Year in review 2011: Respiratory infections, tuberculosis, pleural diseases, bronchoscopic intervention and imaging

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Keywords
endobronchial ultrasonography; pleural effusion; pneumonia; positron emission tomography; tuberculosis

INTRODUCTION

This review highlights important contributions published in Respirology and other reputable respiratory journals in 2011 in four principle respiratory medicine areas, namely pulmonary infections, tuberculosis (TB), pleural diseases and chest imaging/interventional pulmonology. The articles have been selected for their insight, reliability and potential impact on clinical practice. From a total of 111 original articles and 40 review papers published in Respirology that year, 34% and 40%, respectively, were devoted to the earlier topics.

RESPIRATORY INFECTIONS

Marcos I. Restrepo

Lower respiratory tract infections remain an important cause of morbidity, mortality and high medical costs around the world. Over the past year, multiple studies have contributed to
a better understanding on how to assess, diagnose and treat patients with lower respiratory tract infection.

**Epidemiology and microbiology of pneumonia**

A prospective observational study documented additional health-care visits and rehospitalizations within 30 days of discharge in one third of patients with community-acquired pneumonia (CAP). This was mainly due to a worsening of CAP-related signs and symptoms, and/or comorbidities, such as cardiovascular and pulmonary diseases.

A significant controversy persists regarding the differentiation between CAP and health care-associated pneumonia (HCAP). Umeki et al. assessed the clinical features of HCAP from a Japanese cohort of patients with acute pneumonia. They enrolled 202 consecutive patients in a 2-year period and stratified them into three groups: CAP (n = 123), nursing home-acquired pneumonia (n = 46) and other HCAP (n = 33). The authors found the highest mortality among nursing home-acquired pneumonia patients (11%) when compared with CAP (3%) and other HCAP (0%) patients. In addition, CAP patients were more likely to have infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* compared with the methicillin-resistant *Staphylococcus aureus* and Klebsiella pneumoniae in the nursing home-acquired pneumonia, and *S. pneumoniae* and *Klebsiella pneumoniae* in the other HCAP group. Therefore, these data suggest that the term HCAP requires further refinement in that nursing home-acquired pneumonia seems to represent a separate group of patients compared with other HCAP regarding antimicrobial resistance and poor clinical outcomes.

Several authors have also identified a series of pathogens with higher antimicrobial resistance. Vasoo et al. reported a dramatic rise of *S. pneumoniae* antimicrobial resistance over the past decade in children from Singapore when comparing two study periods, 1997 versus 2007–2008. Pneumococcal non-susceptible strains increased from 27% to 69% for penicillin, 33% to 78% for erythromycin, 24% to 46% for clindamycin, 48% to 68% for tetracyclines and resistance to three or more classes of antibiotics from 33% to 75%, respectively. Another pathogen of great concern is community-associated methicillin-resistant *S. aureus* causing pneumonia. Thomas et al. reported the clinical characteristics of 16 patients with community-associated-methicillin-resistant *S. aureus*. More than 85% had productive cough, fever and dyspnoea, while the most common radiological presentations were multilobar consolidation (50%), necrotizing lesions (43%) and empyema (31%). In addition, there was a delay in the initiation of appropriate therapy, which calls for attention to the specific characteristics of community-associated-methicillin-resistant *S. aureus* pneumonia.

Fisher et al. wrote an elegant review on the major challenges faced in Asia in response to the influenza H1N1 2009 pandemic and drew lessons for the future. Martin-Loeches et al. reported 872 confirmed cases of pandemic influenza A (H1N1), of which there were 131 deaths. One third died within the first 2 weeks and were predominantly young with rapidly progressive viral pneumonia and multiorgan dysfunction. Most of the patients required vasopressors (74%), and only 52% received empirical antiviral therapy. López-Mendoza and
Restrepo, in an accompanied editorial, emphasized the importance of autopsy data to support the impact of the primary viral infection.\(^7\)

**Diagnosis of lower respiratory tract infection**

An important topic on lower respiratory tract infection is how clinicians diagnose severe infections and tailor the appropriate therapy. Tetenta and Metersky\(^8\) described one of the important limitations with pathogen identification, utilizing Gram stain from tracheal aspirates from patients with *S. aureus*. They showed that Gram-stain readings by an experienced clinician who was not a microbiologist were not reliable enough to predict the growth of *S. aureus*.

Currently, several biomarkers are under evaluation for differentiating between bacterial infection and colonization in order to make decisions on the use of antimicrobial therapies. Procalcitonin is one of them. Long *et al.* assessed the value of procalcitonin measurements for guiding antibiotic use in 152 low-risk outpatients with CAP.\(^9\) A control group received antibiotics according to current guidelines, whereas in another group, procalcitonin levels mitigated for or against the use of antibiotics. The authors showed a reduction of total antibiotic exposure (relative risk of 0.55, \(P = 0.003\)) and a shorter duration of antibiotics (5 vs 7 days, \(P < 0.001\)) when procalcitonin guidance was compared with standard of care, respectively. In addition, no harm was noted by reducing the duration and amount of antimicrobial therapy. Hsu *et al.* showed that CD64 and CD16 expressions on neutrophils were differentially modulated by sepsis, and particularly the former was better than procalcitonin for identifying patients who required antibiotics.\(^10\) It is possible that the Fc gamma receptor expression on neutrophils may guide the diagnosis of sepsis in critically ill patients with acute respiratory failure. Ruiz-González *et al.* analysed the accuracy of the soluble form of triggering receptor expressed on myeloid cells-1 to predict positive blood cultures in comparison with established clinical prognostic variables.\(^11\) They found that soluble form of triggering receptor expressed on myeloid cells-1 performed better (area under the receiver operating characteristics curve = 0.84) for identifying bacteraemic patients than other clinical parameters, such as pleuritic chest pain (area under the receiver operating characteristics curve = 0.71), tachycardia (area under the receiver operating characteristics curve = 0.73) and extreme white blood cell count (area under the receiver operating characteristics curve = 0.70). Wu *et al.* suggested that soluble form of triggering receptor expressed on myeloid cells-1 collected from the bronchoalveolar lavage may have a prognostic value in patients with ventilator-associated pneumonia.\(^12\)

Leow *et al.* hypothesized that vitamin D deficiency may be associated with lower levels of the antimicrobial peptides cathelicidin and beta-defensin-2, which play an important role in the innate immune response to infection.\(^13\) Second, that vitamin D deficiency would influence the outcome in hospitalized patients with CAP.\(^13\) They found that severe 25-hydroxyvitamin D deficiency (<30 nmol/L) was common in CAP patients (15%) and was associated with a significant higher mortality when compared with normal levels of vitamin D (>50 nmol/L). However, neither cathelicidin nor beta-defensin-2 levels correlated with vitamin D deficiency or predicted mortality. An accompanying editorial highlighted the
failure of this study to take into consideration such well-known confounders as vitamin D supplementation and smoking.\textsuperscript{14}

Finally, Tagami \textit{et al.} found that plasma neutrophil elastase levels were present in patients with severe CAP and correlated with pulmonary vascular permeability, suggesting their possible pathogenetic role.\textsuperscript{15}

\textbf{Acute exacerbations of chronic obstructive pulmonary disease}

A provocative manuscript by MacDonald \textit{et al.} proposed an acronym to facilitate phenotyping patients who developed acute exacerbations of chronic obstructive pulmonary disease (COPD).\textsuperscript{16} The acronym is ABCDEFG-X that stands for Airway viral infection, Bacterial infection, Co-infection, Depression/anxiety, Embolism (pulmonary), Failure (cardiac and lung integrity), General environment and X for no specific cause identified. It has been suggested that phenotyping by aetiology may identify exacerbation subgroups, clarify benefits of therapeutic intervention and improve overall clinical care. A large multinational, prospective study found that the most common pathogens in acute exacerbations of COPD were Gram-negative bacteria, including \textit{Klebsiella} species, \textit{Pseudomonas aeruginosa} and \textit{Acinetobacter} spp.\textsuperscript{17} Zakharkina \textit{et al.} identified the microorganisms associated with an acute exacerbation of COPD by using bacterial nucleic acids in exhaled breath condensate.\textsuperscript{18} However, the results did not correlate well enough with those of spontaneous sputum samples.

\textbf{Bronchiectasis treatment}

Worsening pulmonary function in patients with bronchiectasis is associated with impaired mucus clearance. However, the use of inhaled mannitol to enhance mucus clearance has been associated with a reduction of forced expiratory volume in 1 s in some patients. Briffa \textit{et al.} performed a double-blind, placebo-controlled, randomized cross-over study to investigate whether premedicating with either sodium cromoglycate or eformoterol can protect this patient group from developing mannitol-induced bronchospasm.\textsuperscript{19} They showed that both premedications protected patients with bronchiectasis from developing a significant reduction in forced expiratory volume in 1 s after inhaling dry powder mannitol.

\textbf{Septic shock treatment}

The use and duration of stress dose steroids for patients with septic shock is a matter of controversy. Huh \textit{et al.} performed a pilot study comparing 3 versus 7 days of low-dose hydrocortisone treatment for patients with septic shock and relative adrenal insufficiency.\textsuperscript{20} After 28 days, mortality did not differ between the groups (34\% vs 37\%, \(P = 0.6\)). In addition, there were no differences in intensive care unit mortality or time for withdrawing vasopressor support.

\textbf{TB}

Chi Chiu Leung
Epidemiology

The emergence of drug resistance is threatening the control of TB all over the world. Liu et al. found an ofloxacin resistance rate of 8.6% in a retrospective study of 3546 TB patients admitted to a referral hospital in Beijing, China. The independent risk factors were single migrant living in Beijing, migrant from another area, retreatment case, exposure to fluoroquinolones, COPD, COPD with known exposure to fluoroquinolones, multidrug-resistant TB and poly-resistant TB. With the huge burden of multidrug-resistant TB in China, increasing fluoroquinolone resistance is a serious threat that may herald a future crisis of extensively drug-resistant TB. Apart from effective implementation of the directly observed treatment strategy-plus strategy, judicious use of fluoroquinolones within the community is called for, especially among patients with exacerbations of chronic chest conditions.

In another study by Jiang et al., the prevalence of drug resistance was significantly higher (25.8% vs 17.0%) in immunocompromised patients than immunocompetent ones in Taiwan, especially for isoniazid, rifampicin and streptomycin, and among patients with liver cirrhosis, malignancies and those receiving immunosuppressants. Immunosuppressed patients, with their underlying medical conditions, probably visit health-care facilities institutions frequently. Their higher drug-resistance rate could therefore represent nosocomial transmission, as is well exemplified by a recent study showing a high risk of hospital admissions with multidrug-resistant and extensively drug-resistant TB for South African health-care workers. Mutations conferring drug resistance may also carry a fitness cost. Human immunodeficiency virus (HIV)-infected subjects are more prone to acquire rifampicin resistance on intermittent rifamycin-containing regimens. It is therefore plausible that compromised host immunity could somehow mitigate the competitive disadvantage of certain drug-resistant mutants, thereby accounting for their relative abundance in these hosts. Further studies are required to clarify the situation.

In a meta-analysis of six case-control studies, Wang et al. did not find any significant association between the P2X7 receptor A1513C polymorphism and susceptibility to pulmonary TB, despite earlier studies suggesting a P2X7 receptor role in inducing apoptosis of Mycobacterium tuberculosis-infected macrophages. On the other hand, variants of cytokine-inducible SRC homology 2 domain protein, a suppressor of cytokine signalling, have been associated with susceptibility to diseases caused by diverse infectious pathogens, including Mycobacterium tuberculosis. Genome-wide association studies are being increasingly utilized to define genetic variants underlying susceptibility to major infectious diseases. Hopefully, this research will help to identify translatable targets for drug and vaccine development in the near future.

Diagnosis

A recent meta-analysis concluded that neither interferon-gamma release assay (IGRA) nor tuberculin skin test (TST) can accurately predict the future development of active TB. And, IGRA only has a moderate predictive value comparable with TST. As all existing diagnostic tools for latent TB infection are directed towards the host's immune status rather than the activity of the pathogen itself, none of them are expected to overcome the intrinsic
limitation imposed by the natural history of TB: the positive predictive value cannot exceed the lifetime disease risk of around 10%. However, two other cohorts suggested that IGRA might outperform TST in settings with limited ongoing transmission and/or background prevalence of infection. A recent prospective cohort study also showed that a strongly positive TST reaction (≥15 mm) in primary school children predicted development of active TB in adolescence, thereby suggesting reactivation of latent TB infection in association with some yet uncharacterized changes in host immunity during the adolescent growth spurt.

Zhou et al. performed a meta-analysis of seven studies on the accuracy of IGRA, using both pleural fluid and blood, in the diagnosis of tuberculous pleurisy. The summary estimates of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value and diagnostic odds ratio were 0.75, 0.82, 3.49, 0.24, 0.85, 0.70 and 19.04, respectively, for pleural fluid, and 0.80, 0.72, 2.86, 0.28, 0.78, 0.74 and 11.06, respectively, for blood. Pleural fluid IGRA does not compare favourably with simpler diagnostic tools, such as measurement of adenosine deaminase or interferon-γ levels in pleural fluid. The IGRA was primarily designed for the diagnosis of infection not disease. Its use on cells harvested from the site of the disease process (e.g. BAL fluid) does not appear to overcome this limitation in either tuberculous pleurisy or pulmonary TB.

In Uganda, Yoo et al. found normal chest radiographs (chest X-ray (CXR)) in 16% of 334 consecutive hospitalized HIV-seropositive adult TB suspects, who had presented with cough for 2 weeks or more. Up to 44% of those with a normal CXR were suffering from active TB. A normal CXR in TB patients was associated with younger age, low CD4+ T-cell counts and negative sputum smears, with a trend towards higher 2-month mortality (40% vs 29%, P = 0.15). A normal CXR is therefore not reassuring in symptomatic HIV-infected TB suspects. On the other hand, Van’t Hoog et al. reported a high prevalence of pulmonary TB and inadequate passive case finding by sputum microscopy in rural Western Kenya. Despite a high prevalence of HIV infection in the area, trained nonmedical personnel were able to report the CXR with a high degree of sensitivity for TB, when a lower diagnostic threshold of any radiological abnormality was employed. Symptoms, sputum microscopy and CXR are therefore complementary for TB case finding among HIV-infected subjects in resource-limited settings before affordable new diagnostic tools are developed for large-scale field application under these difficult conditions.

Treatment

A recent randomized controlled trial evaluated four different regimens: rifapentine 900 mg plus isoniazid 900 mg that were administered weekly for 12 weeks, rifampin 600 mg plus isoniazid 900 mg twice weekly for 12 weeks, isoniazid 300 mg daily for up to 6 years (continuous isoniazid), and isoniazid 300 mg daily for 6 months (control group) in the treatment of latent TB infection in South African adults with HIV infection and a positive TST. Incidence rates of active TB or death were comparable for all (3.1, 2.9, 2.7 and 3.6/100 person-years in the rifapentine-isoniazid, rifampin-isoniazid, continuous-isoniazid and control group, respectively). However, serious adverse reactions were significantly more common in the continuous-isoniazid group (18.4/100 person-years) than the others (8.7–15.4/100 person-years).
In another randomized controlled trial among HIV-infected adults in Botswana, the incident rate of TB was significantly lower in the group given 36 months of isoniazid than the control group given 6 months of isoniazid (2.0% vs 3.4%, \( P = 0.047 \)).\(^4\) TB incidence in the control group escalated approximately 200 days after completion of isoniazid therapy. Participants with tuberculin reaction ≥5 mm at enrollment benefited significantly from continued isoniazid treatment, whereas TST-negative participants did not. Severe adverse events and death were comparable. With the conflicting reports between the above two clinical trials, the optimal duration of isoniazid prophylaxis among TST-positive, HIV-infected subjects remains unclear.

Primary isoniazid prophylaxis did not improve TB disease-free survival among HIV-infected infants or TB-infection-free survival among HIV-uninfected infants immunized with bacille Calmette-Guérin vaccine in another randomized controlled trial.\(^4\) Available studies therefore indicate that isoniazid prophylaxis only benefits subjects with evidence of TB infection.

Lim et al. retrospectively investigated 71 patients who underwent silicone stenting for post-TB tracheobronchial stenosis.\(^4\) Stents were successfully removed in 40 patients after a median duration of 12.5 months postinsertion, while the remaining 31 patients required either stent reinsertion (27 patients) or surgical management (four patients). Successful stent removal was independently associated with atelectasis for less than 1 month before bronchoscopic intervention and the absence of complete lobar atelectasis. Early stenting in post-TB tracheobronchial stenosis therefore increases the chance of success.

**PLEURAL DISEASES**

José M. Porcel

In 2011, *Respirology* published an invited review series on pleural diseases, which focused mainly on advances and controversial issues of malignant and infectious effusions, as well as a few original papers that deserve a comment.

**Pleural fluid analysis**

Although the diagnosis of heart failure-associated effusion is usually suggested by the clinical picture, pleural fluid may meet the Light’s exudative criteria in 25% of the cases.\(^4\) That the effusion is caused by heart failure may be established by measuring natriuretic peptides, either B-type natriuretic peptide (BNP) or N-terminal pro-BNP, in the serum or the fluid itself.\(^4\) N-terminal pro-BNP is a more accurate heart failure biomarker than BNP when assayed in the pleural fluid.\(^4\) However, no head-to-head comparison study has evaluated which performs the best in serum samples of patients with different causes of pleural effusion. As for N-terminal pro-BNP, Marinho et al. have demonstrated that pleural fluid BNP concentration measurements provide no additional information beyond the plasma measurement.\(^5\) It was shown that plasma BNP levels greater than 132 pg/mL had both a sensitivity and specificity of 97% for discriminating 34 effusions attributable to heart failure from 43 non-cardiac effusions. The figures for pleural fluid BNP at the best cut-off of 127 pg/mL were 97% sensitivity and 88% specificity. Notably, all 12 patients with heart
failure whose pleural fluid met Light's criteria for exudate would have been correctly labelled as true cardiac transudates by BNP. The recognition of cardiac effusions that are misclassified as exudates by Light's criteria may represent the main clinical application of natriuretic peptides in the work-up of pleural effusions.

The volume of pleural fluid necessary to diagnose malignant effusions is a matter of controversy. A study of 2155 pleural fluid samples from 1584 patients, of which nearly 25% were of malignant origin, examined the plateau phase of a graph of threshold volumes in order to define the minimum amount required for diagnostic purposes. It was determined to be at least 25 mL, but more than 50 mL did not improve sensitivity for the identification of malignancy.

If bacterial infection of the pleural space is suspected, 2–5 mL of pleural fluid should be inoculated into blood culture bottles in addition to the standard culture. In a prospective study of 53 patients with pleural infection, this manoeuvre increased the organism identification rate by 21%. Therefore, processing pleural fluid in blood culture bottles should be a part of routine care.

**Parapneumonic effusions**

A total of 882 (19%) of 4715 consecutive patients with CAP from two Spanish university hospitals had evidence of pleural effusion in a standard CXR. In 261 (30%) of those patients, the condition progressed to complicated parapneumonic effusion or empyema. A microbial aetiology was obtained in 72% of the latter; *S. pneumoniae*, *Streptococcus viridans* and anaerobes caused 66%, 18% and 13% of the isolates, respectively. Thus, empirical antibiotic therapy in outpatients with complicated parapneumonic effusions and empyemas should provide coverage for these microorganisms.

The presence of a parapneumonic effusion is usually confirmed with a posteroanterior and lateral CXR. An anteroposterior view is usually taken with a portable X-ray unit on patients who are unable to stand. It is traditionally taught that pleural fluid is easier to detect on the upright films. Brixey et al. retrospectively compared the sensitivity of posteroanterior, lateral and anteroposterior radiographs in identifying 61 parapneumonic effusions using chest computed tomography (CT) as the reference standard. The specificity of CXR was calculated after examining another 116 patients with pneumonia and no evidence of effusion on CT. Overall, the sensitivity of identifying a parapneumonic effusion was 86% for lateral, 82% for posteroanterior and 78% for anteroposterior CXR, while the respective specificities were 87%, 81% and 76% (both P nonsignificant). The existence of a lower lobe parenchymal consolidation concealed the identification of some pleural effusions. Interestingly, CXR missed 6% of effusions greater than 2 cm on CT, a size that may be significant enough to warrant a diagnostic thoracentesis.

Current guidelines recommend parapneumonic effusions with a thickness of >1 cm in the lateral decubitus position or >5 cm in the lateral erect radiographic view be sampled via thoracentesis. Moffet et al. have demonstrated that these values correlate to more than 2.5 cm when measuring effusions through CT imaging. In other words, to sample a parapneumonic effusion of 2.5 cm or less on CT is unsafe and thus unnecessary.
Concerning the role of intrapleural fibrinolitics in patients with empyema and loculated parapneumonic effusions, we still do not know the effect that the recently published article by Rahman et al. may have, but it seems likely that current practice will change. These researchers have demonstrated that the combination of intrapleural tissue plasminogen activator (10 mg) and DNase therapy (5 mg), each given twice daily for 3 days, improves fluid drainage in patients with pleural infection and is associated with reductions in hospital stay and the need for thoracic surgery. Aside from that, treatment with DNase or tissue plasminogen activator alone was shown to be ineffective.

**Pleurodesis**

Pleurodesis remains the best palliative therapy for symptomatic malignant effusions, although no consensus exists as to the ideal sclerosing agent. Graded talc administered via thoracoscopic insufflation is the most studied and one of the most used agents. A retrospective study showed that the global response to thoracoscopic talc poudrage in 447 patients was 88%, as compared with 79% in 126 patients who were submitted to bedside doxycycline pleurodesis. Mesothelioma and lung cancer were particularly prone to failed procedures, regardless of the agent employed, most likely due to unexpandible lungs. In addition to doxycycline, other inexpensive and widely available sclerosants, such as iodopovidone and silver nitrate, have received increasing attention. A randomized controlled trial found no differences in the efficacy and safety of iodopovidone (20 mL of a 10% solution) or cosmetic talc (5 g) administered through a chest tube in 73 patients with either pleural effusions or pneumothoraces. A complete response was achieved in 92% and 88% of patients in the iodopovidone and talc groups, respectively. However, the need for checking cosmetic talc purity and particle size precludes its use in clinical practice.

It has not been established whether pleurodesis should be offered to all patients with pleural metastases from chemosensitive tumours, such as breast cancer, or just to patients who fail to clear the effusions through chemotherapy. Hirata et al. retrospectively compared the outcomes of 78 patients with metastatic breast cancer receiving systemic chemotherapy along with a therapeutic thoracentesis against 102 patients who were treated with pleural space drainage and pleurodesis (minocycline or OK-432) followed by chemotherapy. The proportion of patients with moderate-to-large effusions (i.e. those occupying more than 25% of the hemithorax) was larger among the latter (72% vs 28%). Pleural progression free survival, defined as the time from the initial therapy to pleural progression or death, was significantly better in the pleurodesis group (8.5 vs 4.1 months). In fact, 63% of patients from the chemotherapy alone group eventually needed pleurodesis due to effusion progression. To sum up, the earlier the pleurodesis procedure, the better the quality of life for patients with metastatic breast cancer. In addition, because most patients with more than a moderate amount of malignant pleural effusion require pleurodesis sooner or later, it is our opinion that the procedure should be carried out as soon as possible regardless of the chemosensitivity of the primary tumour. This could prevent a progressed pleural tumour burden and the subsequent development of a trapped lung from making later pleurodesis unsuccessful.
Miscellaneous

Pleural effusions are highly prevalent after cardiac surgery. Based on the safety and efficacy of colchicine in the prevention of pericarditis, a multicentre, double-blinded, randomized trial was conducted in which a total of 360 consecutive patients who required cardiac surgery (with the exception of heart transplantation) were recruited. The aim was to evaluate the incidence of postoperative pleural effusions in those receiving placebo or colchicine. The latter was given for 1 month starting on the third postoperative day with 1 mg administered twice daily for the first day, followed by a twice-daily maintenance dose of 0.5 mg. The incidence of postoperative pleural effusions was 26% in the placebo group and 12% in the colchicine group, which translates into a relative risk reduction of 52%. This study provides, for the first time, evidence for the pharmacological prevention of postoperative effusions.

Emergency needle decompression is the initial intervention procedure for tension pneumothorax. Guidelines recommend the introduction of a standard 14-G cannula (4.5 cm) in the second anterior intercostal space in the midclavicular line. In a study of 20 unpreserved adult cadavers, only 57.5% of the needles inserted into the traditional second intercostal space, whether right or left, entered the chest cavity. This was due to the chest wall thickness exceeding the 5-cm needle length at this site. Alternatively, selecting the fifth intercostal space at the midaxillary line, where the chest wall was 1 cm thinner, resulted in 100% success. On the other hand, one retrospective study of 159 patients suffering from blunt chest trauma concluded just the opposite, namely, that the lateral approach is less likely to be successful than the anterior approach. The authors found that the median CT distance from the skin to the pleural surface was 4.5 cm at the second anterior intercostal space and 6.2 cm in the lateral fourth intercostal space. Until further studies clarify these seemingly contradictory results, it may be prudent to recommend either a lateral approach for needle placement or using a longer angiocatheter at the traditional site to relieve tension pneumothorax. Ultimately, the appropriate decision should be made on a case by case basis, taking into account the experience of the attending physician and the physical anatomy of the patient.

BRONCHOSCOPIC INTERVENTION AND IMAGING

Pyng Lee

Bronchoscopic intervention

Trisolini et al. sought to determine the performance characteristics and predictors of positive yield from transbronchial needle aspiration (TBNA) of peripheral pulmonary lesions. They found that TBNA was more likely to be the definitive diagnostic procedure for pulmonary nodules or masses that lacked the CT bronchus sign. Pulmonary lesions greater than 2 cm in diameter located in the middle lobe or found to be malignant were strong predictors of a positive TBNA result.

In one study, 40 lymph nodes (33 mediastinal and 7 hilar), 2 lung tumours and 3 mediastinal tumours from 33 patients were evaluated using 21-G and 22-G needles during endobronchial ultrasound (EBUS)-TBNA. Although there was no difference in diagnostic yield between

Respirology. Author manuscript; available in PMC 2014 June 23.
both sizes, the 21 G preserved the histological structure of the samples better. Navani et al. evaluated the utility of combining EBUS-TBNA with standard endobronchial and transbronchial biopsies in 40 patients who had enlarged mediastinal and hilar lymphadenopathies, and were suspected of having pulmonary sarcoidosis (stages I and II). The combined approach improved the diagnostic yield to 93%, and specimens obtained with EBUS-TBNA demonstrated noncaseating granulomas in 85% compared with 35% using standard bronchoscopic techniques.

’Spray as you go’ is one method of administering lidocaine for airway anaesthesia. An investigation sought to compare the efficacy of two anaesthetic techniques during EBUS: standard direct injection of lidocaine through the working channel and spray catheter aerosolization. The latter produced less coughing episodes in the first 30 min of bronchoscopy (primary end-point), and more successful TBNA than the former.

A prospective study compared EBUS performance following training on 15 simulator cases versus conventional training on 15–25 real patients. Incorporation of simulator training led to a more rapid acquisition of skills, yet a major limitation was reliance on the EBUS simulator for metric measurements. A case series illustrated that access to the lung, thyroid, mediastinal and thoracic vertebral lesions could be achieved using the EBUS scope via the esophagus, which represents an alternative approach for the diagnosis of thoracic diseases.

Kotecha et al. evaluated the long-term outcome of 16 patients with upper lobe predominant emphysema who had undergone unilateral and bilateral bronchoscopic lung volume reduction using the Emphasys one-way valve (Emphasys Medical Inc., Redwood City, CA, USA). Thirteen and 11 patients demonstrated better postprocedure forced expiratory volume in 1 s and diffusing capacity of carbon monoxide, respectively. However, only six retained improvements in lung function after 12 months of follow-up. Three patients required lung transplantation, whereas four died at 27, 29, 39 and 50 months of bronchoscopic lung volume reduction.

Three excellent reviews on pleural diseases were featured in 2011. The first by Matin and Gleeson detailed the benefits of performing pleural procedures guided by ultrasound (US) and CT. Incorporating US before thoracentesis aids not only in the selection of the appropriate puncture site but also in the avoidance of cardinal structures such as the heart, adherent lung, diaphragm, liver, spleen and mediastinum. US measures the thickness of the chest wall and helps to determine the needle length required to penetrate the pleural space. Success with US-guided thoracentesis can be as high as 97%, while the incidence of pneumothorax is around 3%. However, US may not reduce the incidence of intercostal vessel lacerations as vascular structures are often not identified sonographically, especially when they run medial to the angle of the rib. Advanced age and the performance of pleural procedures less than 7 cm from the spinous processes of thoracic vertebrae are risk factors for intercostal artery injury. Treatment for this complication is exploratory thoracotomy or, in poor surgical candidates, transcatheter arterial embolization using coils and polyvinyl alcohol particles. Radiofrequency ablation is a minimally invasive treatment for lung cancer in nonsurgical candidates and a palliative measure for intractable pain. Common complications following radiofrequency ablation include pneumothorax (4.5–61%), pleural
effusion (4–19%) and pleuritic chest pain, especially if more than two lesions are ablated or ablation time lasts for more than 2 h.\textsuperscript{71}

The second review revolved around controversies between closed needle biopsy and thoracoscopy.\textsuperscript{72} The authors proposed a diagnostic algorithm for the evaluation of exudative pleural effusion based on contrast-enhanced CT or US imaging of the pleura. Pleural-based masses are suited for US/CT-assisted transthoracic fine needle aspiration with rapid onsite evaluation.\textsuperscript{72} If no diagnostic material is obtained or rapid onsite evaluation is unavailable, an image-guided Trucut needle biopsy should be obtained.\textsuperscript{72} In the presence of pleural thickening (>10 mm) and/or nodularity, an image-guided pleural biopsy with either a Trucut or an Abrams needle is again the best choice.\textsuperscript{72} Finally, in the absence of pleural abnormalities, an image-guided pleural biopsy with an Abrams needle is recommended if TB is suspected, and a low supradiaphragmatic approach is suggested in all other cases, where metastases are more likely to occur.\textsuperscript{72}

The last review dealt with indwelling pleural catheters, which are gaining in popularity as a method of palliation for symptomatic malignant pleural effusions.\textsuperscript{73} They are especially useful in patients with trapped lung where the underlying lung is unable to expand following fluid drainage due to extensive visceral metastases, and therefore, pleurodesis is likely to fail.\textsuperscript{73} Indwelling pleural catheter allows the patient to be treated on an outpatient basis at the cost of long-term need for catheter drainage and care. Spontaneous pleurodesis occurs at 1–2 months in nearly half the patients treated with indwelling pleural catheter, which is in contrast with the 90% success rate achieved with talc.\textsuperscript{73} Studies directly comparing talc pleurodesis with IPC are eagerly awaited.

**Imaging**

Soler et al. sought to determine if SPECT lung perfusion scans were more accurate in quantifying the extent of vascular obstruction in 17 patients with chronic thromboembolic pulmonary hypertension undergoing pulmonary thromboendarterectomy than planar scans that are routinely used to detect perfusion defects.\textsuperscript{74} Clinicopathological evaluation revealed 241 obstructed and 99 unobstructed lung segments. Sensitivity for obstructed vascular segments was significantly better for SPECT than planar scans (63.5\% vs 42.7\%, \(P < 0.01\)), although there was no difference in specificity (62.6\% vs 76.8\%, \(P = 0.092\)). The study was limited by the small sample size and requires a larger trial for validation.

Chest CT for diagnosis and follow-up of patients with IPF can also be used to assess for coronary calcification, which is an indicator of underlying coronary artery disease. In one study, 57 patients with IPF had left heart catheterization that demonstrated significant coronary artery disease in 28\%, mild disease in 40\% and none in 32\%.\textsuperscript{75} The median time interval between left heart catheterization and CT was 39 days. The sensitivity and specificity of CT for moderate-to-severe coronary calcification, indicative of significant coronary artery disease, were 81\% and 85\%, respectively.

In a case-control study of 16 COPD patients matched against 15 normal subjects, submandibular videofluoroscopy was performed, where subjects swallowed graduated volumes of barium.\textsuperscript{76} Higher penetration (contrast entered airway and contact with vocal
folds)/aspiration (contrast passed glottis) scores were observed in COPD patients. Four out of 16 COPD patients had both penetration and aspiration versus 1/15 controls ($P = 0.07$). Penetration/aspiration risk was associated with higher respiratory rates, reduced hyoid elevation, postswallow larynx penetration and oxygen desaturation, suggesting that upper airway protective mechanisms could be flawed in COPD and may contribute to higher morbidity.

Despite the inability of sound to penetrate the air-filled lung, US is emerging as an important tool for the diagnosis of pneumonia, atelectasis, interstitial-alveolar syndrome, pulmonary embolism, pneumothorax and pleural effusion. The low sensitivity of CXR and the logistic difficulties of CT make this bedside radiation-free technique invaluable for the intensive care unit.\textsuperscript{77} US is reliable for the measurement of diaphragm and peripheral muscle thicknesses in both erect and recumbent positions.\textsuperscript{78}

In patients with pulmonary sarcoidosis, the retention index-standardized uptake value calculated from dual time point 18F-positron emission tomography with fluorodeoxyglucose delayed imaging was found to be a useful measure of persistent inflammation, as it correlated with the serum soluble IL-2 receptor.\textsuperscript{79} Higher retention index-standardized uptake values were observed in patients with increased or unchanged pulmonary lesions on CT and showed better diagnostic accuracy than early standardized uptake value or 67Ga uptake.

Minimally invasive imaging methods such as multiphoton microscopy can provide both cellular and extracellular structural details with sufficient specificity, sensitivity and spatial resolution. In the future, this imaging modality may potentially be used as a diagnostic tool for detecting lung cancer and in tissue engineering applications.\textsuperscript{80} Optical coherence tomography is another novel imaging technique that may provide more accurate quantification of airway remodelling in asthma and COPD, visualization of upper airways in patients with obstructive sleep apnoea in real time, detection of early precancerous lesions in smokers and selection of stents for those with tracheal obstruction.\textsuperscript{81}

The 18F-positron emission tomography with fluorodeoxyglucose imaging plays an important role for staging, prognosis, radiotherapy planning and assessing response to therapy in lung cancer. Deoxy-3-fluorothymidine positron emission tomography appears to be superior to fluorodeoxyglucose in assessing response to epidermal growth factor receptor inhibitors (e.g. erlotinib).\textsuperscript{82} Annexin V is a human protein that binds to phosphatidylserine exposed on the cell surface, thus enabling the identification of apoptotic cells at an early stage.\textsuperscript{82} A 99mTc-annexin V SPECT has potential utility in predicting tumour response to chemotherapy.\textsuperscript{82} Finally, immunopositron emission tomography, where monoclonal antibodies (e.g. cetuximab) are labelled with long-lived positron emitters, is in development for localizing epidermal growth factor receptor-expressing tumours.\textsuperscript{82}

**CONCLUSION**

The year 2011 was most notable in documenting that: (i) extremely low vitamin D levels are associated with increased mortality in patients with CAP, although a firm recommendation
on vitamin D supplementation should await further studies; (ii) IGRA is insufficiently accurate for either predicting the development of active TB or diagnosing tuberculous pleurisy; (iii) colchicine is safe and efficacious for the primary prevention of postoperative effusions after cardiac surgery; and (iv) metabolic positron emission tomography/CT imaging using specific molecular tracers appears promising for the diagnosis, staging and monitoring of pleuropulmonary tumours.

Acknowledgments

J.M.P. has received a research grant from the Instituto de Salud Carlos III (FIS 09/00199). M.I.R.’s time is partially covered by the NIH/NHLBI Grant K23HL096054.

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*Respirology*. Author manuscript; available in PMC 2014 June 23.

