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Year in Review 2017: Interventional Pulmonology, Lung Cancer, Pleural Disease and Respiratory Infections

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Key Words:

Bronchoscopy; EBUS (Endobronchial Ultrasound); ILD (Interstitial lung disease); Lung Cancer; Respiratory Infections

Abbreviations:

CAP, community-acquired pneumonia

CCL18, chemokine (C-C motif) ligand 18

CCDS, computerized clinical decision support

CPOE, computerized physician order entry

cTnT, high-sensitivity cardiac troponin

CURB-65, confusion, urea > 7 mmol/L, respiratory rate ≥ 30 breaths/min, low blood pressure (systolic < 90 mm Hg or diastolic ≤ 60 mm Hg) and age > 65 years

DL_{CO} diffusion capacity of carbon monoxide

DRP, drug-resistant pathogens

EBUS Endobronchial ultrasound

ESBL, extended-spectrum beta-lactamase

GAP index Gender, age and physiology index

GGNs ground glass nodules

GNB, gram-negative bacteria

HIT, health information technology

ILD Interstitial lung disease

IPF Idiopathic pulmonary fibrosis

MDR, multi-drug resistant

MRSA, methicillin-resistant *Staphylococcus aureus*

NSCLC Non-small cell lung cancer

PA Physical Activity

PSI, pneumonia severity index

SP-D, surfactant protein-D

TNM Tumour-node-metastasis

$VO2_{peak}$ peak oxygen consumption

6MWD 6-minute walk distance

1. INTRODUCTION

Interventional Pulmonology has for some time been established as an integral component of Respiratory Medicine, and this is reflected in its profile within *Respirology*. The growth of minimally invasive procedures in the space was initially driven by development of Endobronchial Ultrasound (EBUS), which has increasingly moved from being a procedure limited to high-volume academic centres, to becoming standard of care in centres across the region. Accuracy of Thoracic ultrasound for detection of pleural effusion, and to safely guide pleural drainage interventions has been long established but there has also been exponential growth in practice and research within this sub-speciality. Novel steps towards biologic therapies for pleural exudates and outcomes in mesothelioma are also presented. In addition there is a growing interest and literature base in physical activity interventions for patients with lung cancer as well as improvements in minimally invasive procedural approaches to assist with early diagnostics in thoracic oncology.

Respiratory infections remain a leading cause of morbidity and mortality worldwide despite recent advances with pathogen identification and antimicrobial management. Seasonal influenza, community-acquired pneumonia (CAP), nosocomial pneumonia and acute on chronic lower respiratory infections in patients with underlying lung disease continue to pose a challenge to clinicians globally. *Respirology* has added significant contributions to the field with recent work addressing CAP.

In this year in review, we focus on minimally invasive procedural and quality of life improvements and outcomes in the interventional pulmonary, pleural and lung cancer space as well as the seasonality of pathogens identified in community acquired pneumonia (CAP), the emergence of drug-resistant pathogens (DRPs), prognostic biomarkers of CAP severity and the impact of technology on patient outcomes with CAP.

2. INTERVENTIONAL PULMONOLOGY

Daniel Steinfort

Key Points

- Significant complications in EBUS-TBNA are extremely rare
- Simulation-based training in EBUS-TBNA consistently improves skills in EBUS-TBNA, and consistently discriminates on the basis of procedural expertise
- Elastography has a high sensitivity and NPV for detection of malignant involvement of LN during EBUS-TBNA
- High Diagnostic accuracy of thoracic ultrasound can be achieved in centres where procedures are performed by junior doctors with a high staff turnover
- Mortality in paediatric patients undergoing pneumonectomy is 4%, with significantly elevated risk for patients <3yo

2.1 Endobronchial Ultrasound

The exponential growth in practice and research within this sub-speciality was initially driven by development of Endobronchial Ultrasound (EBUS), which has increasingly moved from being a procedure limited to high-volume academic centres, to becoming standard of care in centres across the region. This is perhaps best illustrated by the systematic review meta-analysis published by Ali *et al* (1) examining diagnostic performance of radial EBUS which included 57 papers. Pleasingly, both diagnostic performance (diagnostic yield 70.6% (95% CI: 68-73.1%) and complication rates (chest tube insertion 0.2%) were consistent with an earlier meta-analysis (16 studies),(2) indicating performance consistent with initial reports from high-volume academic centres.

Similarly, an extensive review of published literature by Vaidya *et al* (3) examined the safety of EBUS-TBNA. Pleasingly, rates of significant complications are very low, with cumulative rate of clinical complications among 12,351 procedures reported at 1.02%

(commonest complications reported in Table 1). Twenty-five of 126 events were published as case reports (predominantly infection-related) suggesting overall incidence of complications is lower than identified by Vaidya et al. Pneumothorax is reported in just six patients, of over 10,000 solely undergoing EBUS-TBNA, and major haemorrhage is rarely reported. Respiratory failure appears extremely rare (0.07 to 0.3%). Just five deaths complicating EBUS-TBNA were identified. The commonest complication of EBUS-TBNA reported was damage to the bronchoscope and/or needle apparatus malfunction (over 40% of reported complications), highlighting the safety of EBUS-TBNA.

2.2. Simulation and competency assessment

The unequivocal success of EBUS has seen a new challenge arise in Interventional Pulmonology. Increased procedural numbers are, by necessity, increasingly performed outside high-volume academic centres. Simultaneously. increased trainee interest has increased competition for access to procedural training, and potentially resulted in more sporadic and unpredictable training in advanced bronchoscopic procedures.(4) This exposes the limitations of the apprenticeship model of bronchoscopic training, and the new challenge in IP is addressed in a number of studies published in *Respirology* in 2017 examining simulation-based training.

Sehgal *et al* present a systematic review of training for, and competency assessment in, performance of EBUS-TBNA.(5) The authors identified twenty-seven studies examining three facets of simulation-based training (simulator-based learning (n = 8), tools for assessing competence in EBUS-TBNA (n = 5) and threshold numbers needed to attain proficiency in EBUS-TBNA (n = 16)), which all noted consistently improved skills in EBUS-TBNA. Equally, simulator-based assessment of procedural competency consistently discriminated proceduralists on the basis of expertise, suggesting such tools can be used in regular assessment of progress of trainees. The authors also suggest that that training should be limited to the centres performing at least 150 EBUS-TBNA procedures every year.

There remain a number of complex questions regarding competence assessment

that are explored in an accompanying editorial.(6) It is recognized that no absolute threshold exists, but that a base volume number of procedures allows "way-points" to be inserted into training to add formal structure and periodic assessment, so that trainees can receive structured and repeated feedback. It would also allow use of the Step-by-Step structure increasingly favoured as part of formalized bronchoscopy teaching programs.(7, 8)

As revolutionary as EBUS-TBNA has been in mediastinal staging of NSCLC, there is still potential for novel tools to further improve minimally invasive mediastinal assessment of patients with NSCLC.(9) Elastography involves biomechanically characterizing a zone of tissue on the basis of its response to the application of mechanical stress. Korrungruang and Boonsarngsuk present, in the July issue of *Respirology*, one of the first reports regarding the ability of elastography to differentiate between benign and malignant LNs in patients undergoing EBUS.(10) They report an impressive 100% sensitivity and NPV for detection of LN metastases using both quantitative and qualitative elastographic measures. Potential future roles for elastography are explored in an accompanying editorial.(9)

2.3. Thoracic Ultrasound

Accuracy of Thoracic ultrasound for detection of pleural effusion, and to safely guide pleural drainage interventions has been long established.(11, 12) Hammerschlag *et al* reported that similar diagnostic accuracy and safety outcomes can be achieved in centres where procedures are performed by junior doctors with a high staff turnover.(13) The retrospective review was undertaken within an established consultant-led pleural unit, following a hospital-wide intervention to enhance adherence to pleural procedure guidelines.(14) Diagnostic accuracy for identification of pleural effusions was 98.3%, and ultrasound-guided centesis was successful in 230 of 235 patients (98%).(13) Complications were rare, with chest tube insertion required following just two of 235 centesis procedures (0.9%). Referral to Radiologist colleagues occurred in 10%, emphasizing the importance of collaboration with Radiology to ensure a highly functioning pleural service.

The same issues regarding procedural competence apply to Thoracic/Pleural procedures as apply to bronchoscopic procedures.(15) Consequently, the Thoracic Society of Australia and New Zealand (TSANZ) developed a position paper regarding competence in thoracic ultrasound.(16) The paper presents a pathway to assist pulmonologists achieve and demonstrate competence in thoracic ultrasound, and provides a regional standard for thoracic ultrasound training. The paper outlines four distinct components to attainment of competence, including formative and barrier assessments using validated assessment tools.(17)

2.4. Thoracic Surgery

Pneumonectomy is a high risk procedure when performed in adults, with 90-day mortality exceeding 10% in many series,(18-21) highlighting the risks associated with such extensive resection. Performance of pneumonectomy in children is far rarer than in adults, highlighted by the paucity of reports regarding post-operative outcomes in paediatric populations. Giubergia *et al* present the second-largest series of paediatric patients undergoing pneumonectomy ever published,(22) and make a major contribution to knowledge regarding the peri-operative outcomes in this group. They highlight the differing indications in this group (over 60% performed for post-infectious bronchiectasis), and identify for the first time elevated risk of mortality (OR 16.7) in patients aged <3yo. Mortality (4% at 1 month) and major morbidity rates (23%) were consistent with recent far smaller series.(23, 24)

3. LUNG CANCER

Brett Bade, Gerard Silvestri and Phan Tien Nguyen

Key Points

- Research investigating the impact of physical activity and lung cancer outcomes is an expanding field of interest
- GGNs require additional monitoring time to ensure stability
- Lymphatic invasion in NSCLC portends a poorer prognosis and prognostic factor for recurrence

3.1. Physical Activity

Interest is growing in physical activity (PA) interventions for patients with lung cancer (LC), and a variety of measurements are utilized. Edbrooke et al. systematically-reviewed PA outcome measures used in LC studies.(25) Performance-based and patient-reported measures of PA were included in patients with all stages of disease and during all phases of treatment. Thirty-four studies (n=4970 patients) were identified that used 21 different PA measures. Half of the studies used performance-based measures (i.e., accelerometers, pedometers, or indirect calorimetry), and 19 studies used patient-reported outcomes. Psychometric properties showed significant heterogeneity. Since patients often over-estimate their activity,(26) performance-based regimens are appealing. Until optimal PA measurements for patients with LC are identified, studies should collect both performance-based and patient-reported measurements.

Burtin and colleagues evaluated lower-limb strength and endurance in patients after LC surgery.(27) Maddocks and Granger's editorial recognizes that reduced exercise performance is common in LC, may be associated with worsened outcomes, and muscular weakness may not be identified by cardiorespiratory fitness testing.(28) Burtin's cross-sectional study included 64 patients and identified strong correlations between quadriceps strength, quadriceps endurance, and diffusion capacity of carbon monoxide (DL_{CO}) with peak oxygen consumption ($VO2_{peak}$), peak workload, and 6-minute walk distance (6MWD).(27) In multiple regression analysis, isometric quadriceps strength and DL_{CO} predicted $VO2_{peak}$; quadriceps endurance and DL_{CO} predicted peak workload. Quadriceps endurance capacity

(but not DL_{CO}) was related to 6MWD. Since lower-limb muscle testing correlated with existing exercise measures and may identify otherwise overlooked muscle weakness, the authors suggest that quadriceps strength testing be obtained by exercise programs. In the future, individualized "exercise profiles," may target a patient's needs at presentation.(27, 28)

3.2. Lung Nodules

Sato et al sought to better define the natural history of multiple ground glass nodules (GGNs).(29) Miller's editorial points out that GGNs are common, and management guidelines focus on the most suspicious nodule.(30) Defining GGNs as homogenous densities not obscuring the underlying vascular markings,(29) GGNs $\leq$ 3 cm, ground glass proportion $\geq$ 50%, and those observed for $\geq$ 6 months were included.(29) Retrospectively, 187 patients (78 with multiple GGNs) were identified. Growth (defined as increase in greatest dimension $\geq$ 2 mm, increased solid component $\geq$ 2 mm, or development of a solid component) was seen in 32% of patients with multiple GGNs at 36 months and 5.1% after 36 months. Growth incidence was not different between patients with single or multiple GGNs. Among patients with multiple GGNs and nodule growth, 41% had subsequent nodule growth. Sato's paper emphasizes the importance of longer monitoring for patients with GGNs, particularly patients with nodule growth or a history of LC.(30) Sato et al suggest 36 months as an optimal observation period for GGNs, though the updated Fleischner Society guidelines recommend following subsolid nodules for 5 years.(31)

3.3. *Peripheral radial EBUS and risk of infection*

Radial endobronchial ultrasound (EBUS) for the diagnosis of peripheral lesions is a well-established procedure in many centres worldwide with an overall low complication rate. Previous studies have shown that the risks of pneumothorax (32,33) and infection (34) are low. However, studies have not looked at imaging characteristics to ascertain risk factors for post procedural infections.

Fortin et al (35) analysed CT scans for lesion density and cavitation. Heterogeneity was based on subjective interpretation of CT images by the reviewing physician without the use of objective computer assisted analysis. There was no record of the type of EBUS images obtained to assist in confirming heterogeneity as established by previous groups (36,37). Despite an overall low complication rate in this cohort (4.0%), their results demonstrated an association between CT lesion heterogeneity and increased risk of infectious complications. This study will encourage centres to consider CT characteristics of lesions prior to biopsy and future data could be strengthened by adding in objective computer assisted analysis and record keeping of EBUS image type.

3.4. Idiopathic pulmonary fibrosis (IPF) exacerbations in non-small cell lung cancer (NSCLC)

It is known that patients with IPF have an increased risk of lung cancer (38,39). Many studies have also highlighted rates of acute exacerbation of interstitial lung disease (ILD) in patients with lung cancer and ILD undergoing chemotherapy as highlighted by Kobayashi et al. (40) in the introduction to their paper. They took a modified form of the previously reported gender, age and physiology (GAP) index (41) to evaluate the incidence of IPF exacerbations during lung cancer and the effect on prognosis. The modified gap (mGAP) index derived scores based on gender, age and %FVC and categorized patients into stage I (total score 0-3) and II (total score 4-5). The excluded parameter was %DLco based on the authors consideration that this test is difficult to perform for IPF patients.

In their cohort of 43 patients with IPF and lung cancer, Kobayashi et al. (40) found that with increasing mGAP score, there was an increase in acute exacerbations and a decrease in one-year survival. Due to the small numbers it was difficult to establish statistical significance between stage I and II patients. However, this study presents a model upon which future prospective studies could assess IPF patients with lung cancer and their exacerbation risks and overall survival.

3.5. Lung cancer prognosis

The 8th edition of the tumour-node-metastasis (TNM) staging system for lung cancer has yet to include lymphatic invasion in surgically resected NSCLC as a descriptive factor (42). Moon et al investigated the impact of lymphatic invasion on survival rates of stage IA (size < 3cm) tumours (43). All patients (473) included in their study had a minimum of a lobectomy, with sublobar or incomplete resections excluded. The definition of lymphatic invasion was defined as tumour cells seen in the lymphatic lumen.

Their results showed a strong association between lymphatic invasion and poorer prognosis, and that lymphatic invasion was the only prognostic factor for recurrence in tumours <3cm in size. However, as noted by the authors, the patients with lymphatic invasion had a lower incidence of adenocarcinoma and thus less low grade tumours compared to those in the other groups. Even accounting for tumour subtype in a multivariate anlaysis, lymphatic invasion still was an independent risk factor for recurrence.

These results should encourage future researchers to consider trials of adjuvant therapy in patient with evidence of lymphatic invasion. In turn, this may lead to future editions of the lung cancer staging system to include pathological lymphatic invasion as a prognostic factor.

4. RESPIRATORY INFECTIONS

Kristina Montemayor and Mark Jennings

Key Points:

- Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality worldwide
- The emergence of drug-resistant pathogens poses a challenge to clinicians and has been associated with poor clinical outcomes
- There has been a recent focus on biomarkers in CAP which have been associated with both short-term and long-term mortality.

4.1. Seasonality of Respiratory Infections

It is widely known that CAP is a leading cause of morbidity and mortality across the globe. There has been a paucity of evidence investigating the impact of seasonality and associated pathogen identification. To address this need, Cilloniz *et. Al*. (44) prospectively 14nfluenz a cohort of patients in a large university hospital in Barcelona, Spain. Authors found that the highest incidence of CAP occurred in the winter (34%), followed by spring (27%), autumn (23%) and summer (16%). Additionally, the authors investigated the seasonal distribution of microbiology etiology and found significant differences. *Streptococcus pneumoniae* was the most frequent pathogen identified, affecting 17% of patients, which supports previous reports on the prevalence of *Strep. Pneumoniae* in CAP. Following *Strep. Pneumoniae,* the most common pathogens included respiratory viruses (7%), polymicbrobial infections (6%), atypical pathogens (excluding *Legionella pneumophilia*) (3%), *Legionella pneumophilia* (2%), *Staphylococcus aureus* (1%) and *Haemophilus 14nfluenza* (1%). Notably, *Strep. Pneumoniae* was prevalent in winter (21%), followed by spring, summer, and autumn (17%, 14%, 13%, respectively) ($p< 0.001$). Influenza viruses had increased prevalence in autumn and winter (6% and 5%, respectively) followed by spring and summer (3% and 1%, respectively). *Legionella pneumophilia* was more common in autumn and summer (4% and 4%, respectively) followed by spring and winter (2% and 1%, respectively). In addition, the authors found that mortality differed between seasons ($p=0.02$) with rates being significantly higher in winter compared to spring (8.3% and 5.2%, respectively) ($p< 0.05$).

4.2. Drug Resistant Pathogens

Recent data has supported the emergence of Gram-negative bacteria (GNB) as pathogens associated with lower respiratory tract infections, CAP, and nosocomial infections. The adaptation of these pathogens has led to drug-resistant and multi-drug resistant (MDR) organisms, which are a threat to healthcare worldwide. These resistant infections have been associated with prolonged hospitalizations, higher healthcare costs, and increased mortality. Drug-resistant pathogens (DRPs) are typically described as organisms resistant to < 3 groups of antibiotics, while multi-drug resistant organisms are described as being resistant to ≥ 3

groups of antibiotics. (45) Studies have shown that the most common MDR GNB isolated in respiratory infections are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii,* and *Stenotrophomonas maltophilia*. (46)

The prevalence of resistant GNB in respiratory infections and their impact on clinical outcomes was recently reviewed by Rodrigo-Troyano and Sibila. (45) A review of the literature from the last 10 years revealed several key findings. The authors found that the prevalence of GNB was >50% in patients with nosocomial pneumonia, 20% in CAP and 10-50% in patients with underlying COPD and/or bronchiectasis. The prevalence of GNB varied based on geographical region, with a higher prevalence of GNB in patients with CAP, nosocomial pneumonia, and COPD in Asia. Specifically, *P. aeruginosa* and *K. pneumoniae* were the most common GNB isolated in European and Asian studies, respectively. Furthermore, MDR *P. aeruginosa* was more prevalent in Europe. Extended-spectrum beta-lactamase (ESBL) producing pathogens, *K. pneumoniae* and *E. coli*, were more prevalent in the Asia-Pacific region.

Infection with MDR-GNB has been associated with poor clinical outcomes, including a decline in lung function, increased exacerbations in patients with COPD and/or bronchiectasis, and increased mortality. Overall, the authors conclude that increasing prevalence of MDR-GNB and the limited availability of new, effective antibiotics presents a significant challenge to healthcare providers around the world.

Shindo and Hasegawa (47) published a review examining the regional differences in the prevalence of DRPs in patients with CAP. The pathogens most represented included methicillin-resistant *Staphylococcus aureus* (MRSA), MDR *P. aeruginosa* and ESBL-producing *Enterobacteriaceae*. The prevalence of DRPs was found to vary by region and country with a range of percentages of DRPs in culture-positive CAP being 7.2-36.0% in the Asia-Pacific region; 20.0-45.2% in North America; and 5.9-33.0% in Europe. Furthermore, risk factors for DRPs were evaluated. Prior antibiotic use and prior hospitalization were identified as common risk factors for DRPs among the included regions. Additional risk factors, such as

immunosuppression, diabetes mellitus, chronic kidney disease and prior colonization with DRPs, were identified but varied between regions. Based on the literature review, Shindo and Hasegawa formulated a treatment strategy incorporating risk factors for DRPs in patients with CAP. Briefly, non-broad spectrum antibiotics including a non-antipseudomonal beta-lactam +/- a macrolide should be considered for patients with low-risk for DRPs. Alternatively, in patients with high-risk for DRPs, broad-spectrum antibiotics including an antipseudomonal beta-lactam +/- macrolide with consideration of a fluoroquinolone or aminoglycoside in patients with severe disease should be considered. Those patients at risk for MRSA should be considered for Linezolid or Vancomycin while considering local factors.

4.3. Biomarkers: Predictors of Mortality

Several studies have highlighted the association between CAP and acute cardiac events including arrhythmias, heart failure, and myocardial infarction, leading to both short-term and long-term mortality. (48) Cardiac biomarkers in CAP have been studied, with a recent focus on high-sensitivity cardiac troponin T (cTnT). In a study by Vestjens *et al*., (49) the prognostic value of cTnT was further investigated. Individuals with an elevated or high cTnT tended to be older and have underlying co-morbidities including diabetes mellitus, chronic kidney disease and heart failure. After conducting a multivariate analysis, authors found that an elevated level of cTnT (> 14 ng/L) on admission was a significant predictor of both short (30 days) and long-term (1-4.1 years) mortality.

In addition to cardiac biomarkers, original data on lung-specific biomarkers was presented by Spoorenberg *et al*. (50) this past year. The prognostic value of YKL-40, chemokine (C-C motif) ligand 18, surfactant protein-D (SP-D) and CA 15-3 was studied. Authors concluded that YKL-40, CCL18 and SP-D were higher in patients with more severe pneumonia which was determined by a Pneumonia Severity Index (PSI) (51) score of 4-5 and CURB-65 (52)score >2 which suggests higher degrees of lung inflammation in this population. In addition, YKL-40, CCL18 and SP-D were found to be significant predictors of both short-term and long-term mortality in hospitalized patients with CAP. In an *Editorial,*

Faverio and Sibila (53) suggest that implementation of these biomarkers in clinical practice could provide improved accuracy regarding the severity of CAP in regards to pulmonary inflammation and risk stratification, while acknowledging certain limitations of a biomarker-guided approach to disease severity. Absence of universally accepted cut-off values, cost, and limited availability of obtaining these tests are noted as barriers to implementation in routine care.

4.4. On the Horizon

With recent technological advances, healthcare systems worldwide are incorporating health information technology (HIT) into routine clinical care. As pneumonia remains a leading cause of morbidity and mortality, several have postulated whether using HIT in this population could improve clinician adherence with recent guidelines as well as improve patient outcomes. Mecham *et al*. (54) published a recent review examining HIT in the management of CAP. Studies showed that interventions such as, automated pharmacy technology, computerized clinical decision support (CCDS) and computerized physician order entry (CPOE) improved guideline and CMS core measure adherence, though results have been inconsistent across studies. Future directions include improvement in usability, efficiency, and clinician engagement with HIT. Mecham and colleagues conclude that HIT should not replace physician decision-making, but rather serve as a tool that can be used to improve patient care and outcomes.

5. PLEURAL DISEASE

Majid Shafiq and Lonny Yarmus

Key Points:

- Growing evidence continues to expand the utility and cost efficacy of indwelling pleural catheters
- Efforts investigating biologic therapies for pleural disease continue to mature in animal models with future promise for human studies

5.1. Potential for biologic therapy in pleural exudates

Building on recent studies identifying the vital role of monocyte chemotactic protein-1 in pathogenesis of exudative pleural effusions, an interesting study demonstrated the significant therapeutic potential of MCP-1 pathway blockade in a mouse model of pleurisy. (55) This could potentially open the door to novel pharmacologic ways of dealing with pleural exudates.

5.2. Prognostic impact of socioeconomic status in malignant pleural mesothelioma

Multivariable analysis of data from the New South Wales Cancer Registry revealed that the more socioeconomically disadvantaged a malignant pleural mesothelioma patient is (by decreasing quintile on the "Index of Relative Socioeconomic Advantage and Disadvantage"), the worse their prognosis. Intriguingly, this association was not confounded by geographic distance from an oncological multidisciplinary team. (56) These findings are expected to lead to further investigation and potentially public health intervention within the context of the regional healthcare system.

5.3. Choosing between IPC and pleurodesis for malignant pleural effusion

Using utility and cost data directly from the landmark TIME2 trial, this study examined whether and when one of the two therapeutic alternatives was more cost-effective. The study results help bring additional clarity on this subject, with indwelling pleural catheter standing out as a more cost-effective for all patients with an estimated survival <14 weeks and chemical pleurodesis appearing to be more cost-effective for patients with longer estimated survival who would be expected to need two or more hours per week of nursing care should they undergo catheter placement. (57)

5.4. Malignant effusion – innocent bystander or willful accomplice in mesothelioma pathobiology?

Taking a leap from prior studies detecting plentiful growth factors in malignant pleural effusions, the effects of malignant pleural fluid sampled from mesothelioma patients on

mesothelioma cell lines was compared with those of saline controls. The malignant fluid positively affected growth, cell migration, and resistance to anti-neoplastic therapy. (58) The findings suggest that there may be a therapeutic argument for management of malignant effusions too rather than merely a palliative one.

5.5. To drain or not to drain a parapneumonic effusion

Given the advent of – and advances in – antimicrobial therapy, it is worth pondering over whether the dictum of "the sun should never set on a parapneumonic effusion" still holds weight. Findings from a retrospective study of 150 patients with a clinical diagnosis of parapneumonic effusion revealed that not only do many such patients never get chest tube drainage as part of real-world practice (including some with frank pus on thoracentesis), many of these remain clinically well with resolution of the infection using antibiotics alone. (59) A thought-provoking accompanying editorial draws parallels between this approach and the current standard of care for spontaneous bacterial peritonitis and abscesses of the lung and liver, which are often treated successfully with systemic therapy alone. (60) The evidence to date challenges old notions and calls for further research to enable more personalized decision-making for future patients.

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TABLE 1: Commonly reported complications of EBUS-TBNA

(Reproduced from Vaidya et al.[3], with permission)

Complication	Number of cases	Percentage (out of 275)
Hemorrhage	56	20%
Infection	54	19%
Anesthesia related	29	11%
Pneumothorax	11	4%
Respiratory failure	8	3%
EBUS bronchoscope damage	98	36%
EBUS-TBNA needle apparatus malfunction	19	7%
Total	**275**	**100%**

EBUS, endobronchial ultrasound; EBUS-TBNA, EBUS-guided transbronchial needle aspiration