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Review

ERS International Virtual Congress 2021: Highlights from the Turkish Thoracic Society Early Career Members

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Abstract

This review aimed to highlight some important points derived from the presentations of the European Respiratory Society 2021 Virtual International Congress by a committee formed by the Early Career Task Group of the Turkish Thoracic Society. We summarized a wide range of topics including current developments of respiratory diseases and provided an overview of important and striking topics of the congress. Our primary motivation was to give some up-to-date information and new developments discussed during congress especially for the pulmonologists who did not have a chance to follow the congress. This review also committed an opportunity to get an overview of the newest data in the diverse fields of respiratory medicine such as post-coronavirus disease 2019, some new interventional and technologic developments related to respiratory health, and new treatment strategies.

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INTRODUCTION

The committee formed by the Early Career Task Group of the Turkish Thoracic Society closely followed the European Respiratory Society (ERS) congresses and summarized the prominent issues from the perspective of young academics since 2020. European Respiratory Society Congress 2021 was held virtually because of the coronavirus disease 2019 (COVID-19) pandemic. The ERS congresses have always been a good opportunity to follow advances and new research areas in the pulmonology area. Virtual congresses have some advantages such as easier participation, higher number of physicians capable of following the sessions even after live sessions with recordings. But also, face-to-face interactions are always our first choice. Especially, young pulmonologists at the beginning of their careers may have a chance to meet the leading names, network with peers, as well as participate in their sessions through the congress.

This article reviewed carefully selected sessions to touch main topics including respiratory critical care, airway diseases, post-COVID lung diseases, pulmonary rehabilitation, interventional pulmonology, thoracic oncology, pulmonary vascular diseases, sleep disorders, interstitial lung diseases (ILDs), infectious diseases of the lung, and pediatric respiratory diseases at the ERS Congress 2021. The Early Career Task Group Members of the Turkish Thoracic Society (ECM-Early Career Members) closely followed the congress and summarized the selected sessions. We aimed to identify key points of the congress from the eyes of early career members. So, we thought that some pulmonologists who had no chance to participate in the congress could reach the highlights and updates altogether.

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Respiratory Critical Care

A wide variety of sessions about respiratory critical care were presented at the ERS Congress 2021. The first session was a guideline session that started with the presentation about the physiologic rationale for the use of a high-flow nasal cannula (HFNC) in acute respiratory failure and clinical pitfalls. High-flow nasal cannula is a ventilatory support device that consists of a flow meter giving current up to 60 L/min, an air-oxygen mixer, and an active humidifier. It improves gas exchange, decreases work of breathing and respiratory effort, and provides comfort with a nasal interface. It improves oxygenation and ventilation through 3 important mechanisms:[1-3] (1) by reducing respiratory effort with the flow, (2) by facilitating recruitment with the positive end-expiratory pressure effect provided by the high flow and improve oxygenation, and (3) by reducing the dead space by providing effective clearance of the tracer gas in the upper airways. Although the improvement of oxygenation, reduction of respiratory rate, and respiratory effort with helmet-noninvasive ventilation (NIV) in hypoxemic patients are better, delirium, accumulation of secretion, patient–ventilator asynchrony, patient self-inflicted lung injury (P-SILI) are some problems that arise due to the use of NIV.[4,5] The risk of P-SILI seems to be lower with HFNC.[4] During the pandemic, HFNC has been widely used to prevent pressure-related complications such as pneumothorax and pneumomediastinum in progressive disease in patients. Besides these positive effects, failure of HFNC might cause delayed intubation and worse clinical outcomes.[6]

The second session was a symposium about acute respiratory distress syndrome (ARDS). Acute respiratory distress syndrome is a very heterogeneous picture that develops due to many reasons. It is stated that categorization of the disease into subtypes may be useful in a systemic way. They determined 3 groups according to cytokine clusters, SOFA (Sequential Organ Failure Assessment) score, and gene expressions: (1) adaptive type is due to lymphocyte activation, (2) endothelial leak type is due to isolated respiratory deterioration and related with low serum albumin level, and (3) neutrophil-induced type is leading to multi-organ failure. Mechanically, there are different types of ARDS, their clinical course is different, and treatment must be individualized.

MAIN POINTS

- This study gives an overview of the newest data in the diverse fields of respiratory medicine.
- Post-coronavirus disease 2019 was attractive, and the management was discussed extensively.
- New technologies including algorithmic decision systems-based managements, electronic monitoring devices, health applications, machine learning algorithms, and artificial intelligence algorithms ultimately targeting the benefit of the patient were discussed accordingly in the new era.
- Personalized medicine and management of the diseases were offered.
- Respiratory medicine is one of the most related fields with environmental changes that were pointed out during congress.

A high PaO_2/FiO_2 ratio indicates an improvement in ARDS prognosis. Factors that increase mortality in ARDS and COVID-19 are low PaO_2/FiO_2, high peak pressure, low pH, low platelet count, low bicarbonate, and high ventilation rate.[7] Different treatment modalities are being developed for different patients with multimodal phenotypes.

The third session was a skills lab session about continuous positive airway pressure (CPAP), non-invasive ventilation, and mechanical ventilation. In the evaluation of a confirmed COVID-19 pneumonia patient, due to the poor prognosis in the clinical course, first CPAP with a helmet mask, then invasive mechanical ventilation, extracorporeal membrane oxygenation, and tracheostomy were performed to follow-up patient. With the prone position application, ventilation/perfusion compliance, reduction of transpulmonary pressure, improvement of right ventricular function, and removal of weight pressure from the lung are provided.[8] It is recommended to avoid Non-invasive mechanical ventilation (NIMV) in de novo respiratory failure and viral conditions. In addition, correct positioning of tracheostomy ensures less granulation tissue. Before the tracheostomy is opened, it should be checked that there is no obstruction in the upper airways by imaging. Tracheostomy should be performed after good ventilation settings and effective tracheal suction. In the next process, the time without mask should be increased gradually. Cough should be increased with high-frequency chest wall oscillation and intrapulmonary percussive ventilation. In the rehabilitation and physiotherapy approach after acute respiratory failure, there is an algorithm in which all patients are mobilized.[9] It is aimed to perform physiotherapy in order to ensure that patients wean from ventilation, with at least 50% maximal inspiratory pressure of respiratory muscle strength.

Airway Diseases

Recent clinical advances in airway diseases were also presented, and new treatment strategies were discussed during the congress. For the patients with asthma who are not controlled by high-dose inhaled corticosteroids (ICS), adding tiotropium reduces exacerbations and improves lung function.[12] Airflow obstruction was significantly reduced with the addition of tiotropium, as compared with the addition of placebo as a result of the study. At 24 weeks, the mean difference between the tiotropium group and the placebo group in the change in the adjusted peak forced expiratory volume in 1 second (FEV_1) from baseline in the first 3 hours after the administration of tiotropium was 86-154 mL higher significantly. As per Global Initiative for Asthma (GINA), in track 1 in step 4 high-dose ICS is not recommended. Adding long-acting muscarinic antagonists (LAMA) is recommended for this group. In track 2, there is an option for step 4, which is high-dose ICS. For step 5, add-on LAMA is recommended to medium or high-dose ICS-LABA. There is a question about the efficacy of triple therapy in one single inhaler. New GINA, in track 1, offers low-dose ICS-formoterol at every step as-needed reliever therapy. Also in track 2, step 1 recommends ICS whenever short-acting beta-agonists (SABA) are taken. Budesonide-formoterol is more effective than salbutamol both in terms of exacerbation preventation and asthma control even in mild intermittent asthma.[13]

Over the last 60 years, the inhaler technique of patients has not improved.[14] Suboptimal use of inhalers affects clinical efficacy. True inhalation technique increases lung deposition. ACT on Inhalers (Access, Choose, and Train) is an algorithm for tailoring the right inhalation device. It is based on asking the patient if he/she takes a slow and steady breath or a quick and deep breath. If the patient can perform slow and steady, we should consider a metered-dose inhaler, soft mist inhaler, or breath-actuated inhaler; if the patient can perform quick and deep breath, we should consider a dry powder inhaler. After choosing the device, we should teach the inhaler technique to the patients.[15]

Some updates about inhalers in the COVID-19 pandemic were also presented. Cleaning the inhaler mouthpiece, spacers, or peak flow and not sharing the inhalers with anyone has been suggested. We should prefer pMDI+spacers for SABA instead of aerosol-generating procedures like nebulizers.[16] There are smart inhalers, also referred to as e-inhalers, which have sensors, Bluetooth connection linked to an app. They may be the way forward. Most e-inhalers monitor dose usage and inhalation profile hence providing real-life feedback on inhalation technique.[17] These connected inhalers may help to solve inhaler technique problems, improve adherence, and provide early detection of exacerbations by monitoring inhalation volumes.

New treatments for chronic cough were also discussed. After excluding and treating obvious causes, refractory unexplained idiopathic chronic cough existed. There are studies about standard care for refractory chronic cough with low-dose morphine and gabapentin with substantial side effects and risk of abuse and addiction. New therapies are focusing on P2X3 receptors and pathways and block these receptors at the larynx and airways. P2X3 antagonism with Gefapixant provides a 75% reduction in cough; however, all the patients complained of taste disturbance.[18] Second-generation P2X3 pathway antagonists including sivopixant and eliapixant are more effective in trying to avoid taste adverse effects. Other mechanisms that may be effective in chronic cough are voltage-gated sodium (Na V) channel blockers and airway sensory nerve blockers. Nebulised lidocaine that blocks Na V channels is also effective.

Lung Health

Environmental changes have some causal relationships between adverse environmental exposures and respiratory outcomes. Strategies to decrease the burden of resulting respiratory diseases have been discussed during the congress. The interactions of poverty and environmental exposures as an additional "new" risk for respiratory health, new World Health Organization (WHO) Air Quality Guidelines (AQG), which are based on the expert evaluation of the latest scientific evidence on the health effects of air pollution, what potential implications the new WHO AQG will have on the air quality legislation in European Union, which is in the heart of European Green Deal, and how respiratory clinicians can use the new guideline in their clinical work were some important points of the presentation.

Sex and hormonal influence on respiratory diseases and if we need a gender-specific approach for health interventions were other questions discussed during the congress. Some hot points are as follows: females have smaller lungs and airways compared to males of the same height in adulthood, stronger immune response, and a higher incidence of autoimmune diseases.[19] Asthma is more prevalent in young boys, but after puberty, more severe and prevalent in women.[20] Estrogen seems to induce airway inflammation while androgens may reduce. Women have a greater susceptibility to chronic obstructive pulmonary diseases, more severe disease with earlier onset, a higher risk of hospitalization and death from respiratory failure and comorbidities, and a faster annual decline in FEV_1 even when they smoke fewer cigarettes.[21]

Societies identify certain roles, behaviors, activities, attributes, and opportunities for women, men, boys, girls, and people with non-binary identities.[22] Gender is a social determinant of inequality as well as being effective on its own. Gender norms and expectations influence exposure to unhealthy products, care-seeking, health protection patterns, and whether people smoke. Gender inequalities worsened during the COVID-19 pandemic. Globally, tobacco use is associated with gender, and exposure to passive smoking is more pronounced in females.[23]

Adolescents are experimenting with various types of nicotine-containing products. In the United States, 35% of high school students use ≥2 nicotine products at the same time. The most frequent ones are electronic cigarettes (EC) and small cigars.[24] Among 14-17 years olds, EC use ranges between 5% and 39%.[25] Nicotine and cannabis use can induce significant long-term deficits in the developing brain by interfering with the cholinergic regulatory processes.[26] Cannabis is a risk factor for bronchial asthma or the use of asthma medication even when known risk factors are taken into consideration.[27] It can also cause serious lung diseases with increasing years of use. There are behavioral interventions for smoking cessation in young people. Studies applying a single intervention can be grouped by theoretical basis: stage of change models, motivational interviewing, and social cognitive theory.[28] The most important strategy for countries is to protect children from starting smoking and/or vaping. Pricing and smoke-free policies combined with regulations that restrict youth access to nicotine products are the major strategies proven to prevent and reduce tobacco use for young people.[29-31]

New technologies in respiratory health are in the upcoming rising situation that is pointed out during the congress, and ethics, risks, and patients' perspectives were discussed. Algorithmic decision systems-based management has some risks such as digital divide differences, sample bias, systemic bias, automation bias (from the doctor), decrease in trust, pressure to meet objectives, continuous competition with others, threat to internal motivation, threat to autonomy, loss of accuracy over time, and threat to the environment. Electronic monitoring devices are considered the current gold standard, facilitate patient self-management, and provide intervention for compliance. The COVID-19 pandemic has led to a rapid increase in the use of home monitoring in patients with a variety of chronic respiratory conditions.[32] Real-time monitoring of heart rate, oxygen saturation, and respiratory rate is possible with wearable technologies. Sensors can detect

cough and other respiratory sounds.[33] Health applications can be used interactively for monitoring treatment use, symptom tracking, providing environmental data to help prevent triggers, and asthma education.[34] Recent technological advances offer an opportunity to improve the care of children with respiratory diseases.

Machine learning algorithms can process and assimilate data from large numbers of patients, far greater than the ones a single physician can manage and comprehend in an entire career.[35] Machine learning approaches are used for predicting asthma and chronic obstructive pulmonary disease (COPD) exacerbations.[36] The COVID-19 pandemic has brought about the widespread use of digital tools in all aspects of our lives. It should be strongly highlighted that the final decision and responsibility for all medical decisions remain in the hands of the treating physicians, supported by the computing power of the artificial intelligence algorithm, ultimately targeting the benefit of the patient.

Pulmonary Vascular Diseases

Optimal outpatient in acute pulmonary embolism (PE), treatment and prophylaxis applications in cancer-related venous thromboembolism (VTE), comparison between interventional treatments in PE and systemic treatments, imaging methods in pulmonary arterial hypertension risk classification, and some special situations were discussed during the congress. Cancer is a risk factor for VTE, but cancer screening is not routinely recommended after acute PE; screening is recommended in patients who cannot find a provoking cause for PE.[37] It has been shown that there can be an increased risk of VTE in patients who has anaplastic lymphoma kinase mutations in lung cancer (LC). It may be important for personalized risk assessment.[38] Real-life studies suggest that individualized therapy may have potential advantages.

The risk of recurrent embolism and bleeding in cancer-associated thrombosis (CAT) is higher than in non-cancer-related VTE.[39] Low-molecular-weight heparin comes to the fore in CAT treatment and prophylaxis, as it has a lower risk of a recurrent embolism when compared to vitamin K antagonist and the risk of bleeding may be higher with direct oral anticoagulants.[40] Thrombolysis increases the risk of major bleeding and stroke although it may prevent hemodynamic decompensation and reduce mortality in patients with medium-high risk PE.[41,42] Although half-dose thrombolytic treatment is effective and causes less bleeding complications, additional treatment and higher costs can be required.[43] Ultrasound-assisted thrombolysis (USAT) and ultrasound at the catheter tip can separate fibrin threads and allow better penetration of tissue plasminogen activator. But there was no difference in terms of results while comparing between USAT and catheter-directed thrombolysis, and USAT was more costly.[44] Catheter-directed thrombolysis can provide effective treatment with less bleeding risk in medium-high risk PE, and the superiority of USAT is still controversial.

There are 3 steps in the treatment of recurrent VTE: to confirm the diagnosis of recurrent VTE, to determine the cause, and to change/escalate therapy. The residual disease is frequent. Over 50% of patients have residual deep vein thrombosis (DVT) or PE imaging abnormalities >6 months after treatment.[45-47] This leads to many false-positive results. We must compare current imaging to past imaging if we suspected acute recurrent VTE. Risk assessment for pulmonary arterial hypertension is also important in the follow-up of PE. Risk assessment can be performed without invasive methods and may facilitate routine follow-up.[48] Risk assessment based on cardiac magnetic resonance imaging was found to be equivalent to right heart catheterization in the 1-year follow-up.[49]

Pediatric Respiratory Diseases

Bronchiectasis, a chronic lung disorder, is an umbrella term used for a clinical syndrome of recurrent or persistent wet cough, airway infection/inflammation, and abnormal bronchial dilatation on chest computed tomography (CT) scan. Bronchiectasis may be reversible over time with effective treatment, therefore, early recognition is important.[50,51] Bronchiectasis is not considered rare but is an overlooked lung pathology with high economic cost and poor quality-of-life (QoL) in children/adolescents and their parents.[52] However, all likely etiologies involve airway infection causing inflammation, impaired mucociliary clearance, and airway destruction.[53] High-resolution multidetector chest CT with high-resolution CT (HRCT) is used instead of conventional HRCT to diagnose bronchiectasis in children/adolescents.[54] Respiratory exacerbation is defined when a child/adolescent has increased respiratory symptoms (predominantly increased cough ± increased sputum quantity and/or purulence) for longer than 3 days. When dyspnea and/or hypoxia is accompanied, it should be considered a severe exacerbation. Regular airway clearance techniques are recommended; however, recombinant-human DNAse, bromhexine, inhaled mannitol, and hypertonic saline are not recommended for routine usage.[50,55] Anti-asthma agents should not be used routinely. During an acute respiratory exacerbation, a systemic course of an appropriate antibiotic is used for 14 days. For patients who have recurrent exacerbations, treatment with long-term macrolide antibiotics has been shown to reduce exacerbations.[56,57] Surgery should be performed rarely and only in the specialized center in patients with no recurrent localized disease.[58] Parents of children/adolescents with bronchiectasis must be informed about the disorder and get an active role in the disease management.

Asthma is the most common chronic respiratory disorder that affects approximately 9.4% of children in the European Union.[59] International asthma guidelines and individual country guidelines are inconsistent, which results in confusion in the diagnosis of asthma. There is no single gold standard test to confirm the diagnosis. The Task Force (TF) of the ERS guidelines for diagnosing asthma in children aged 5-16 years is not recommended as it is diagnosing asthma based on symptoms alone. The TF recommended measuring fractional exhaled nitric oxide (FeNO), performing spirometry, using bronchodilator reversibility test in children with abnormal spirometry, and doing a direct bronchial challenge test as a part of the diagnostic work-up of children aged 5-16 years with suspected asthma; however, it is not recommended to use skin prick test, serum total and specific IgE tests, peak expiratory flow rate variability testing as a primary objective.[60,61]

Severe asthma remains uncontrolled despite high-dose ICS-LABA treatment of contributory factors or needs high-dose

ICS-LABA to prevent becoming uncontrolled. T2-high inflammation of the airway means high production of IL4, IL13, and IL5. Current biologics for severe T2-high asthma: Anti-IgE: Omalizumab, it is available for > 6 years; anti-IL5/anti-IL5R: mepolizumab, age > 6 years; benralizumab, age > 12 years; reslizumab, age > 18 years; anti-IL4R α blocking IL4+IL13 receptor: dupilumab, age ≥ 12 years. Omalizumab has additional effects on viral asthma exacerbation.[62] Treatment evaluation is recommended after 4-6 months. All biologics reduced exacerbation nearly to 50%. In the future, new biologics are expected to be developed with alarmins. Alarmins are proteins coming from epithelial cell layers with different triggers like pollution and smoking. Auto-alarmins are IL-33 and IL-25, which have broad effects. Before starting biological treatment be convinced that patients had severe asthma and T2-high inflammation has been demonstrated by high eosinophils, FeNO, or IgE. The transition of care from childhood to adulthood is important. New non-invasive biomarkers are needed.

Treating asthma by endotypes may be more successful. Prednisolone is very useful in the treatment of chronic asthma, provided the sputum contains a large number of eosinophils, and in the absence of eosinophilic sputum, it is not effective enough.[63] In preschool wheeze, ERS TF defines 2 patterns: episodic (viral) wheeze (EVW) and multiple-trigger wheeze (MTW). These 2 are in 2 different mechanisms. Montelukast can be started when symptoms of viral cold develop for EVW, and maintenance treatment with ICS should be started for MTW as trial therapy and should be stopped when there are no benefits.[64] However, phenotypes can switch over time.[65] Four pathophysiological clusters (endotypes) were identified in recurrent severe preschool wheeze; atopic, non-atopic with non-infection rate and high ICS use, non-atopic with high infection rates, non-atopic with low infection rate, and no ICS.[66] In young children with asthma, biomarkers may be useful for guiding treatment selection. Sensitized patients and patients with eosinophilia (≥300 cells/μL) have good responses to ICS.[67]

Stridor is a symptom of airway narrowing, whether it is purely inspiratory or purely expiratory (wheezing) or a group "in-between" characterized with different breathing sounds and complex airway anomalies. Physicians usually evaluate upper airways to assess the nasal cavity for congestion, atresia, adenoids, tonsils, pharyngeal collapse, vocal cord movement, obstruction, reflux disease, laryngomalacia, fistula, and cleft with the airway endoscopy. Severe laryngomalacia and laryngeal cleft are often accompanied by swallowing issues and airway breathing problems and may need swallowing therapy or surgery. Laryngotracheal stenosis is related to multiple comorbidities and a high degree of pulmonary disease. For complex airway cases, upper airway and pulmonology follow-up program is suggested, and after the surgery, pulmonary function tests should be performed for follow-up.

Lung involvement in sickle cell disease (SCD) includes acute chest syndrome, asthma, recurrent wheezing, pulmonary fibrosis and restrictive lung disease, hypoxemia, sickle chronic lung disease, sleep-disordered breathing, and pulmonary hypertension. Pulmonary complications are the major cause of morbidity and premature death. Recurrent acute chest syndrome episodes may lead to sickle cell chronic lung disease, and lung function deteriorates with the increasing age. Acute chest syndrome which starts with the vaso-occlusive crisis has a high mortality rate if there is a delay in diagnosis, and treatment is divided into supportive care (oxygenation, prevention of atelectasis, intravenous fluids, analgesia) and modifiable factors (bronchodilators, transfusion, respiratory infection). Airway obstruction and bronchial hyperreactivity are more prevalent in patients with SCD and may be independent of asthma. Obstructive lung function abnormalities also reflect pulmonary vascular abnormalities. Hypoxemia should also be promptly treated as it triggers red cell sickling and acute or chronic complications. Hydroxyurea treatment and long-term home oxygen therapy are recommended in these cases. Hematopoietic stem cell transplantation and gene therapy are curative in SCD.[68,69]

Interventional Pulmonology

Interventional pulmonology session described new diagnostic and therapeutic techniques and procedural aspects with detailed videos. Robotic bronchoscopy combined with needle-based confocal laser endomicroscopy for peripheral LC enables real-time microscopic imaging of cells and is a helpful tool for the diagnosis of LC in the absence of endobronchial abnormalities. External sheet enables the fiberoptic bronchoscope to move safely to peripheral lesions, and endomicroscopy enables visualizing malignant cells. The accuracy of this technique is between 89% and 95%.[70]

Endobronchial valves for lung emphysema help reduce hyperinflation in COPD patients resulting in better FEV1 % predicted, 6-minute walking test, and quality of life. Placing endobronchial valves is a relatively safe procedure, and reported complications are as follows: pneumothorax 10-33%, expectoration of valves 5%, and granulation tissue formation 10%.[71]

Target lung denervation for COPD targets parasympathetic nerves and aims to reduce airway hyper-responsiveness, mucus secretion, and inflammation. With this technique, the epithelium of the bronchus is protected, and controlled radiofrequency energy is delivered. Results from AIRFLOW 1 and 2 indicate that moderate or severe exacerbation rates are reduced in treated patients.[72,73]

Cryobiopsy in ILDs has a similar diagnostic yield with surgical sampling in ILDs but has advantages on length of stay in hospital and complications.[74-76] Sampling should be done from 2 separate sites and patients with increased pneumothorax risk should be monitored carefully. New innovative guidance systems like radial ultrasound, CT-fluoroscopy, and navigation systems are described within this session.

First-line treatment for localized LC is surgery, but medical comorbidities prevent surgery in 10-25% of the patients. Percutaneous radiofrequency ablation of LC was described in 2004 and was recommended in ACCP/STS (American College of Chest Chest Physicians/Society of Thoracic Surgeons) consensus 2012. However, bronchoscopic radiofrequency ablation is relatively very new. It was shown that it is a safe and feasible option, appears to achieve well-targeted and complete ablation zones.[77] The efficacy of this procedure is still being investigated.

Rheoplasty in chronic bronchitis aims to control symptoms in chronic bronchitis by reducing goblet cells and goblet cell hyperplasia.[78] Recent studies performed to the fifth- to seventh-generation of airways to carina showed improvement in CAT and St. George's Respiratory Questionnaire (SGRQ) scores.

The first use of shape-sensing robotic bronchoscopy system for solitary pulmonary nodules smaller than 2 cm in 2019 showed safety with 96.6% target nodule reach and sampling.[79] Another study presented in congress showed biopsy completion in 98% of cases.

Endobronchial ultrasound combined with endoscopic ultrasound through esophagus for a complete endoscopic staging of LC increases diagnostic yield and is currently considered as an optimal non-surgical mediastinal staging tool for LC.[80,81]

Interstitial Lung Diseases

According to the official ATS/ERS/JRS/ALAT Guideline about idiopathic pulmonary fibrosis,[82] there are 4 terms: usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, and alternative diagnosis. Radiologically, subpleural (anterior in upper lobes and posterior in lower lobes) and basal dominant honeycombing demonstrates UIP. If other features are similar, but there is no honeycombing, the term probable UIP is eligible. It has been emphasized that findings can be asymmetric in these 2 patterns. Indeterminate for UIP category includes patients with subpleural and basal predominant subtle reticulation and features and/or distribution of lung fibrosis that do not suggest any specific etiology. In addition, it has been mentioned that the positive predictive value of HRCT diagnosis of UIP pattern for pathological UIP pattern is 90-100%. However, diagnosis of UIP patterns is not easy and needs a multidisciplinary evaluation.

It was shown that there are persistent functional alterations and persistent HRCT opacities even 12 months after severe COVID-19 pneumonia.[83] Risk factors for this severe persistent condition are male, older age, increased body mass index, the severity of the initial injury, traction bronchiectasis at discharge, and some blood markers. KL-6, leucocyte telomere length, cytokine cocktail, 50-gene signature, fibrocyte ratio at the time of diagnosis, and 9 weeks evaluation of MMP7, HGF, LCN2 are determined risky blood markers.[83-86] LCN-2 is associated with epithelial injury, MMP-7 is related to epithelial injury and fibrosis, HGF is a marker of epithelial repair.[87] It has been shown that nintedanib does not affect survival but provides shorter ventilation duration and increases ventilator-free days.[88]

During the session, early post-COVID ILD was discussed, and the features of the early auto-inflammatory phenotype were mentioned. Histopathologic findings are consistent with lymphoid inflammation and organizing pneumonia in most cases, and patients are responsive to corticosteroid treatment.[89,90] The mechanism of this period is related to the immuno-inflammatory cascade, invasion of the epithelial and endothelial components. Hence, immunomodulation and anti-thromboembolism prophylaxis has been offered during the presentation.[91] There are two-hit hypotheses, genetic predisposition or pre-existing ILD and pro-fibrotic cascade. There is an indication to treat with anti-fibrotic drugs only in cases of disease progression despite immunomodulation, and cases are clinically reclassified as IPF (idiopathic pulmonary fibrosis) or progressive fibrotic ILDs.[82,92,93] Take-home messages of this presentation were about the percentages of post-COVID ILD, unknown clinical significance, different phenotypes, possible underlying auto-inflammatory background, and importance of immunomodulatory therapies.

Another session was about LC associated with fibrotic ILD (fILD). Interstitial lung diseases are a variety of parenchymal lung diseases that have various origins and causes, related either to inflammation or to fibrosis. Associated comorbidities highly influence morbidity and mortality, and one of them is LC. When the IPF group and non-IPF ILD group were compared, the incidence of LC was found higher in the IPF group, all suggesting that fILD has increased risk for LC development.[94] Risk factors for cancer in fILD have been identified in different studies as older age at diagnosis, smoking, emphysema, male gender, and rapid annual decline in forced vital capacity. So, it is suggested that there might be a connection between the fibrotic process and carcinogenesis. Squamous cell carcinoma is the most frequently encountered cancer in fILDs, whereas it is adenocarcinoma in the general population. Cancer survival is worse in patients with fILD. Cancer stage, treatment options like surgery, chemotherapy, and radiotherapy cause IPF exacerbations thus increasing disease severity and mortality.[94]

Some molecular biology markers indicating dysplasia in IPF are also observed in lung carcinomas and invasive tumors of other parts of the body, such as the BRAF (B-Raf proto-oncogene) pathway.[95] With these findings, IPF could be considered not mainly a fibrotic disease but also a bronchiolar epithelial proliferation that the lung parenchyma is rebuilt by basal bronchiolar cells. The honeycombing change may be considered a pre-neoplastic lesion.

All treatment options for LC have a major risk of triggering acute IPF exacerbations. But with a major anti-fibrotic protective effect, more effective cancer therapy in LC-fILD can be achieved, and this strategy could improve survival in LC-fILD cases. There is no human data on anti-fibrotic therapy reducing the risk of radiation pneumonitis, and there is uncertainty on chemotherapy for lung cancer in IPF because of the pulmonary toxicity.

Sleep Disorders

It is not an appropriate approach to evaluate obstructive sleep apnea (OSA) cases with different phenotypes with the same diagnostic technique and to evaluate them with the same treatment method.[96] The clustering approach is important for the treatment of homogeneous groups defined for personalized medicine. Obstructive sleep apnea cases are clustered according to their characteristics such as age, degree of obesity, the severity of sleep apnea, sleepiness, smoking habit, and the burden of comorbidities is evaluated. Phenotypes are associated with cardiometabolic risk and treatment response. Apnea–hypopnea index (AHI) was defined at thresholds to classify the disease severity of OSA,[97] and AHI has no correlation with Patient and Parent Epworth Sleepiness Score,[98] health-related QoL, and also objective sleepiness on Multiple Sleep Latency Test (MSLT).[99]

Mild OSA is highly prevalent with 25% of the general population having AHI 5-15.[100] Symptom profile especially sleepiness has no association with sleep disorder breathing severity measured by AHI.[101] Continuous positive airway pressure benefits sleepiness and QoL but there is no convincing evidence that active therapy of mild OSA affects comorbidities.[102] Pathophysiology of cardiometabolic complications of OSA is still incompletely understood, and intermittent hypoxia is likely the key factor. It has a unique pattern rather than other chronic lung and cardiac diseases and activates proinflammatory pathways.[103-105] Basal, minimal SpO_2, and percentage of sleep under SpO_2 < 90% Total Sleep Time (TST), and oxygen desaturation index (ODI) are used for predicting intermittent hypoxia. The hypoxic burden is a new marker for intermittent hypoxia calculated by the total area under the respiratory curve for individual apnea and hypopnea and divided into total sleep time.[106] Hypoxic burden predicts cardiovascular mortality better than AHI and ODI.[107]

Physiological sleepiness is defined by a biological drive to sleep which can be measured by MSLT, pupillography, and electroencephalography. Manifest sleepiness that involves behavioral signs of sleepiness, performance deficit on psychomotor or cognitive tasks can be measured by maintenance of wakefulness test, vigilance, and performance test. Introspective sleepiness which is how the individual self-assesses sleepiness can be measured by sleepiness scoring systems.[108] Excessive sleepiness at the time of OSA diagnosis may not resolve after CPAP treatment. Residual sleepiness in sleep apnea patients treated with CPAP therapy was more prevalent in patients with moderate OSA than in patients with severe OSA and was not associated with diabetes or cardiovascular disease. Residual sleepiness was more prevalent in low compliance groups. Patients with residual sleepiness should be evaluated with other possible causes of excessive daytime sleepiness (EDS) (obesity, diabetes, mood disorders, drug/alcohol use, anemia, hypothyroidism, neurologic disorders). Residual EDS should be assessed at least after 3 months of CPAP treatment, and other causes of EDS excluded, before starting drug therapy.

The P4 medicine (prediction, prevention, personalization, and participation) is an evolving approach to personalized medicine for OSA. Prediction determines whether patients with OSA will benefit from treatment and respond to therapy. Prevention is divided into primary, secondary, and tertiary. Personalization includes diagnosis and management of OSA. Participation contains patient-centered outcomes. To approach OSA with an integrative approach, subgroups should be well defined.[109] The clinical clusters were provided an opportunity for a more personalized approach to the management of OSA.[110]

Telemedicine can be used in diagnosis, consultation phases and CPAP education, titration, and follow-up period for patients with sleep breathing disorders (SBD).[111] Despite potential clinical interest, literature remains scarce because of the complexity of the procedure. In the upcoming years, new measurement indexes other than the AHI will be important, and miniaturized and wearable devices will become part of the SBD diagnosis.[112,113] In a global view of integrating management for CPAP patients, telemonitoring by PAP devices and smartphone applications for coaching education and engagement are going to take an important place in improving not only adherence but also the quality of care.[114]

Thoracic Oncology

Repair and regeneration in chronic lung disease and lung cancer sessions were presented, and it has been mentioned that lung cancer is a syndrome, not a disease. Various mutations are seen in lung cancer subtypes, most commonly in adenocarcinoma. Environmental, hereditary, and replicative factors are effective in mutations.[115] KRAS, TP53, and some mutation signatures are more common in smokers with lung adenocarcinoma (LA).[116] In mouse models of LA developed by tobacco and chemical exposure, it has been shown that club cells in the airway are also involved in the tumor, in addition to alveolar cells. Again, KRAS mutations were observed in club cells in mice, and it was observed that these cells were the origin of lung cancer with tobacco exposure.[117] While club cells, bronchoalveolar stem cells, and alveolar type 2 cells are involved in transgenetic LA models, club cells are primarily involved in those originating from tobacco exposure. Affected by environmental exposure and genetic mutations, these cells can also be targeted therapeutically.

The extracellular matrix (ECM) consists of various connective tissue elements, mainly collagen, elastin, and fibronectin. Lung fibrosis is characterized by increased deposition in the ECM and changes in cell remodeling and attachment. Proteins associated with ECM-derived pathological gene expressions were more produced in fibroblasts in IPF.[118] Extracellular matrix content also varies in asthmatic patients. It has been shown that fibulin-1 expression is increased in these patients and is associated with exaggerated proliferation.[119] Fibulin-1 regulates TGF-ß activity by binding to LTBP-1. Especially the absence of fibulin-1C is protective against chronic asthma and pulmonary fibrosis.[120]

Currently, 4000 lung transplantations are performed each year. However, due to the difficulties in finding donors, there is a need to explore different options. Human tissues can be produced with the 3D bioprinting method; however, there is a need for the development of bioinks for more advanced and complex structures. Reinforced with ECM derived from decellularized tissue is a bioink developed for the production of small airways. It promotes cell differentiation and minimizes tissue rejection. Studies have shown that it is biocompatible in T-cell-immunodeficient and -immunocompetent mice. It also supports vascularization in the full graft.[121] It is promising for the future of lung transplantation.

Repair damage is one of the important factors in the development of COPD. Regenerative approaches play an important role in the course of diseases. Mesenchymal stem/stromal cells regulate properties such as immunomodulation, tissue repair, and antimicrobial activity in lung tissue with the factors they secrete, and it has been reported that they may be useful in the treatment of emphysema.[122] Stimulating lung progenitor cells supports alveolar differentiation and provides tissue repair.[123]

Respiratory Infections

Community-acquired pneumonia (CAP) in the post-COVID era and updates on pneumonia including critical analysis

of the new guidelines and new diagnostic and therapeutic options in light of recent experience with COVID-19 pneumonia were discussed in the session. The microbiologic etiology of CAP in the adult population in the United States and Europe remains undetected in nearly 2/3 of patients. *Streptococcus pneumoniae* constitutes the majority of detectable pathogens. Difficulties in obtaining samples from the lower respiratory tract, the effect of antibiotic use before sample collection, and low sensitivity of some diagnostic tests are some possible reasons that might explain the difficulties in identifying the etiology of pneumonia.[124]

Prevalence of multidrug-resistant (MDR) organisms in CAP diversifies by region and by pathogens, 3% MRSA-CAP,[125] 1% MDR *Pseudomonas aureginosa* CAP.[126] Inappropriate use of antibiotic therapy contributes to the development of drug resistance, excessive costs, and increased mortality.

The antibacterial pipeline is dominated by derivatives of established classes and most of the display-limited innovation. Nonetheless, new antibiotics including ceftaroline and ceftobiprole, which are from the cephalosporin group; solithromycin from the macrolide group; nemonaxacin and delafloxacin from quinolone group, lastly omedacycline and lefamulinare are currently under development to treat CAP.[127]

The mortality rate due to CAP is highly significant. Depending on the patients who are in septic shock or need IMV, mortality is highest up to 40%.[128] There are several scoring systems that assess the severity of pneumonia-diagnosed patients. According to the study of Fan,[129] comparing the scoring systems like A-DROP, CURB-65, PSI, SMART-CAP, NEWS2 CRB-65, and Q-SOFA in COVID-19 patients, it is found that A-DROP, developed by the Japanese Society of Pneumology, has the best performance.

Bacterial coinfection is less common in COVID-19 when compared with influenza (33%).[130] Along with COVID-19, increased use of HFNO (High-flow nasal oxygen) due to having more ventilator-free days and a decrease in length of stay in ICU was observed.[131] In a study comparing NIMV and HFNO, it was shown that the intubation and mortality rates were lower in the HFNO subgroup.[132] Moreover, intubations rates are reduced with the help of awake prone positioning.

Along with the H1N1 pandemic, real-time diagnosis has also revealed the presence of viral pathogens. The treatment of viral infections varies and depends on the causative agents. Specific diagnostic tools are required to commence the optimal treatment for patients. With the COVID-19 pandemic, specific analytic patterns including inflammation, superinfection, and thrombosis are detected, which lead to a more personalized treatment strategy.[133]

CONCLUSION

Early Career Members of the Turkish Thoracic Society have closely followed the congress and prepared messages that collectively constituted this paper. One of the rising points during the congress is the importance of personalized therapy which is important to manage diseases. Another point is that, after the COVID-19 pandemic, the application of telemedicine increases in both clinical practice and research providing an opportunity to improve responses to medications, individualize treatment and monitoring, and lower costs. Also, with this paper prepared by the early career members, notes provide up-to-date information and may lead to new scientific research or developments.

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