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Year in Review 2016: Respiratory infections, acute respiratory distress syndrome, pleural diseases, lung cancer, and interventional pulmonology

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1. RESPIRATORY INFECTIONS

Marcos I Restrepo and James D Chalmers

Respirology has made important contributions related to respiratory infections over the past year. In this review, we focus on bronchiectasis, pneumonia, tuberculosis and non-tuberculous mycobacteria infections as the most relevant topics in the area of respiratory diseases.

1.1. Bronchiectasis

Park *et al.* reported a study of 155 patients with bronchiectasis to identify the predictors of radiological progression of the disease.[1] Treatment in bronchiectasis aims to reduce inflammation and airway infection to prevent further lung damage.[2] Therefore identifying the drivers of poor outcome is important. In this analysis, older patients, those with lower body mass index (BMI) and patients infected with *Pseudomonas aeruginosa* or non-tuberculous mycobacteria (NTM) were more likely to show radiological progression, measured using the Bhalla score.[1] In multivariable analysis, only *P. aeruginosa* and BMI were statistically significant. The results are supported by existing literature. *P. aeruginosa* colonisation and BMI are both incorporated into the bronchiectasis severity index, a validated prediction tool, and *P. aeruginosa* in particular is strongly associated with other indicators of progression such as quality of life, forced expiratory volume in one second (FEV1), exacerbation frequency and mortality.[3,4] However, the most important step in the treatment of bronchiectasis is identifying the underlying cause, since many causes such as NTM infection, rheumatoid arthritis, primary ciliary dyskinesia, immunodeficiency or allergic bronchopulmonary aspergillosis require specific treatments.[5,6] Gao *et al.*[7] conducted a systematic review into the underlying causes of bronchiectasis identified in 56 studies (N=8608).[7] The study was limited by the high variability in testing across different studies, and the variable definitions used, but was able to suggest that 18.3% of bronchiectasis patients have an aetiology with a specific treatment.[7]

1.2. Pneumonia and other respiratory infections

Among the different respiratory infection papers published in *Respirology*, the vast majority were in the area of pneumonia as evidence of this important health care priority. We now summarize the most relevant contributions to the journal, focusing on the mechanism of disease secondary to infection, the controversial issue of microbiological diagnosis, biomarkers, treatment, health related outcomes and complications of patients with pneumonia.

Mechanism of disease

Tang FS *et al.*[8] showed that neutrophils from patients with asthma release CXCL8, NE and MMP-9 in response to viral surrogates. In addition, Toll-like receptor (TLR7/8) dysregulation may play a role in neutrophilic inflammation in viral-induced exacerbations. This evidence suggest that neutrophils carry important immunological properties to directly detect and respond to both viral and bacterial pathogens.[8] In addition, out of the three respiratory viruses including rhinovirus, influenza and respiratory syncytial virus (RSV), only RSV was able to activate neutrophils.[8] The neutrophil activation and inflammation observed in asthma may be the result of the complex interactions between infectious pathogens and airway epithelium and smooth muscles.[8] The authors also suggest that it may not be only the neutrophil activation that plays the leading role during exacerbations, but also the resolution or regulation of neutrophilic inflammation following infection.[8] In an editorial Vlahos and Bozinovski [9] suggest that neutrophils do indeed play an important role in the immune response of patients with asthma. The presence of overactivation of neutrophils during exacerbations increases asthma disease severity and emphasises the different mechanisms by which neutrophils may contribute to the exacerbation period or the resolution period.[9]

Microbiological diagnosis

Appropriate antimicrobial therapy and antimicrobial stewardship requires a knowledge of the underlying causative pathogen of community acquired pneumonia (CAP). Several studies published in *Respirology* attempted to address the issue about the aetiology in patients with CAP. Sahuquillo-Arce *et al.*used a large Spanish dataset to examine the impact of age on the aetiology of CAP.[10] The study found that older patients were more likely to have Gram-negative infection, particularly with *Haemophilus influenzae* and enteric Gram-negative organisms. Co-morbidities were as, or more important than age, with diabetes being associated with pneumococcal and *S. aureus* pneumonia, and COPD associated with *H. influenzae*. [10] The study confirms previous reports and points to the increasing problem of the aging population changing the microbiology of CAP towards an increase in Gram-negative organisms. [10] Along with an aging population, there is also an increasing expansion of patients receiving immunosuppressive drugs, such as patients receiving chemotherapy for malignancy.[11] Guidol *et al.*[12] studied 1723 patients with bacteraemia which included 795 patients with neutropenia and underlying malignancy. The most frequent cause was *P. aeruginosa* and the mortality rate was 46.2%. 12.8% of Gram-negative organisms identified were multidrug resistant.[12] This study again emphasises the need to consider unusual or resistant organisms in patients with immunosuppression.[12] Metersky [13] and colleagues presented data from the large USA Veterans Hospital database from 2002 to 2012, and found that a small proportion of patients with risk factors for Health Care Associated Pneumonia (HCAP) had pseudomonas pneumonia (1.9%) and MRSA pneumonia (1.0%). In order to stratify who had one pathogen or the other, the authors suggest that MRSA pneumonia patients were more likely to be males, elderly (age >74 years of age), diabetics, have COPD, recent nursing home or hospital stay, recent exposure to fluoroquinolone or antibiotics treating Gram-positive organisms, and severe pneumonia. In addition, patients with Pseudomonas pneumonia were more likely to have a prior hospitalization, immunosuppression, COPD, hemiplegia, recent exposure to inhaled corticosteroids, β-lactam/cephalosporin/carbapenem antibiotics, antibiotics against Gram-positive organisms, 'other antibiotics' and severe pneumonia requiring ICU

admission, vasopressors or use of invasive mechanical ventilation within 48 hours of hospital admission.[13] These results suggest that the appropriate selection of antibiotics may be driven by identifying the characteristics of patients with HCAP due to pseudomonas or MRSA. In an elegant editorial Waterer [14] suggest that the key aspect of antibiotic utilization is to know whether the pathogen causing pneumonia is present at the time of evaluation, rather than identifying whether the patients have HCAP or not. In addition, Dr Waterer[14] stresses the point that these pathogen-specific risk factors had a positive or negative predictive value sufficient to reliably determine empiric antibiotic therapy as also recently pointed out in the literature.[15] Cillóniz *et al.*[16] presented an elegant review manuscript emphasizing the importance and clinical relevance of polymicrobial infections as the cause of CAP. The authors suggest that polymicrobial infection is an understudied and growing entity with distinct inflammatory, host response and disease related characteristics that differ from other patients with CAP.[16]

Rapid identification of pathogens is the best solution to this problem. Diagnosis within hours using PCR or similar methods is not yet fully established, but matrix-assisted laser desorption/isonization time of flight mass spectrometry (MALTI-TOF MS) is now in use in many centres to give a more rapid identification of pathogens. Mok *et al.*[17] examined the impact of MALTI-TOF on their practice in severe pneumonia, showing that identification of pathogens from bronchoalveolar lavage in severe CAP, hospital acquired pneumonia and ventilator associated pneumonia, was more rapid with MALDI-TOF resulting in earlier de-escalation of antibiotics.[17]

Specific pathogens can usually not be identified from their presenting features alone. Two papers reported on the characteristics of less frequently identified pathogens in CAP. An organism increasingly identified in hospital acquired pneumonia is *Acinetobacter baumannii* and its related pathogens. It is frequently multidrug resistance and is a challenge globally. Ozbatan *et al.*[18] reported on 356 adult patients from Turkey of whom the large majority had ventilator associated pneumonia. Mortality was high (53.1% at 30-days) and reduced by combination antibiotic therapy. Adenovirus is

an unusual pathogen in immunocompetent CAP patients, but Yoon *et al.*[19] reported a large case series of 91 patients with adenovirus pneumonia compared to 55 patients without adenovirus detected. Not surprisingly, there were no clinical features that could accurately identify an adenoviral pneumonia. The authors showed that adenovirus can be associated with the broad spectrum of disease, from mild CAP to CAP in the ICU.[19] Monocytopenia was the only factor found to be clearly different between adenoviral and non-adenoviral CAP.[19] Legionnaires disease is a relatively common cause of CAP, account for 1-10% of cases outside of epidemics.[20,21] While *Legionella pneumophila* is most frequently encountered worldwide, Isenman *et al.*[22] provided a timely reminder that *Legionella longbeachae* is the predominant cause in some regions including parts of Australasia. [22] The disease presents similarly to *pneumophila*, with a middle age to elderly male predominance, diarrhoea, myalgia, hyponatraemia and abnormal liver function tests- the classical features of Legionnaires disease, all common. Admission to the ICU was common at 25% but outcomes were relatively good if appropriate antibiotics were used.[22]

Biomarkers and pneumonia

Procalcitonin (PCT) is thought to be a useful marker when trying to decide whether to withhold antibiotics from low risk patients with respiratory infections. Ito *et al.*tested whether PCT could be used to predict mortality. Ito and collaborators[23] found C-reactive protein, PCT and CURB65 were predictive of 30-day mortality, and PCT was additive to CURB65. In addition to markers of systemic inflammation, the journal presented data on markers of coagulation in pneumonia with the latest in series from Cangemi *et al.*[24] They showed in 104 patients that multiple markers of thrombosis were altered in acute pneumonia with evidence of prothrombotic state. This may contribute to the excess risk of cardiovascular disease that is consistently reported in patients with community-acquired pneumonia. [25] Another study published by Liu D and collaborators[26] presented a systematic review and meta-analysis that evaluated the prognostic value of procalcitonin in patients with pneumonia. The authors identified 21 studies with 6,007 patients in which high procalcitonin levels was

associated with an increased risk of death among patients with low severity of illness score according to a low CURB-65 score and critically ill patients, respectively.[26] In addition, this study questions the use of the procalcitonin cut-off of 0.5 ng/ml due to the low sensitivity and the inability to recognize patients at risk of death.[26] Finally, the study suggested that there are no differences in the procalcitonin performance characteristics between patients with CAP and ventilator associated pneumonia.[26]

Pneumonia treatment

Beta-lactam plus macrolides have become the standard of care for the management of patients with CAP. Horita *et al.*[27] performed a systematic review and meta-analysis evaluating whether beta-lactam plus macrolide antibiotics lead to better survival than beta-lactam alone in patients with CAP. The authors included 14 studies, two open-label randomized controlled trials (RCTs) comprising 1975 patients, one non-RCT interventional study comprising 1,011 patients and 11 observational studies comprising 33,332 patients.[27] Horita and collaborators[27] found that CAP patients treated with beta-lactam plus macrolide compared with beta-lactam alone had a lower all-cause death with substantial heterogeneity. However, in the subgroup of patients with severe CAP the use of combination therapy had a protective effect for mortality compared to beta-lactam antibiotic therapy alone.[27] Therefore, despite the suggested beneficial effect of combination therapy with macrolides observed mainly in the severe CAP group, the data are limited by the number of observational studies identified in this systematic review.[27]

Jefferies *et al.*[28] performed a double-blind randomized controlled trial to assess the clinical efficacy of paracetamol as anti-pyretic treatment for adult patients with influenza infection. The original concern was derived from animal models that suggested a higher mortality when infected with influenza.[28] Among 80 adult patients with influenza-like symptoms and positive influenza rapid antigen test, the use of 1g paracetamol four times a day for 5 days was not associated with viral shedding, temperature change, time to resolution of influenza illness or improved clinical symptoms

compared to the placebo treated group.[28] A following elegant editorial by MJ Peters[29], highlights the importance of challenging the collective therapeutic intuition and the conventional general wisdom of policy and guidelines regarding therapies such as paracetamol and suggest that similar studies should be performed with aspirin or other antiinflammatory medications.

Pneumonia outcomes and clinical complications

Quality of care, such as timely antibiotic administration, resuscitation and oxygen therapy, determine outcome from CAP.[30] Many countries have reduce availability of staff and resources at weekends compared to weekdays leading to concerns of a "weekend effect" of increased mortality from common diseases. Uematsu *et al.*[31] investigated this in a nationwide Japanese database and showed that from 23,532 patients with severe CAP, weekend admission was associated with a 10% increase in mortality even after adjustment for confounders. A clue to poorer quality of care was suggested by a lower frequency of microbiological tests, but the dataset was not sufficiently detailed to dig deeper into other markers of quality of care.[31] These data are similar in many countries but are controversial because of the different characteristics of patients admitted at weekends and therefore the risk of residual confounding.

Kim *et al.*[32] evaluated the predictors of prolonged stay in patients with community-acquired pneumonia and complicated parapneumonic effusions in Korean tertiary cohort of patients. The authors performed a retrospective cohort study in 158 CAP patients with complicated parapneumonic effusions and identified that patients tended to stay at least 18 days in the hospital and require at least 10 days of chest tube placement.[32] The most common pathogen was *Streptococcus viridans* and 54% of the patients received intrapleural fibrinolytics.[32] A prolonged hospital stay was independently associated with fever, lower oxygen level, haemoglobin level, neutrophilia, pathogen identification and ineffective pleural drainage, suggesting a possible beneficial effect of an early thoracotomy, but further studies are need to test this observation. [32]

1.3. Tuberculosis

During the past year, there were two interesting contributions to the journal in the area of tuberculosis. The first corresponds to the work presented from Hong Kong on HIV-infected patients by Leung and collaborators. [33] The authors assess the diagnostic characteristics of tuberculin skin test (TST), T-Spot-TB (T-Spot) and QuantiFERON-TB Gold-In Tube (QFT) to determine latent tuberculosis (LTBI) in this high-risk group of patients. They identified 110 HIV-infected patients without previous history of LTBI, with 75% of them receiving anti-retroviral therapy and a median CD4 count (414/µL) with low median viral load (<75/µL). [33] The results showed almost complete discordance between positive baseline TST (5.5%), T-Spot (5.6%) and QFT (4.9%), respectively. There were no correlations between CD4 count or viral load with positive LTBI testing. [33] Test conversion rates were higher for QFT (10.7%) and TST (8.9%), and lower in T-spot test (5.0%) with no correlation with CD4 count or viral load. More than half of the positive T-spot and QFT results reverted to negative during the follow-up period. [33] None of these tests picked up the single case of culture-confirmed tuberculosis observed after 798 person-years of follow-up. [33] The authors conclude that the major discordant results found in TST, T-spot and QFT tests limit the ability of these tests to identify LTBI patients in high-risk populations. [33] In addition, it suggests that programs directed at screening HIV-infected patients in intermediate tuberculosis burden areas may lack accuracy and requires further assessment.[33]

Regarding novel treatments for the management drug resistant tuberculosis, Bai and colleagues[34] tested “Curcumin” as a direct anti-TB and immune response stimulator. Curcumin is a spice of bright yellow- colour of turmeric, derived from the root of the perennial herb *Curcuma longa*. [34] Curcumin is recognised as a potent inducer of apoptosis, linked to the mechanism of how ~~an effector inducer used by the~~ macrophages ~~to~~ kill MTB intracellularly ~~MTB~~. The authors used an in vitro human macrophage infection model to test whether curcumin affects MTB survival. [34] The authors found that MTB clearance was enhanced by THP-1 human monocytes and primary human alveolar

macrophages. [34] They also found that curcumin was an inducer of caspase-3-dependent apoptosis and autophagy and mediates these anti-MTB cellular functions, in part, via inhibition of nuclear factor-kappa B (NFκB) activation. [34] Therefore, curcumin seems to present immunomodulatory properties against MTB infection in human macrophages, but further animal and translational studies are encouraged in order to treat patients at risk for drug resistance development. [34]

1.4. Non-tuberculous mycobacteria (NTM)

Several manuscripts addressed the clinical characteristics, the clinical outcomes and the treatment of NTM pulmonary infections. The classic patients with NTM is described as being a middle aged female with low body mass index (BMI) and *Mycobacterium avium* infection. In 2016 the United States Bronchiectasis registry has recently published their first results showing 63% of patients with bronchiectasis in the US have a history of NTM isolation or disease, the majority of whom were female and had *M. avium* infection. [35] Nishimura *et al.*[36] assessed the prior conceived association that body habitus is associated with Mycobacterium avium complex (MAC) pulmonary disease. The classic literature regarding MAC, has linked middle-aged white women with thin body habitus with the diagnosis of MAC lung disease. The authors found that among 1033 healthy subjects, the body habitus was not associated with MAC lung disease.[36] Differences may relate to environmental, genetic or microbiological differences between Asia and the United States, or differences in the included study populations.

Yeung *et al.*[37] reported a systematic review to determine the health-related quality of life, comorbidities and mortality in pulmonary NTM infections. The authors identified 17 studies, mainly from Taiwan (n = 5) and the USA (n = 4). [37] This systematic review concludes that there is high clinical heterogeneity and important bias limiting the ability to define trends, despite the suggested increased health burden from respiratory diseases and increased mortality associated with pulmonary NTM disease. [37] In the February issue of *Respirology*, Ellender *et al.*[38] reported a retrospective study of 45 patients treated with intravenous amikacin for difficult NTM. Patients have

a mixture of *M. avium complex*, *M. abscessus* and one case of *M. fortuitum* and received intravenous amikacin as an add-on to multidrug regimens. [38] Reflecting the difficulties in treatment in this patient population, sputum conversion was achieved in only 38% but the treatment was well tolerated.

1.5. Conclusions

We hope that these important contributions in the area of respiratory infections will assist scientists and health care providers in their day to day practice taking care of patients with these problems. We as associated editors would like to promote and motivate the scientific community all over the world to submit your research findings to the Respiratory journal in order to help disseminate research discoveries and advances that might help the patients with respiratory infections.

2. ARDS – FROM PATHOPHYSIOLOGY TO PROGNOSIS

Yuanlin Song

2.1. Pathophysiology

Ventilator-induced lung injury (VILI) is a major drawback of mechanical ventilation when used improperly in patients with acute respiratory distress syndrome (ARDS). The exact mechanisms leading to VILI have not been completely elucidated but volume trauma, barotraumas, and biotrauma have been proposed as likely causes[39]. Extensive studies using a low tidal volume strategy showed improved survival benefit in ARDS patients[40], and recent recalculation of lung mechanics using large clinical trial data suggested low driving pressure is the main contributor to the survival benefit[41]. Given the fact that, in the majority of cases, driving pressure by itself could not be directly correlated to VILI if breathing rate was not included, it has been proposed that lung strain, and energy load may collectively account for VILI rather than various single components[42].

Identification ofnovel key factors of particular signalling pathways may provide potential therapeutic targets against ARDS. In an animal model, high volume ventilation or cell culture model cyclic stretch

induced degradation of p120-catenin, an adhesion molecule that plays an important role in epithelium integrity. In dissecting the mechanism, inhibition of PKCα could successfully block c-Src kinase activation and p120-catenin degradation in VILI model, suggesting inhibition of PKCα may have potential application in reducing VILI[43].

2.2. Treatment

ARDS has been considered a heterogeneous disease with hyper-inflammation in the lungs and systemic circulation. Oxidation has been considered a strong risk factor for ARDS development due to endothelium and epithelium damage through reactive oxygen species (ROS) activity. It is therefore proposed that N-acteycysteine may attenuate acute lung injury through free radicals eradication. However, in a human lung resection study which simulated acute lung injury (ALI), perioperative administration of N-acetylcysteine did not prevent local and systemic inflammation after lung resection[44], in which plasma interleukin-6, 8-isoprostane and ischaemia-modified albumin were almost identical between pre- and post-operation. Statin has also been considered an anti-inflammation medicine and has potential application in ALI/ARDS, however, a meta-analysis summarising 13 studies including 12145 patients didn't show an improvement in clinical outcomes following statin administration in high risk ALI/ARDS patients[45]. According to these two studies, the anti-inflammation and anti-oxidation action of these two molecules may not be of benefit in ALI/ARDS patients.

2.3. Prognosis

Sepsis is the leading risk factor for ALI/ARDS, and it is interesting to know whether the infection site (e.g. lung, abdominal cavity, urinary tract, etc) affects the outcome prediction in patients with ALI. In a group of sepsis patients (624) who developed ALI (251), there was a strong correlation between sepsis location and ARDS development but not in non-ALI sepsis patients. Sepsis due to lung infection contributed largely to ALI development compared to other infection sites, and morbidity of ALI was associated with higher mortality in sepsis from pulmonary and other sources, but not in

abdominal sepsis[46]. This evidence suggests that lung infection and lung infection-induced sepsis is a leading cause of ALI with high mortality and morbidity, and deserves a high level of attention in research and clinical practice.

Activin-A belongs to the TGF-beta family of molecules, with a potential role in cell proliferation and division. In a study enrolling 138 clinically suspected sepsis patients, high serum Activin-A was associated with sepsis severity, APACHE-II score and SOFA score[47], suggesting Activin-A may be potentially useful in sepsis outcome prediction.

The weaning process is challenging when the patient has delirium. A study enrolling 393 mechanical ventilation patients showed that mental status such as delirium significantly delayed the weaning process using the spontaneous breathing test (SBT) method[48]. When confounding factors were balanced, delirium was still associated with difficult but not prolonged weaning.

Aspiration in non-invasive ventilation is a serious complication and needs to be avoided as much as possible. A study using a healthy young and a healthy elder population investigated aspiration rate in different ventilation modes (BiPAP, CPAP and control) and showed a high probability of aspiration after swallow during BiPAP use[49] compared to CPAP and control. This suggests swallow with the detection of non-inspiratory flow may increase the risk of aspiration through triggering inspiratory support in BiPAP mode, which has been widely used in clinical practice.

In general, various factors were associated with ARDS patients' prognosis. Improved understanding of risk factors in each patient will enable more accurate prognostication and lead to better outcomes in ALI/ARDS.

3. LUNG CANCER

Christopher Mallow and Lonny Yarmus

3.1. Imaging

Both ultra-low dose computed tomography (LDCT) and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) were evaluated in the past year. Murray *et al.*[50] evaluated the use of LDCT on asbestos-exposed population screening. Of 906 patients who underwent LDCT for annual screening, they identified 104 indeterminate nodules in 77 participants over a 12-month period. They found no correlation between the number of nodules and cumulative asbestos exposure, the pack years of smoking or time since quitting. Parietal pleural plaques were identified in 64% of participants, in which 88.3% were calcified. Visceral Pleural Plaques were identified in 11.7% of patients, diffuse pleural thickening in 7.9%, and diaphragmatic plaques in 56.4% of patients. A total of 162 (17.8%) of subjects were recalled for further investigation due to indeterminate nodules or other incidental findings.

DCE-MRI was evaluated by Karaman *et al.*[51] to evaluate its use in identifying characters of cystic-cavitary lung lesions that may aid in distinguishing malignant versus benign lesions in comparison to CT alone. This was a prospective study of 36 patients with cystic and/or cavitary lung lesions of which 11 were found to have malignant lesions. Inner wall irregularity was more sensitive in malignant lesions on DCE-MRI (82% vs 64%), but specificity was higher with the CT (96% vs 88%). Due to the DCE-MRI's ability to better distinguish tissue from fluid, biopsy site was changed in two patients, and cancelled in 3 patients who had indeterminate lesions on CT. Malignant lesions had a greater increase in contrast enhancement in the early phase and had a higher maximal peak ($p=0.001$). Although these findings were promising, the small study size requires that further investigation be performed before formal recommendations can be made in regards to its use in screening.

3.2. Diagnosis and Prognosis

Guisier *et al.*[53] evaluated the adequacy of molecular analysis of peripheral non-small cell lung cancer (NSCLC) sampled by radial-EBUS. They performed 362 radial endobronchial ultrasound (r-EBUS) procedures of which 194 cancers were identified, 113 were non-squamous NSCLC and 88 had sufficient material for molecular analysis. The mean nodule diameter was 28mm, and all 88 samples were analyzed for EGFR, KRAS, ALK, HER2, PI3K and BRAF. Upper and middle lobe biopsies, as well as at least three biopsies were predictive factors of molecular analysis feasibility. The authors concluded that multi-gene molecular analysis can be performed in 79% of non-squamous NSCLC, and that the sensitivity of molecular analysis, although limited due to repeat sampling in only 22 patients, is approximately 95%.

Prognostic indicators were assessed both using circulating tumor cell counts (CTC) and the presence of COPD and emphysema.[54,55] Zhang *et al.*[54] investigated whether patients with NSCLC had detectable CTC's that could provide prognostic information. 46 patients were enrolled and CTC's were measured at baseline in all patients. They found a presence of CTC's in 40 patients, with a range of CTC's from zero to 80 cells/3.2 mL (mean 6.11 cells/3.2 mL). They found that the baseline CTC count greater than 8 (unfavorable group) was a predictor of a shorter PFS and OS. The median OS in the favorable group (CTC<8) was significantly longer than in the unfavorable group (21.3 vs 9.0 months; p=0.026). The median PFS was also longer in the favorable group (7.4 vs 5.3 months; p=0.018). These remained significant in multivariate analysis. They did not find a correlation between CTC count and tumor size after cycles of chemotherapy.

A meta-analysis of studies that evaluated COPD and/or emphysema and survival in patients with lung cancer was done by Gao *et al.*[55] They found that the presence of COPD was associated with poorer OS in patients with COPD versus without COPD (HR 1.17, p<0.001), although there was high heterogeneity amongst the studies (I2=74%, p<0.001). Six of the studies also evaluated DFS and found that COPD was also associated with worse DFS (HR 1.52, p=0.03), also with high heterogeneity

(I2=78%, p<0.001). The presence of emphysema was associated with poorer OS (HR 1.66, p<0.001)). The overall conclusion was that there is a strong association between both COPD and emphysema and survival.

3.3. Treatment Modalities

Numan *et al.*[56] prospectively analyzed a cohort of patients with pulmonary metastases to decipher which surgical option, VATS versus thoracotomy, led to superior quality of life (QOL). 100 patients were assigned either VATS or thoracotomy, with their SF-36 and Brief Pain Inventory scores assessed preoperatively and at 1,3 and 6 months postoperatively. There was a significant difference in bodily pain and physical performance at 1 month, favoring the VATS group. VATS patients also had an average shorter hospital stay (5 vs 7 days, p<0.001), an average shorter duration of chest drainage (3 vs 4 days, p=0.005) as well as a mean shorter duration of epidural analgesia (4 vs 5 days, p=0.002). Despite this, the two groups performed similarly beyond the 1-month time point, and both returned to their baseline QOL scores by 6 months. Due to these initial findings, the authors concluded that VATS is the preferable surgical approach in this patient population.

Systemic immunomodulatory therapy was reviewed by Steven et al[57] describing the multiple steps that can be manipulated by immune therapy. The first immunotherapy they describe is ipilimumab, a monoclonal antibody that binds to CTLA-4 and a phase II study in which phased ipilimumab had improved immune-related progression-free survival in comparison to the control group (HR=0.72; median 5.7 vs 4.6 months, p=0.05), as well as progression free survival(PFS) (HR=0.69; median 5.1 vs 4.2 months, p=0.02). Overall survival (OS) also appeared to be higher than the control group (12.2 vs 8.3 months) although not statistically significant. A post hoc analysis identified that patients with squamous cell histology had improved PFS and OS (HR=0.40 and 0.48, respectively). Further studies are ongoing in patients with squamous cell histology to compare chemotherapy alone to chemotherapy with phased ipilimumab.

Nivolumab, a monoclonal antibody to PD-1, has been approved by the FDA for the treatment of squamous and non-squamous NSCLC with progression on platinum based chemotherapy, or after receiving platinum based chemotherapy. Nivolumab lead to a median OS of 14.9 months, 1-year survival of 56% and 2-year survival of 45%. Nivolumab was also compared directly against docetaxel in advanced NSCLC. The Nivolumab group had a median OS of 9.2 months versus the docetaxel groups median OS of 6.0 months. Median PFS was also higher in the nivolumab group. Interestingly, they did not find any prognostic or predictive benefit if patient's tumourexpressed PD-L1.

Pembrolizumab, another PD-1 inhibitor, is approved as second-line treatment for NSCLC after chemotherapy. A phase I study, showed a response rate of 19.4% in all patients with advanced NSCLC. Median PFS was 3.7 months for all patients, 3.0 months for previously treated patients and 6 months for untreated patients. Median OS was 12.0 months for all patients, 9.3 months for previously treated, and 16.2 months for untreated patients.

Stevens *et al.*[57] also analyzed literature regarding the use of biomarkers to predict responsiveness to immunotherapy. In non-squamous NSCLC, positive PD-L1 expression, in patients treated with nivolumab, predicted a better clinical response. Unfortunately, the PD-L1 expression was not associated with a clinical response in squamous NSCLC. The complexity of PD-L1 expression leads the authors to conclude that it requires further investigation prior to its use as predictive biomarker.

4. PLEURAL DISEASE

Justin Hewlett and Fabien Maldonado

4.1. Imaging

Patients with unexplained pleural effusions often require urgent investigations, and while many questions relevant to the diagnostic algorithm of pleural effusions have been addressed, whether an effusion should be drained before diagnostic imaging occurs remains an important question. This

question has now been formally addressed. In 110 patients who underwent medical thoracoscopy with paired pre- and post-drainage chest X-rays (32 patients also had computed tomography scans), post drainage imaging did not appear to provide additional information. As it is unlikely that more definitive information will be forthcoming, it seems reasonable not to delay imaging based on this study.[58]

4.2. Medical thoracoscopy

Medical thoracoscopy (MT) is now established as the standard of care after non-diagnostic thoracentesis. One issue is whether pleurodesis should be performed in the same setting, which is generally justified when malignancy is identified, and if the lung is expandable. An interesting survey of experienced thoracoscopists clarifies this issue. Participating clinicians were given 20 video clips and asked their opinion on whether each clip represented a malignant (including histologic type) or benign process, if the lung was trapped or not, and if they would perform pleurodesis. Clinicians were correct 60% of the time (83.5% for metastatic disease, 60% for mesothelioma, and 51.4% for benign disease). Interestingly, only 12.5% correctly predicted unexpandable lung, and in 16.9% of cases pleurodesis would have been performed for benign disease. These results raise concerns for the practice of pleurodesis before histologic confirmation and demonstration of expandable lung.[59]

The low specificity of physician assessment of gross appearance of pleural disease on MT highlights the need for more rapid pathologic assessment. In a series of 62 patients undergoing MT, rapid on site evaluation (ROSE) of biopsy specimens with Hemacolor rapid staining was assessed for accuracy compared to clinician impression and histopathologic examination of tissue samples. ROSE had a sensitivity of 79.17% and a specificity of 95.59% (accuracy of 88.5%). This compared favorably with the thoracoscopist's impression with sensitivity of 100%, but specificity of only 44.7%. ROSE during medical thoracoscopy may become an important component of MT when frozen section analysis is not available, with the possible caveat that malignant pleural mesothelioma diagnosis may be difficult by ROSE.[60]

4.3. Tunnelled Indwelling Catheters

The long-term integrity of indwelling pleural catheters (IPC) is unknown. Histopathologic assessment of 41 IPC used for management of MPE was conducted to assess for the possibility of catheter breakdown, tumor growth along the catheter, or invasion into the catheter. The median indwelling duration for the pleural catheters was 126 days. Analysis showed cancer cells found within fibrous debris in the lumen of 27% of the catheters, but no evidence of direct tumor invasion or growth along catheters surfaces was noted. Reassuringly, all catheters were intact without evidence of breakdown both macroscopically or histologically.[61] In an accompanying editorial, Akulian and Yarmus suggest that the confirmed durability of IPCs could bring about a new era of treatment for pleural or systemic malignancy, with IPC used as a conduit for intrapleural drug delivery, drug-eluting devices or as a channel to monitor tumor response and drug concentration.[62]

5. INTERVENTIONAL PULMONOLOGY

Justin Hewlett and Fabien Maldonado

5.1. Diagnostic Bronchoscopy

Massive bleeding is a rare but life threatening complication of flexible bronchoscopy. A large 12-year multicenter retrospective study included 520,343 patients, all patients from 33 tertiary hospitals. There were 194 cases of massive bleeding (defined as >100ml of blood loss during bronchoscopy). Overall incidence was 0.037%. Mortality per episode was 10.8%. Risk factors for mortality were age ≥ 65 years, tracheal bleeding, blood loss >500ml and occurrence of shock. This confirmed that while the mortality for each individual massive bleed is high, the incidence of massive bleeding during flexible bronchoscopy remains a very rare event.[63]

Peripheral cryobiopsy is becoming a more commonly used bronchoscopic technique. A few small studies have shown that cryobiopsy provides larger samples with better diagnostic yield, but with

higher complication rates of bleeding and pneumothorax. A meta-analysis of 8 studies comparing cryobiopsy to standard forceps biopsy involving 916 patients showed that cryobiopsy allowed significantly larger specimens with a higher diagnostic rate (risk ratio 1.36, P = 0.0002) for all lesions. Bleeding was assessed in 3 of the studies and showed similar rates of bleeding for cryobiopsy and forceps biopsy (23.76% and 20.83% respectively). However, the largest of the studies, including 563 patients, showed higher bleeding rates in the cryobiopsy group. The relative diagnostic benefit of cryobiopsy over forceps biopsy was greater in interstitial lung disease (RR 1.77, P<0.0001). This suggests that cryobiopsy is a reasonably safe and effective procedure. More data are needed.[64]

Radial endobronchial ultrasonography with guided sheath transbronchial biopsy (EBUS-GS TBB) is recommended for the evaluation of peripheral pulmonary lesions. Whether adding conventional biopsies to guided sheath biopsies offers benefits is unclear. A retrospective analysis of 88 patients undergoing both procedures was conducted to assess the diagnostic utility of conventional TBB after EBUS-GS TBB. EBUS-GS TBB successfully obtained diagnostic sample in 65% of patients. Of the remaining patients, conventional TBB was able to obtain diagnostic tissue in 48%. Multivariate analysis showed that conventional TBB was favored if the shortest distance between the radial EBUS probe and the outer border of the peripheral lesion was less than 2.5 mm.[65]

5.2. Therapeutic Bronchoscopy

Iatrogenic tracheal injuries are rare, but potentially life threatening complications of intubation with reported incidence rate of 0.05-0.37%. Prior case series suggest that a conservative approach may often lead to spontaneous healing. A retrospective review of the management of 35 cases of iatrogenic tracheal injuries over 10 years at one institution was conducted. Four of these cases were associated with tracheo-esophageal fistula (TEF) with 3 managed surgically and 1 managed with esophageal stenting due to prohibitive surgical risk. The remaining 31 who did not have TEF were managed conservatively with serial bronchoscopy for non-ventilated patients (7 patients) and either placement of the endotracheal or tracheostomy tube below the site of injury or placement of a

silicone “Y” stent for more distal injuries in mechanically ventilated patients. Success was achieved with this conservative approach in 88.57%. This suggests that a conservative approach to tracheal injuries is reasonable in the absence of a TEF.[66]

5.3. Sedation

Fractionated propofol administration (FPA) for sedation can lead to unintended consequences of oversedation, hypoxia, and hypotension during bronchoscopy. Target controlled infusion (TCI) propofol administration uses a computerized infusion device to target an effect site concentration based on patient characteristics with more controlled administration and, perhaps, better safety profile. An unblinded randomized non-inferiority trial comparing FPA to TCI propofol for sedation was performed in 77 patients. TCI was noninferior to fractionated propofol with no significant differences in lowest SpO2, procedure length, or recovery time. This suggests that TCI propofol is non-inferior to FPA, but did not show a better safety profile in this small study.[67]

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REFERENCES

1. Park J, Kim S, Lee YJ, Park JS, Cho YJ, Yoon HI, Lee KW, Lee CT, Lee JH. Factors associated with radiological progression of non-cystic fibrosis bronchiectasis during long-term follow-up. *Respirology* 2016;21(6):1049-54.

2. Aliberti S, Masefield S, Polverino E, De Soyza A, Loebinger MR, Menendez R, Ringshausen FC, Vendrell M, Powell P, Chalmers JD; EMBARC Study Group.. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *Eur Respir J* 2016; 48(3):632-47.

3. McDonnell MJ, Aliberti S, Goeminne PC, Dimakou K, Zucchetti SC, Davidson J, Ward C, Laffey JG, Finch S, Pesci A, Dupont LJ, Fardon TC, Skrbic D, Obradovic D, Cowman S, Loebinger MR, Rutherford RM, De Soyza A, Chalmers JD. Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. *Thorax* 2016 doi: 10.1136/thoraxjnl-2016-208481. [Epub ahead of print]

4. Aliberti S, Lonni S, Dore S, McDonnell MJ, Goeminne PC, Dimakou K, Fardon TC, Rutherford R, Pesci A, Restrepo MI, Sotgiu G, Chalmers JD. Clinical phenotypes in adult patients with bronchiectasis. *Eur Respir J* 2016;47(4):1113-22.

5. Agarwal R, Aggarwal AN, Dhooria S, Singh Sehgal I, Garg M, Saikia B, Behera D, Chakrabarti A.. A randomized trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J* 2016;47(2):490-8.

6. Goutaki M, Meier AB Halbeisen FS, Lucas JS, Dell SD, Maurer E, Casaulta C, Jurca M, Spycher BD, Kuehni CE. Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. *Eur Respir J* 2016;48(4):1081-95.

7. Gao YH, Guan WJ, Liu SX, Wang L, Cui JJ, Chen RC, Zhang GJ. Aetiology of bronchiectasis in adults: a systematic literature review. *Respirology* 2016; 21(8):1376-1383.

8. Tang FS, Van Ly D, Spann K, Reading PC, Burgess JK, Hartl D, Baines KJ, Oliver BG. Differential neutrophil activation in viral infections: Enhanced TLR-7/8-mediated CXCL8 release in

asthma. *Respirology* 2016; 21(1):172-9.

9. Vlahos R, Bozinovski S. Do anti-viral neutrophil responses exacerbate lung inflammation in asthma? *Respirology* 2016; 21(1):10-1.
10. Sahuquillo-Arce JM, Menéndez R, Méndez R, Amara-Elori I, Zalacain R, Capelastegui A, Aspa J, Borderías L, Martín-Villasclaras JJ, Bello S, Alfageme I, de Castro FR, Rello J, Molinos L, Ruiz-Manzano J, Torres A..Age-related risk factors for bacterial aetiology in community-acquired pneumonia. *Respirology* 2016;21(8):1472-1479.
11. Sibila O, Rodrigo-Troyano A, Shindo Y, Aliberti S, Restrepo MI. Multidrug-resistant pathogens in patient with pneumonia coming from the community. *Curr Opin Pulm Med* 2016;22(3):219-26.
12. Guidol C, Royo-Cebrecos C, Lapore J, Ardanuy C, Garcia-Vidal C, Antonio M, Arnan M, Carratalà J. Clinical features, aetiology, and outcome of bacteraemic pneumonia in neutropenic cancer patients. *Respirology* 2016; 21(8):1411-1418.
13. Metersky ML, Frei CR, Mortensen EM. Predictors of Pseudomonas and methicillin-resistant Staphylococcus aureus in hospitalized patients with healthcare-associated pneumonia. *Respirology* 2016; 21(1):157-63.
14. Waterer GW. Healthcare-associated pneumonia: Can we salvage anything from the wreckage? *Respirology* 2016; 21(1):8-9.
15. Aliberti S, Reyes LF, Faverio P, Sotgiu G, Dore S, Rodriguez AH, Soni NJ, Restrepo MI; GLIMP investigators. Global initiative for meticillin-resistant Staphylococcus aureus pneumonia (GLIMP): an international, observational cohort study. Lancet Infect Dis. 2016 doi: 10.1016/S1473-3099(16)30267-5. [Epub 2016 Sep 1.]
16. Cillóniz C, Civljak R, Nicolini A, Torres A. Polymicrobial community-acquired pneumonia: An emerging entity. *Respirology* 2016; 21(1):65-75.
17. Mok JH, Eom JS, Jo EJ, Kim MH, Lee K, Kim KU, Park HK, Yi J, Lee MK. Clinical Utility of rapid pathogen identification using matrix-assisted laser desorption/ionization time of flight mass

spectrometry in ventilated patients with pneumonia: a pilot study. *Respirology* 2016;21(2):321-8.

18. Özvatan T, Akalın H, Sınırtaş M, Ocakoğlu G, Yılmaz E, Heper Y, Kelebek N, İşçimen R, Kahveci F. Nosocomial Acinetobacter pneumonia: treatment and prognostic factors in 356 cases. *Respirology* 2016;21(2):363-9.
19. Yoon H, Jhun BW, Kim SJ, Kim K. Clinical Characteristics and factors predicting respiratory failure in adenovirus pneumonia. *Respirology* 2016;21(7):1243-50.
20. Taylor JK, Fleming GB, Singanayagam A, Hill AT, Chalmers JD. Risk factors for aspiration in community-acquired pneumonia. Analysis of a hospitalized UK cohort. *Am J Med* 2013; 126(11):995-1001.
21. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM *et al.* Community-acquired pneumonia requiring hospitalization among US adults. *N Engl J Med* 2015;373(5):415-27.
22. Isenman HL, Chambers ST, Pithie AD, MacDonald SL, Hegarty JM, Fenwick JL, Maze MJ, Metcalf SC, Murdoch DR.. Legionnaires disease caused by *Legionella longbeachae*: clinical features and outcomes of 107 cases from an endemic area. *Respirology* 2016; 21(7):1292-9.
23. Ito A, Ishida T, Tachibana H, Ito Y, Takaiwa T..Serial procalcitonin levels for predicting prognosis in community-acquired pneumonia. *Respirology* 2016;21(8):1459-1464.
24. Cangemi R, Della Valle P, Calvieri C, Taliani G, Ferroni P, Falcone M, Carnevale R, Bartimoccia S, D'Angelo A, Violi F; SIXTUS Study Group.. Low-grade endotoxemia and clotting activation in the early phases of pneumonia. *Respirology* 2016;21(8):1465-71.
25. Sibila O, Mortensen EM, Anzueto A, Laserna E, Restrepo MI.. Prior cardiovascular disease increases long-term mortality in COPD patients with pneumonia. *Eur Respir J* 2014;43(1):36-42.
26. Liu D, Su LX, Guan W, Xiao K, Xie LX. Prognostic value of procalcitonin in pneumonia: A systematic review and meta-analysis. *Respirology* 2016; 21(2):280-8.

27. Horita N, Otsuka T, Haranaga S, Namkoong H, Miki M, Miyashita N, Higa F, Takahashi H, Yoshida M, Kohno S, Kaneko T. Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis. *Respirology* 2016; 21(7):1193-200.
28. Jefferies S, Braithwaite I, Walker S, Weatherall M, Jennings L, Luck M, Barrett K, Siebers R, Blackmore T, Beasley R, Perrin K; Pi Study Group. Randomized controlled trial of the effect of regular paracetamol on influenza infection. *Respirology* 2016; 21(2):370-7.
29. Peters MJ. Disruptive thinking: The virtue of challenging collective therapeutic intuition. *Respirology* 2016; 21(2):207-8.
30. Amaro R, Liapikou A, Cilloniz C, Gabarrus A, Marco F, Sellares J, Polverino E, Garau J, Ferrer M, Musher DM, Torres A.. Predictive and prognostic factors in patients with blood-culture-positive community-acquired pneumococcal pneumonia. *Eur Respir J* 2016;48(3):797-807.
31. Uematsu H, Kunisawa S, Yamashita K, Fushima K, Imanaka Y . Impact of weekend admission on in-hospital mortality in severe community-acquired pneumonia patients in Japan. *Respirology* 2016;21(5):905-10.
32. Kim J, Park JS, Cho YJ, Yoon HI, Lee JH, Lee CT, Lim HJ, Kim DK. Predictors of prolonged stay in patients with community-acquired pneumonia and complicated parapneumonic effusion. *Respirology* 2016; 21(1):164-71.
33. Leung CC, Chan K, Yam WC, Lee MP, Chan CK, Wong KH, Ho PL, Mak I, Tam CM. Poor agreement between diagnostic tests for latent tuberculosis infection among HIV-infected persons in Hong Kong. *Respirology* 2016;21(7):1322-9.
34. Bai X, Oberley-Deegan RE, Bai A, Ovrutsky AR, Kinney WH, Weaver M, Zhang G, Honda JR, Chan ED. Curcumin enhances human macrophage control of Mycobacterium tuberculosis infection. *Respirology* 2016; 21(5):951-7.
35. Aksamit TR, O'Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels ML, Johnson M, Eden E, Griffith D, Knowles M, Metersky M, Salathe M, Thomashow B, Tino G, Turino G, Carretta B,

Daley CL Adult bronchiectasis patients: a first look at the United States Bronchiectasis Research Registry. *Chest* 2016 doi: 10.1016/j.chest.2016.10.055. [Epub ahead of print]

36. Nishimura T, Fujita-Suzuki Y, Mori M, Carpenter SM, Fujiwara H, Uwamino Y, Tamizu E, Yano I, Kawabe H, Hasegawa N. Middle-aged to elderly women have a higher asymptomatic infection rate with Mycobacterium avium complex, regardless of body habitus. *Respirology* 2016; 21(3):553-5.
37. Yeung MW, Khoo E, Brode SK, Jamieson FB, Kamiya H, Kwong JC, Macdonald L, Marras TK, Morimoto K, Sander B. Health-related quality of life, comorbidities and mortality in pulmonary nontuberculous mycobacterial infections: A systematic review. *Respirology* 2016; 21(6):1015-25.
38. Ellender CM, Law DB, Thomson RM, Eather GW. Safety of IV amikacin in the treatment of pulmonary non-tuberculous mycobacterial disease. *Respirology* 2016;21(2):357-62.
39. Arthur S. Slutsky, and V. Marco Ranieri. Ventilator-Induced Lung Injury. N Engl J Med 2013; 369:2126-2136
40. Ventilation With Lower Tidal Volumes As Compared With Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 342: 1301–1308, 2000
41. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747-55.
42. Nieman GF, Satalin J, Andrews P, Habashi NM, Gatto LA. Lung stress, strain, and energy load: engineering concepts to understand the mechanism of ventilator-induced lung injury (VILI). Intensive Care Med Exp. 2016;4(1):16.
43. Zhao T, Zhao H, Li G, Zheng S, Liu M, Gu C, Wang Y. Role of the PKCα-c-Src tyrosine kinase pathway in the mediation of p120-catenin degradation in ventilator-induced lung injury. *Respirology*. 2016;21(8):1404-1410.

44. Bastin AJ, Davies N, Lim E, Quinlan GJ, Griffiths MJ. Systemic inflammation and oxidative stress post-lung resection: Effect of pretreatment with N-acetylcysteine. *Respirology*. 2016;21(1):180-7.
45. Xiong B, Wang C, Tan J, Cao Y, Zou Y, Yao Y, Qian J, Rong S, Huang Y, Huang J. Statins for the prevention and treatment of acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. *Respirology*. 2016;21(6):1026-33.
46. Fujishima S, Gando S, Daizoh S, Kushimoto S, Ogura H, Mayumi T, Takuma K, Kotani J, Yamashita N, Tsuruta R, Takeyama N, Shiraishi S, Araki T, Suzuki K, Ikeda H, Miki Y, Suzuki Y, Yamaguchi Y, Aikawa N. Infection site is predictive of outcome in acute lung injury associated with severe sepsis and septic shock. *Respirology*. 2016;21(5):898-904.
47. Lee JK, Choi SM, Lee J, Park YS, Lee CH, Yim JJ, Yoo CG, Kim YW, Han SK, Lee SM. Serum activin-A as a predictive and prognostic marker in critically ill patients with sepsis. *Respirology*. 2016;21(5):891-7.
48. Jeon K, Jeong BH, Ko MG, Nam J, Yoo H, Chung CR, Suh GY. Impact of delirium on weaning from mechanical ventilation in medical patients. *Respirology*. 2016;21(2):313-20.
49. Hori R, Isaka M, Oonishi K, Yabe T, Oku Y. Coordination between respiration and swallowing during non-invasive positive pressure ventilation. *Respirology*. 2016;21(6):1062-7.
50. Murray CP, Wong PM, Teh J, de Klerk N, Rosenow T, Alfonso H, Reid A, Franklin P, Musk AW, Brims FJ. Ultra low dose CT screen-detected non-malignant incidental findings in the Western Australian Asbestos Review Programme. *Respirology*. 2016;21(8):1419-1424.
51. Karaman A, Araz O, Durur-Subasi I, Alper F, Subasi M, Karakaya AD, Akgun M. Added value of DCE-MRI in the management of cystic-cavitary lung lesions. *Respirology*. 2016;21(4):739-745.
52. Rosenow T. 'Enhanced' characterization of cystic–cavitary lesions using DCE-MRI. *Respirology*. 2016;21(4):576-577.

53. Guisier F, Salaün M, Lachkar S, Lamy A, Piton N, Obstoy B, Sabourin JC, Thiberville L. Molecular analysis of peripheral non-squamous non-small cell lung cancer sampled by radial EBUS. *Respirology*. 2016;21(4):718-726.
54. Zhang Z, Xiao Y, Zhao J, Chen M, Xu Y, Zhong W, Xing J, Wang M. Relationship between circulating tumour cell count and prognosis following chemotherapy in patients with advanced non-small-cell lung cancer. *Respirology*. 2016;21(3):519-525.
55. Gao Y-h, Guan W-j, Liu Q, Wang HQ, Zhu YN, Chen RC, Zhang GJ. Impact of COPD and emphysema on survival of patients with lung cancer: A meta-analysis of observational studies. *Respirology*. 2016;21(2):269-279.
56. Numan RC, Baas P, Klomp HM, Wouters MW. Optimal surgical management of pulmonary metastases: VATS versus thoracotomy. *Respirology*. 2016;21(1):188-190.
57. Steven A, Fisher SA, Robinson BW. Immunotherapy for lung cancer. *Respirology*. 2016;21(5):821-833.
58. Corcoran JP, Acton L, Ahmed A, Hallifax RJ, Psallidas I, Wrightson JM, Rahman NM, Gleeson FV. Diagnostic value of radiological imaging pre- and post-drainage of pleural effusions. *Respirology*. 2016;21(2):392-395.
59. Hallifax RJ, Corcoran JP, Psallidas I, Rahaman NM. Medical thoracoscopy: Survey of current practice – How successful are medical thoracoscopists at predicting malignancy? *Respirology*. 2016;21(5):958-960.
60. Porfyridis I, Georgiadis G, Michael M, Frangopoulos F, Vogazianos P, Papadopoulos A, Kara P, Charalampous C, Georgiou A. Rapid on-site evaluation with the Hemacolor rapid staining method of medical thoracoscopy biopsy specimens for the management of pleural disease. *Respirology*. 2016;21(6):1106-1112.
61. Tobin C, Thomas R, Chai SM, Segal A, Lee YC. Histopathology of removed indwelling pleural catheters from patients with malignant effusions. *Respirology*. 2016;21(5):939-942.

62. Akulian JA, Yarmus L. If they don't degrade can indwelling pleural catheters evolve? *Respirology*. 2016;21(5):787-788.
63. Zhou GW, Zhang W, Dong YC, Huang HD, Hu C, Sun J, Jin F, Gu Y, Li Q, Li S. Flexible bronchoscopy-induced massive bleeding: A 12-year multicentre retrospective cohort study. *Respirology*. 2016;21(5):927-931.
64. Ganganah O, Guo SL, Chiniah M, Li YS. Efficacy and safety of cryobiopsy versus forceps biopsy for interstitial lung diseases and lung tumours: A systematic review and meta-analysis. *Respirology*. 2016;21(5):834-841.
65. Kunimasa K, Tachihara M, Tamura D, Tokunaga S, Nakata K, Hazeki N, Kamiryo H, Kobayashi K, Sakai Y, Nishimura Y. Diagnostic utility of additional conventional techniques after endobronchial ultrasonography guidance during transbronchial biopsy. *Respirology*. 2016;21(6):1100-1105.
66. Tazi-Mezalek R, Musani AI, Laroumagne S, Astoul PJ, D'Journo XB, Thomas PA, Dutau H. Airway stenting in the management of iatrogenic tracheal injuries: 10-year experience. *Respirology*. 2016;21(8):1452-1458.
67. Franzen D, Bratton D, Clarenbach C, Freitag L, Kohler M. Target-controlled versus fractionated propofol sedation in flexible bronchoscopy: A randomized noninferiority trial. *Respirology*. 2016;21(8):1445-1451.