorbid disease as expected. The audit found a high prevalence (56%) of CV comorbid disease in hospitalised COPD patients. Among patients who had ever taken statins, 82% had some form of CVD. A total of 64% of patients had an indication for statin use, of whom 38% were currently on statins and 26% were not on statins (**Table 1**). Somewhat concerning was that among patients who had NEVER taken statins, 32% had some form of CVD. Furthermore, current statin use was documented in only 55% of TIA/stroke patients, 63% of patients with combined CVD, and 65% of MI/angina patients. Regarding the STATCOPE study, only 19% of patients would have been eligible, which concurs with the authors' editorial in *Thorax*.[6]

Table 1. An audit of statin use in COPD at Auckland City Hospital

Question	Answer
What proportion of unselected COPD patients are taking statins?	38%
Are there differences among COPD patients taking vs not taking statins that might explain the "healthy-user-effect"?	Apart from more comorbid disease and paradoxically better outcomes, COPD patients taking statins have the same clinical profiles as those not taking statins.
What proportion of COPD patients should be taking statins but are currently not?	26% ('unhealthy users')
What proportion of unselected COPD patients would be eligible for the STATCOPE study?	19%

Implications and basis of under-treatment

There has been enormous interest in CAD in COPD. An editorial in *Chest*[7] compared ischaemic heart disease in COPD patients versus non-COPD patients and made a number of observations in the COPD patients:

- More multi-vessel disease, distal short (non-occlusive) plaques
- Risk factors included smoking, diabetes, hypertension and old age
- Involves small coronary vessels and associated with ischaemic cardiomyopathy and heart failure
- Associated with systemic inflammation, oxidative stress and hypoxia (perfect storm of an acute exacerbation)
- Type 2 MI accounts for 50% of all MI (vs 25% in non-COPD)
- Coronary artery plaque burden is greater
- More non-obstructive coronary occlusions
- Low rates of PCI and angiograms due to higher mortality and more revascularisation

In conclusion, this 'unhealthy nonuser' group of COPD patients are grossly undertreated in terms of CV risk. Current inhaler therapies do not improve mortality so greater focus should be placed on improving CV outcomes. COPD patients are not only under-diagnosed but also under-treated.

ASTHMA: AIR SUPPLY DATA SUB-ANALYSIS

Professor Lutz Beckert, University of Otago and Dr Angela Moran, Canterbury District Health Board

The Air Supply dataset evaluated asthma control in Australia and New Zealand and was a cross-sectional web-based survey in a large nationally representative population (n=27,606). Among these individuals, 6339 had ever experienced asthma and 3475 had current asthma; 2686 subjects completed the survey. Subjects took the Asthma Control Test which asked a variety of questions regarding demographics, asthma history, asthma treatment, and routine and urgent healthcare utilisation. Adherence to asthma medication was also assessed.

In New Zealand, 69% of patients took any inhaled corticosteroid (ICS) therapy, with 44% of these patients taking it as combination ICS/long-acting beta-agonist (LABA). In Australia, 61% of patients took any ICS therapy, of which 82% took it as combination ICS/LABA. Despite this difference, asthma symptom control, as measured by mean Asthma Control Test score (~19), and levels of urgent health care for asthma (~28%), were similar in both countries.

In conclusion, the greater reliance on ICS monotherapy (relative to ICS/LABA) in New Zealand does not appear to have compromised asthma control outcomes. The different historical and current regulatory requirements relating to ICS/LABA within New Zealand and Australia may have contributed to differences in prescribing, but further investigation is needed.

PLASMA EGFR AND THE LIQUID BIOPSY IN DIAGNOSIS AND MONITORING OF NSCLC

Dr Tim Sutton, Pathlab, Bay of Plenty

Introduction

Tissue epidermal growth factor receptor (EGFR) on paraffin-embedded and cytology specimens has been available for four years in New Zealand. In non-small-cell lung cancer (NSCLC), current guidelines recommend one test at the time of diagnosis for the determination of eligibility for tyrosine kinase inhibitor (TKI) therapy. However, there are many drawbacks to using tissue, such as small sample size, poor quality, cytology specimens, bone decal specimens, patients who are frail/difficult to biopsy and tumour heterogeneity. Liquid biopsies are now available in New Zealand. This raises the possibility that one day tissue biopsies may no longer need to be taken. Liquid biopsy has advantages over tissue biopsy including ease of sampling and ability to repeatedly monitor patients without re-biopsy.

Tumour heterogeneity

Within the last decade, researchers have recognised that different parts of the same tumour and different metastases have different molecular profiles, known as tumour heterogeneity. Small tissue biopsy samples, small samples of larger specimens and selective sampling of metastases may not be representative of the full spectrum of a tumour's molecular profile. Therefore, intratumoural heterogeneity can lead to underestimation of the tumour landscape and may foster tumour adaptation and therapeutic failure through Darwinian selection.[8] Liquid biopsy may provide a more representative sampling of the true tumour molecular anatomy.

Circulating cell-free plasma DNA

There are three types of circulating DNA in blood: cell-free (cf) DNA, circulating tumour cell (CTC) DNA, and exosome and microvesicular DNA.

Originally circulating cfDNA was a nonspecific marker of cancer, but with the recognition of specific driver DNA mutations (KRAS, EGFR, BRAF) cfDNA has become a much more specific marker. While there is often sufficient levels of cfDNA in most patients with stage 3-4 NSCLC, there is often significantly less cfDNA in the earlier stages of disease. Also, tumour-specific cfDNA can represent as little as 0.01-1% of circulating DNA. Fragmented and degraded DNA, historically an issue, can now be amplified using current PCR methods.

Potential clinical applications of cell-free DNA liquid biopsy

- Early detection of disease
- Detecting minimal residual disease
- Assessment of tumour heterogeneity
- Monitoring tumour dynamics
- Identification of genetic determinants for targeted therapy
- Evaluation of early response to treatment
- Assessment of evolution of resistance
- Identification of high risk recurrence
- Correlation with changes in tumour burden

Practical issues with EGFR plasma liquid biopsy

The rapidity of change in diagnostic research means laboratories and diagnostic companies are struggling to keep up. Currently, there is a lack of standardisation between the different EGFR plasma tests and a bewildering array of manufacturers and suppliers, not to mention high cost and limited availability throughout the country. New Zealand is also unprepared with a lack of genetic training in this country. There is frequently difficulty in converting a test from the research setting to routine clinical use, issues such as turnaround time, reliability, and requirement for very large data management. Finally there is a lack of robust literature with large, statistically significant patient numbers.

Food for thought

It is now generally agreed that cfDNA paints a more representative picture of cancer. What is unknown is whether tumours that have spread to other organs release as much DNA as the original tumours and whether all cells in the tumour release as much DNA as each other. The answers to these two questions are a work in progress. Diaz et al. suggested 'warm autopsies' - to take samples and characterise all of a person's tumours very soon after death, and compare them with cfDNA samples extracted in life.[9]

Does an accurate picture of tumour burden, or a real-time look at emerging mutations actually save patients or improve their QOL? The answer is probably yes, looking at currently available data - patients closely monitored seem to respond and live a lot longer. Even if doctors discover that a patient's tumour has developed a resistance mutation, that insight is useless if there are no drugs that target the mutation - our approaches to understanding cancer may be outstripping our clinical options.

Conclusions

Tissue EGFR remains the gold standard analysis of EGFR mutations. There is good correlation between plasma and tissue EGFR (77-93%).[10-12] The currently available plasma EGFR is robust, cost effective and reliable with acceptable sensitivity (46-65%) and good specificity (94-97%).[10-12] However, there are still issues regarding the cost of repeated testing and the experience to be able to fully use the information. Future directions include improved sensitivity using newer technologies and use as a diagnostic modality in conjunction with radiology and possibly technology that can assess a wide number of mutations such as ALK, ROS, Met, KRAS, etc. Lack of clinical data is still an issue as is EGFR plasma's utility and place in treatment planning and modification of treatment. Testing is expensive and must get more affordable; however, EGFR plasma allows optimal use of drugs that are currently also very expensive.

LUNG CANCER MUTATION MAPPING IN NZ: FINDINGS OF THE EGFR MUTATION TESTING STUDY

Professor Mark McKeage, University of Auckland

Lung cancer is a major cause of death in New Zealand, disproportionately so for Maori and Pacific people. The potential for addressing poor outcomes from lung cancer with molecularly targeted drug therapies was recently recognised. For selected patients with lung cancer driven by clinically actionable mutations in the EGFR, ALK, BRAF, ROS1 or RET genes, approved drug therapies are now available. This presentation described ongoing research that aims to assist in improving access to lung cancer genetic testing and targeted therapies in New Zealand through (1) evaluation of the clinical performance of a single platform multiplexed genotyping platform for detecting lung cancer driver mutations across multiple genes in tumour and blood specimens from New Zealand patients; (2) defining the prevalence, demographic profiles and outcomes of genetically-defined forms of lung cancer in New Zealand, and by; (3) identifying factors limiting the uptake of lung cancer genetic testing and targeted therapy in the New Zealand healthcare system.

THE ROLE OF T790M MUTATION IN NSCLC RESISTANCE

Professor Kenneth O'Byrne, Princess Alexandra Hospital, Queensland

In patients with lung cancer whose tumours harbour activating EGFR mutations, treatment with EGFR TKIs induces initial tumour shrinkage, but patients progress after a median of 8-16 months.[13-16]

First-generation TKIs

How should patients be managed when they initially become resistant to EGFR TKIs? Patients often continue TKI treatment until they became symptomatic and treatment is then changed to chemotherapy. In the phase II ASPIRATION trial, patients with EGFR mutation-positive NSCLC were treated with erlotinib.[17] Of 176 patients who progressed on erlotinib, approximately half decided to continue with treatment. The continuing patients remained on erlotinib for an average of 14.1 months before they discontinued and received chemotherapy. This study supports the efficacy of first-line erlotinib therapy in patients with EGFR mutation-positive NSCLC and that treatment beyond progression is feasible and may delay salvage therapy in selected patients. What's not feasible is to combine TKIs and chemotherapy - which has always been the case in first-line treatment, but is also the case in maintenance therapy. This was revealed in the IMPRESS trial where patients received gefitinib plus chemotherapy after progression on first-line gefitinib and had no benefit in terms of progression-free survival (PFS).[18]

A randomised phase II study from Japan of erlotinib versus erlotinib plus bevacizumab in patients with advanced non-squamous NSCLC harbouring EGFR mutations showed an improvement in median PFS from 9.7 months with erlotinib alone to 16 months with the combination (HR 0·54, 95% CI 0·36-0·79; p=0·0015).[19] The results of this study are supported by the phase II BELIEF study, which shows a similar median PFS benefit of 13.8 months with erlotinib plus bevacizumab.[20] These data need to be confirmed in a randomised phase III trial.

Second-generation TKIs

The second-generation TKI afatinib targets and binds irreversibly to all four of the HER receptors and is active against tumour cells bearing the T790M mutation.[21] The LUX-Lung 3 and 6 trials showed that afatinib is associated with prolongation of PFS when compared to standard doublet chemotherapy in patients with advanced lung adenocarcinoma and EGFR mutations.[22,23]

In a phase II trial, 319 patients with advanced adenocarcinoma of the lung were randomised to receive afatinib or gefitinib.[24] Patients had received no prior treatment for advanced/metastatic disease and could continue beyond progression at the investigators discretion. Afatinib significantly improved PFS relative to gefitinib (11 vs 10.9 months, respectively [HR 0.73, 95% CI 0.57-0.95; p=0.0165]). Up to about 1 year, PFS survival curves showed little difference between groups. However, at 18 months estimated PFS was 27% and 15%, respectively (p=0.0176) and at 24 months was 18% and 8%, respectively (p=0.0184), suggesting afatinib benefitted a subset of patients. Afatinib treatment was also associated with a significant improvement in response rate (data not available) and median time to treatment failure (13.7 months vs 11.5 months for gefitinib [HR 0.73, 95% CI 0.58-0.92; p=0.0073]). The improvement in efficacy was observed in both Del19 and L858R populations. AEs in both groups were consistent with previous experience, and were manageable leading to equally low rates of treatment discontinuation.

The problem with the first and second generation TKIs is that they also target wild type EGFR. Therefore, as efficacy is increased and higher doses are given, patients experience more toxicity, particularly skin rash and diarrhoea.

Third-generation TKIs

All first- and second-generation EGFR inhibitors possess a structurally related quinazoline based core scaffold and were identified as ATP-competitive inhibitors of wild type EGFR. In 2009, Zhou and colleagues identified a covalent pyrimidine EGFR inhibitor by screening an irreversible kinase inhibitor library specifically against EGFR T790M.[25] These agents were more potent against EGFR T790M, and up to 100-fold less potent against wild type EGFR, than quinazoline-based EGFR inhibitors *in vitro* and were effective in murine models of lung cancer driven by EGFR T790M. Some of these drugs are entering or have completed clinical trials in patients who have progressed on first-line drugs.

Conclusions

Acquired resistance to EGFR TKIs remains a clinical challenge but big steps forward are being made. Mechanisms responsible for acquired resistance can be identified through biopsy on progression. Potential strategies to overcome resistance include mutation selective third generation EGFR TKIs active against T790M. The third generation agents have been investigated in first line EGFR TKI-naïve patients as well as in relapsed disease; randomised phase III trials are completed in the first line versus first generation EGFR TKIs and in the relapsed setting. But the question will eventually arise: what next after resistance to third generation TKIs develops?

BRONCHOSCOPIC LUNG VOLUME REDUCTION IN COPD

Dr Chris Lewis, Auckland District Health Board

QOL in the COPD patient is affected by exertional dyspnoea due to irreversible airflow obstruction, destruction of alveoli by emphysema and particularly due to static and dynamic pulmonary hyperinflation. Surgical resection of the most diseased portions of the lungs improves the mechanics of respiration. The National Emphysema Treatment Trial (NETT), published in 2003, showed that lung volume reduction surgery (LVRS) achieved significant improvements in exercise capacity and QOL in patients with predominantly upper-lobe emphysema.[26] However, postoperative mortality was high—7.9% after 90 days. This prompted the development of minimally invasive lung volume reduction procedures with the goal of reducing morbidity and mortality. The three modalities currently used are implantation of coils, bronchoscopic thermal vapour ablation and endobronchial valves.

Implantation of coils

Coils are inserted into lung segments via a catheter and flexible bronchoscope. Coil 'memory' makes them take on a curved shape. The idea is to reduce lung volume by tensile force. However, the coils can't be removed, and there is a risk of infection. Furthermore, due to the need for 10 to 15 coils per lobe to be effective, they are very expensive at $3000 to $5000 each. In a European multicentre prospective series (n=60), LVR coil treatment resulted in significant but modest clinical improvements in patients with severe emphysema, with a good safety profile and sustained results for up to 1 year.[27]

Bronchoscopic thermal vapour ablation

Bronchoscopic thermal vapour ablation is the insufflation of hot steam into lung segments via bronchoscopy under general anaesthetic. This causes a thermal injury to the lung, with subsequent scarring and volume loss and thus LVR. Again, this is reasonably expensive. Early studies showed modest benefits but as the volume of treated lung increased, so did the risk of serious AEs.[28,29] The STEP-UP trial assessed whether selective sequential treatment of the more diseased upper lobe segments with bronchoscopic vapour ablation leads to clinical improvement with a more acceptable safety profile.[30] Seventy patients with severe, upper lobe-predominant emphysema were enrolled. Significant improvements in FEV_1 and QOL between the treatment group versus the control group were observed. COPD exacerbation was the most common serious AE, with one exacerbation possibly related to treatment resulting in a patient death 84 days after treatment. No pneumothorax occurred within 30 days of treatment. Questions remain about the magnitude of response and cost effectiveness, both of which are not yet apparent.

Endobronchial valves

Endobronchial valves are one-way valves designed to allow secretions out of the lung, but prevent air going in. They are relatively easy to place via a flexible bronchoscope. The impression currently is that endobronchial valves have gone from being relatively safe but ineffective in COPD, to being quite effective but more hazardous than initially appreciated. It is also becoming increasingly apparent that they only benefit a minority of patients.

The original endobronchial valve study was the VENT trial published in the *NEJM* in 2010.[31] At 6 months, there was an increase in FEV_1 in the valve group, compared with a decrease in the control group. This difference was statistically significant (p=0.005) but not particularly clinically significant. Interestingly, greater radiographic evidence of emphysema heterogeneity and fissure completeness was associated with an enhanced response to treatment in the VENT trial, on post-hoc analysis. This may be because fissural integrity affects collateral ventilation - if the fissure of an occluded lobe is not intact, air will still enter that lobe from the adjacent lobe.

The UK BeLieVeR-hifi study was the first randomised study to specifically evaluate patients with heterogeneous emphysema and intact interlobular fissures.[32] Fifty patients were randomised to receive endobronchial valves or sham procedure (control). In the endobronchial valve group, FEV_1 increased significantly versus the control group (p=0·0326). There were two deaths in the endobronchial valve group and one control patient had a prolonged pneumothorax. QOL improvement was greater in the valve group, and there was only a small "placebo" improvement in the sham group - this is important as many such studies have a "no treatment" rather than sham control group. In an open-label extension, 14 control patients received endobronchial valves; one patient died of pneumothorax three days after valve placement.

Another study (n=68) also randomly assigned patients with severe emphysema and absence of collateral ventilation to bronchoscopic endobronchial-valve treatment or standard medical care.[33] Significantly greater improvements were seen in the valve group than in the control group from baseline to 6 months for the increase in FEV_1, FVC, and the 6-minute walk distance ($p<0.01$ for all comparisons). By 6 months, 23 serious AEs had been reported in the valve group, as compared with 5 in the control group ($p<0.001$). One patient in the valve group died. Serious treatment-related AEs in this group included pneumothorax (18% of patients) and events requiring valve replacement (12%) or removal (15%).

Pneumothorax

A key issue that needs to be investigated further is the safety of this treatment approach. It has become apparent that patients with intact fissures receiving endobronchial valves are at quite high risk of pneumothorax. With this in mind, a group of experts have proposed a rational management plan that attempts to guide physicians in daily practice.[34] Given optimised patient selection, the risk-benefit ratio of a pneumothorax appears to be acceptable, as the majority of these patients develop substantial improvements in functional outcomes after resolution of the pneumothorax. It is clear that this procedure cannot be undertaken as a "day case", and that a multi-disciplinary team approach to management is likely to lead to the best and safest outcomes.

Conclusions

- Endobronchial valve placement may be useful and cost effective for LVR in COPD, but:
  - Patients need to be very carefully selected
  - Multidisciplinary assessment and management is required
  - Complications are significant and care is needed
- Other forms of LVR need to await more data – vapour is likely to be the most promising for patients unsuitable for valve placement.

THE ROLE OF THE LUNG MICROBIOME IN LUNG DISEASES

Dr Conroy Wong, Middlemore Hospital

Until recently, the lungs were thought to be sterile; however, a shift towards molecular methods for the quantification and sequencing of bacterial DNA has revealed that the airways harbour a unique steady-state microbiota in both healthy and diseased states. This new understanding is changing the way that respiratory research is approached, with a clear need now to consider the effects of host-microorganism interactions in both healthy and diseased lungs. Akin to recent discoveries in gut research, dysbiosis of the airway microbiota could underlie susceptibility to, and progression and chronicity of lung disease.[35]

The healthy lung has a much lower bacterial load than the gut. The main phyla found in the healthy lung are Bacteroidetes and Firmicutes. Resident bacteria can influence the mucosal epithelial in the healthy lung, providing metabolism, proliferation, protection and barrier functions.

The composition of the respiratory microbiome is determined by three factors: microbial immigration, microbial elimination and the relative reproduction rates of its members.[36] Any alteration detected in disease states must be attributable to some combination of these three factors. In the healthy lung, community membership is primarily determined by immigration and elimination; in advanced lung disease, membership is primarily determined by regional growth conditions. As the lung becomes diseased, there is a change in community composition from Bacteroidetes to Proteobacteria, resulting in an altered microbiome. It is unclear whether this contributes to disease pathogenesis or is simply a marker of injury and inflammation. Microbiome analysis in cystic

fibrosis shows that the microbiome is extremely complex with multiple organisms that have not yet been identified, with many anaerobic organisms present. With age, worsening lung function and antibiotics there is a decrease in diversity of species.

Respiratory dysbiosis

Respiratory exacerbations lack the features of bacterial infections, including increased bacterial burden and decreased diversity of microbial communities. Dickson et al. proposed that exacerbations are occasions of respiratory tract dysbiosis -- a disorder of the respiratory tract microbial ecosystem with negative effects on host biology (**Figure 3**). Respiratory tract dysbiosis provokes a dysregulated host immune response, which in turn alters growth conditions for microbes in airways, promoting further dysbiosis and perpetuating a cycle of inflammation and disordered microbiota. Differences in the composition of baseline respiratory tract microbiota might help to explain the so-called frequent-exacerbator phenotype observed in several disease states.

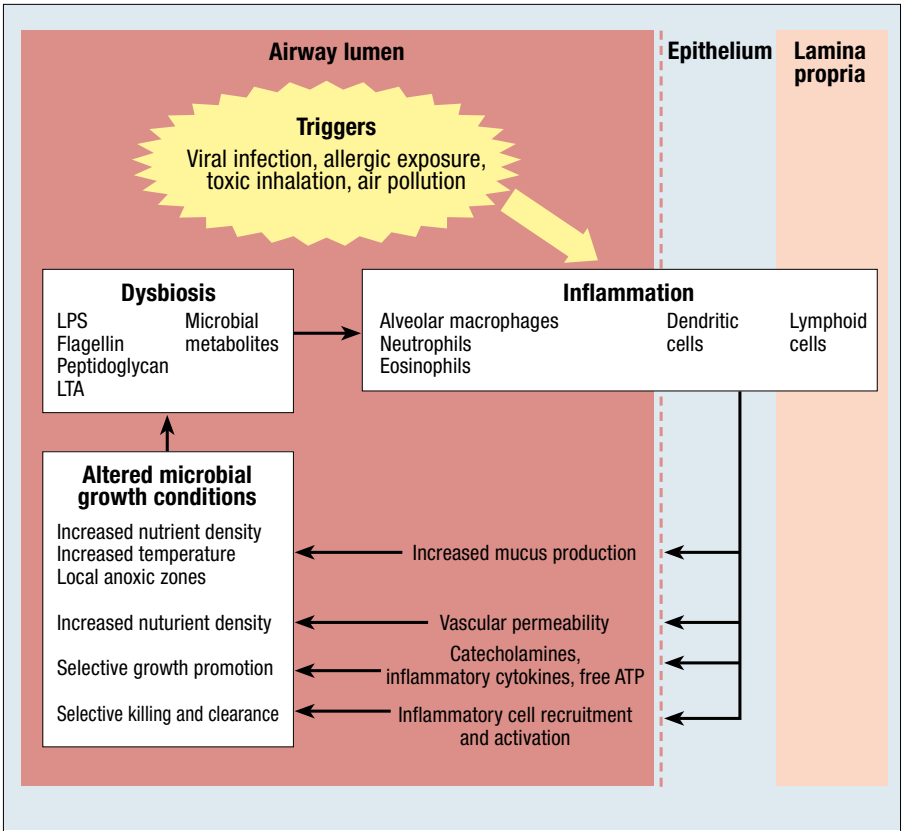

Figure 3. The respiratory dysbiosis-inflammation cycle[36]

Summary

- The role of the microbiome in lung health and disease is in its infancy.
- There are diverse communities of microbes in the airways of healthy and diseased lungs.
- In healthy lungs, the most common bacterial phyla are Bacteroidetes and Firmicutes.
- Distinct lung microbiota exists in patients with cystic fibrosis, bronchiectasis, COPD and asthma. There is a shift to Proteobacteria.
- Disruption of the complex microbial ecosystems (dysbiosis) results in pulmonary exacerbations.

THE ROLE OF THE GUT MICROBIOME IN LUNG DISEASES

Professor Rob Young, University of Auckland

A number of studies support the idea that the gut microbiome is important in pathogenesis of lung disease. There is a complex interrelationship between bacterial exposure in the lung, susceptibility of the lung, and systemic inflammation; it is possible that diet may modify the innate immune system and contribute to pulmonary inflammation.

It is known that mortality from COPD and lung cancer is lowest in Hispanic people, compared to non-Hispanics. This observation, described as the "Hispanic paradox", persists after adjusting for smoking exposure and sociodemographic factors. While differences in genetic predisposition might underlie this observation, differences in diet remain a possible explanation. It is thought that a diet rich in legumes may partly explain the Hispanic paradox.[37] Legumes are very high in fibre and have recently been shown to significantly attenuate systemic inflammation, which has previously been linked to susceptibility to COPD and lung cancer in large prospective studies. A similar protective effect could be attributed to the consumption of soy products in Asian subjects, for whom a lower incidence of COPD and lung cancer has also been reported.

A large epidemiological study examined the development of new cases of COPD in the Nurses' Health Study and the Health Professionals FU Study.[38] Around 120,000 patients were followed for between 12 and 16 years. The risk of developing COPD was reduced by about 33% if patients followed a healthy Mediterranean-type diet, with the benefit coming primarily from whole grains.

Gut-liver-lung axis

The mechanisms behind the benefit of a high-fibre diet remain unknown, but, as fibre is not absorbed by the gut, this suggests that the gut may play an active role in pathogenic pathways underlying COPD.[39] There is a growing awareness that aberrant activity of the innate immune system, characterised by increased neutrophil and macrophage activation, may contribute to the development or progression of COPD. Innate immunity is modulated in large part by the liver, where hepatic cells function in immune surveillance of the portal circulation, as well as providing a rich source of systemic inflammatory cytokines and immune mediators (notably, IL-6 and C-reactive protein). The beneficial effect of dietary fibre on lung function may occur via modulation of innate immunity and subsequent attenuation of the pulmonary response to inflammatory stimuli, most apparent in current or former smokers. The "gut-liver-lung axis" may play a modifying role in the pathogenesis of COPD.

Evidence from animal studies

Data from a murine model showed that the allergic response to dust mites can be profoundly affected by diet.[40] Mice fed a high fibre diet had a much more dampened immune response than mice not fed a high fibre diet. It was hypothesised that this occurred via effects of small chain fatty acids on bone marrow and dendritic cells, thereby suggesting a gut-lung axis.

Another animal study showed that the gut microbiota plays a protective role in the host defence against pneumococcal pneumonia.[41] Microbiota-depleted mice had greater bacterial dissemination, more pulmonary inflammation and greater mortality. The depleted mice had a greater polymorphonuclear leukocyte influx and alveolar macrophages could not phagocytose *S. pneumoniae*. Levels of the systemic cytokines IL-6 and IL-1β were higher in the depleted mice while IL-10 was lower. In depleted mice, after faecal microbiota transplantation, the response to pneumococcal infection was normalised and mortality improved. The researchers concluded that the gut microbiota modifies innate immunity by controlling polymorphonuclear leukocyte influx and enhancing alveolar macrophage function in the lung.

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