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LETTER TO THE EDITOR

GUIDELINES

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Differences in right ventricular dysfunction in patients with idiopathic pulmonary hypertension versus secondary pulmonary hypertension

Abstract

Introduction: Right ventricular (RV) function in the setting of pulmonary hypertension based on different etiologies has not been well studied. In this study, we evaluated the RV function in patients with idiopathic pulmonary hypertension (IPH) *versus* secondary pulmonary hypertension (SPH) due to congestive heart failure.

Material and method: Forty-five patients with pulmonary hypertension and New York Heart Association (NYHA) functional class II or III were enrolled. Of these, 22 were diagnosed with IPH and 23 with SPH. Echocardiographic data, including Doppler and Doppler based strain, were assessed according to the American Society of Echocardiography (ASE) guidelines for detailed evaluation of RV function in these two groups.

Results: Mean PAP was 60 $\pm$ 14.5 mm Hg in patients with IPH *versus* 43 $\pm$ 11.5 mm Hg in patients with SPH ($p = 0.001$). Considering conventional indexes of RV function, only Sm and dp/dt were significantly better in the first group compared with the second group (p-value for Sm $= 0.042$ and for dp/dt $= 0.039$). RV end diastolic dimension was significantly higher in the IPH group ($p = 0.013$). Using deformation indexes of RV function, the basal and mid portion of RV free wall strain and basal RV strain rates were significantly worse in the chronic systolic heart failure (PH-HF) group in comparison to the IPH group ($p < 0.001$ in basal RV strain, $p = 0.034$ in mid RV strain and $p = 0.046$ in basal RV strain rate respectively).

Conclusion: IPH has less impact on RV function in comparison to PH-HF. Considering both entities are in the category of RV pressure overload, we conclude that the etiology of pulmonary hypertension also plays an important role in RV function in addition to pressure overload.

Key words: pulmonary artery hypertension, pulmonary hypertension, right ventricular function, Doppler echocardiography, myocardial strain

Adv Respir Med. 2020; 88: 1–5

Introduction

The right ventricle can suffer from pressure overload due to pulmonary valve stenosis or from chronic pulmonary hypertension due to any cause. Initially, pressure overload will lead to myocardial hypertrophy and later, to progressive contractile dysfunction. Chamber dilatation will occur as a compensatory mechanism in order to maintain stroke volume despite reduced fractional shortening. As right ventricular function declines, right ventricular failure can occur. This failure manifests

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as increasing filling pressures, diastolic dysfunction, and reduced cardiac output. This can lead to annular dilatation leading to tricuspid regurgitation [1, 2]. Therefore, the right ventricular function and size are not only indicators of the severity and chronicity of pulmonary hypertension, but can also lead to symptoms and reduced long term survival. Right ventricular function is one of the most important factors for long term survival in patients with pulmonary arterial hypertension [3]. In general, the RV adjusts better to volume overload than to pressure overload. In atrial septal defect (ASD) and significant tricuspid regurgitation, the RV may tolerate volume overload much better without a significant decrease in RV systolic function.

Two examples of chronic pressure overload that are well tolerated by the RV include Eisenmenger syndrome and congenital pulmonary stenosis. Some studies have previously evaluated the RV function in RV volume and RV pressure overloads [4]. It has been shown that RV function is better preserved in pulmonary stenosis than in pulmonary hypertension [5], but a comparison of RV function in different types of pulmonary hypertension has not yet been evaluated.

Previously, we reported the usefulness of RV echo findings in predicting pulmonary vascular resistance in patients with IPH [6]. The aim of this study was to determine whether the RV function is similarly affected by different types of PH (idiopathic PH or PH secondary to left heart disease).

Patient selection

Forty-five patients were enrolled according to the following inclusion/exclusion criteria: The inclusion criteria were pulmonary hypertension with mean PAP ≥ 25 mm Hg found during right heart catheterization as well as New York Heart Association (NYHA) functional classes II or III. The exclusion criteria were comprised of atrial flutter/fibrillation (or any other arrhythmias) confounding the echocardiographic measurements, a history of previous cardiac surgery (such as coronary artery bypass grafting and/or any valve repair or replacement), severe tricuspid regurgitation, advanced documented lung disease and/or a poor echocardiographic window. We used echo finding for analysis and the cardiac catheterization findings as criteria for enrolling patients in the study. Approximately 50% of participants had been involved in previous studies at our institution.

2D echocardiography–derived parameters of RV function

All echocardiographic studies were performed with commercially available echocardiography systems equipped with a 3.5-MHz transducer (Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway). Routine digital grayscale 2D and tissue Doppler cine loops were obtained at end-expiratory apnea from apical and parasternal views. Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate regardless of heart rate. Frame rate was adjusted from 60 to 90 Hz. All measurements were obtained by an observer blinded to cardiac catheterization data.

Conventional echocardiographic assessment of RV performance

TAPSE was determined from an M-mode through the lateral tricuspid annulus by calculating the amount of longitudinal motion of the annulus at peak systole [7]. RV FAC was calculated as

$$\frac{\text{RV end–diastolic area} - \text{RV end–systolic area}}{\text{RV end–diastolic area} - \text{RV end–systolic area}} \times 100.$$

The RV endocardium was traced in systole and diastole from the annulus, along the free wall, to the apex and back along the interventricular septum using the apical four-chamber view. Attempts were made to trace the free wall beneath trabeculations. The RV isovolumic relaxation time (IVRTT), isovolumic contraction time (IVCT), and ejection time (ET) were measured by pulsed wave tissue Doppler from the lateral tricuspid valve annulus. The RV myocardial performance index (RVMPI, Tei index) was calculated as:

$$\frac{(\text{IVRTT} + \text{IVCTT})}{\text{ET}}.$$

We calculated RV dP/dt by measuring the time required for the TR jet to increase in velocity from 0.5 to 2 m/s. Using the simplified Bernoulli equation, this represents a 15 mm Hg increase in pressure. The dP/dt is therefore calculated as 15 mm Hg divided by this time (in seconds), yielding a value in millimeters of mercury per second [8].

Tricuspid annular peak systolic velocity

Doppler tissue imaging recordings were obtained from the modified apical four-chamber view with a high frame rate (> 150 frames/sec).

To avoid aliasing, the Nyquist limit was adjusted to the lowest level. Pulsed Doppler tissue imaging was performed at the lateral corner of the tricuspid annulus. The tricuspid annular peak systolic (Sa), early diastolic (Ea.), and atrial (Aa) wave velocities and Ea/Aa ratio were measured [9].

Strain rate imaging in the right ventricle

Real-time 2-D color Doppler myocardial imaging was recorded from the RV, using standard 4-chamber apical views at a high frame rate (> 150 FPS) and at the narrowest sector angle possible. The region of interest was placed at the basal and mid segments of the RV free wall and kept at the center of the ultrasound sector to ensure the accuracy of the angle with the long-axis motion to measure peak systolic longitudinal strain (RVSTR) and peak systolic longitudinal strain rate (RVSR). A sample volume of 7 mm to 10 mm was utilized for the calculation of longitudinal SR. The data obtained were stored in digital format and analyzed offline with dedicated software by an experienced person who was blinded to the clinical characteristics of the patients. For each variable, 3 representative beats were analyzed and the mean was calculated.

Statistical analysis

All the analyses were conducted using Statistical Package for Social Sciences (SPSS) software, version 22 (SPSS Inc., Chicago, IL, USA). A descriptive analysis of the demographic and echocardiographic data of the patients was performed. The categorical variables are presented as numbers and percentages and the quantitative variables as means ± standard deviation. Comparisons were made between the groups of patients using the chi-square test for the categorical data and the independent sample T test, as appropriate. All the P values were two-tailed, and a P value of < 0.05 was considered statistically significant. Interobserver and intraobserver variability were calculated as the absolute difference divided by the average of the two observations for all of the parameters. Eleven cases were analyzed for the calculation of the interobserver and intraobserver variability.

Results

Forty-five patients were enrolled in this study. Among them, 20 were females and 25 were males. Mean ± SD age was 38.3 ± 11.6 years (minimum 18 years and maximum 64 years respectively). In our study, Mean ± SD for mean PAP was 51.5 ± 15.5 mm Hg (minimum 33 mm Hg and maximum 88 mm Hg). For systolic PAP, the Mean ± SD was 78.5 ± 22 mm Hg (minimum 50 mm Hg and maximum 130 mm Hg). Based on two etiologies we separated our patients into 2 groups. Group 1 included patients with IPAH (N = 22) and group 2 was comprised of patients with PH secondary to chronic systolic heart failure (PH-HF) (n = 23). Mean ± SD of age in the first group was 35.5 ± 11.5 years. In the second group, the Mean ± SD was 41 ± 11.2 years ($p = 0.11$). Most of the patients in group 1 were females (68%), whereas only 21% of participants in the second group were female ($p = 0.002$). In the IPAH group, Mean ± SD for mean PAP was 60 ± 14.5 mm Hg in comparison to 43 ± 11.5 mm Hg ($p = 0.001$) in the second group. For systolic PAP the Mean ± SD in the first group was 93 ± 19.5 mm Hg in comparison to 64 ± 13.5 mm Hg in the second group ($p < 0.001$).

Considering conventional indexes of RV function, only Sm and dp/dt were significantly better in the first group in comparison to the second one (p-value for Sm = 0.042 and for dp/dt = 0.039). RVEDD was significantly higher in the IPAH group (4.36 ± 0.72 Cm in IPAH group in comparison to 3.91 ± 0.42 Cm in PH-HF group, $p = 0.013$). Although other indices of TAPSE and MPI were better in the IPAH group, they were not statistically significant (means in TAPSE in IPAH group was 15.2 ± 3.5 in comparison to 14.4 ± 4.4 in PH-HF group, $p > 0.5$). All indices of conventional indexes are shown in the Table 1. Considering deformation indexes of RV function, the basal and mid portion of RV free wall strain and basal RV strain rates were significantly worse in the PH-HF group in comparison to the IPAH group ($p < 0.001$ in basal RV strain, $p = 0.034$ in mid RV strain and $p = 0.046$ in basal RV strain rate respectively). Although FAC was better in the IPAH group, it did not reach statistical significance (FAC = 19.6 ± 5.5 in IPAH in comparison to 18.4 ± 8 in PH-HF, $p > 0.5$) (Table 1).

Discussion

It is well known that the most common cause of pulmonary hypertension is related to left ventricle failure. Reeves and Groves have shown that 44% of patients with coronary artery disease during coronary arteriography and right heart catheterization have pulmonary hypertension.

Table 1. Echocardiographic indices in patients with idiopathic (Group I) *versus* secondary (Group II) pulmonary hypertension

	Group I	Group II	P value
RVEDD (Cm)	4.3 ± 0.72	3.9 ± 0.42	0.013
TAPSE (mm)	15.2 ± 3.5	14.4 ± 4.4	0.52
Sm (Cm/s)	8.9 ± 2.4	7.6 ± 1.6	0.042
Dp/dt	490 ± 171	376 ± 173	0.039
MPI	0.8 ± 0.21	0.69 ± 0.3	0.17
FAC (%)	19.6 ± 5.5	18.4 ± 8	0.57
RV base Strain (%)	-19.7 ± 5.5	-14.7 ± 4.5	< 0.001
RV mid Strain(%)	-13.5 ± 2.9	-11.4 ± 3.2	0.034
RV base SR (S-1)	1.1 ± 0.47	0.91 ± 0.34	0.046
RV mid SR (S-1)	0.89 ± 0.49	0.69 ± 0.32	0.11

Our study showed that patients with pulmonary hypertension secondary to chronic systolic dysfunction have worse RV indexes of function. RV dysfunction in PH may have many underling etiologies: 1) Left ventricular failure increases pulmonary arterial afterload by increasing pulmonary venous and pulmonary arterial pressure. It is a protective mechanism against pulmonary edema; 2) The same pathological mechanism that causes left ventricular dysfunction could simultaneously affect the right ventricle; 3) Myocardial ischemia may involve both ventricles; 4) Left ventricular dysfunction can reduce coronary pressure in the right ventricle thus reducing right ventricular function; 5) Ventricular interdependence due to septal dysfunction can occur 6) leading to left ventricular dysfunction related to pericardial constrain.

In the failing RV, excessive sympathetic adrenergic stimulation can adversely affect ventricular remodeling and survival [10, 11]. In patients with PAH, elevated catecholamine levels have been found to be related to higher pulmonary vascular resistance and lower cardiac index [12, 13].

Furthermore, right ventricular wall stress and thickness appear to be inversely related [14] to RV function in IPAH patients. Abraham WT *et al.* have shown that the ACE DD genotype is significantly increased in patients with severe PPH in comparison to controls suggesting that some individuals could be genetically at risk for developing pulmonary hypertension [15]. The ACE DD genotype is related to preserved right ventricular function in PPH patients supporting the theory of the important role of Ang II in patients with RV pressure overload conditions. It is interesting to note that in a recent study [16] of patients with normal left ventricular function, right ventricular morphology was found to indicate the reason for increased afterload in patients with pulmonary hypertension. Furthermore, echocardiographic volumetric reconstruction and measurements of the right ventricle have shown improvement with successful treatment of pulmonary hypertension [17] suggesting that echocardiographic abnormalities can improve with successful treatment.

To the best of our knowledge, this is the first study assessing the relationship between these echocardiographic indices and the hemodynamic parameters indicative of RV failure. Based on our results, IPH has less impact on RV function in comparison to HF-PH. Considering both entities are in the category of RV pressure overload, we conclude that the etiology of pulmonary hypertension also plays an important role in RV function in addition to pressure overload.

Study limitation

The main limitation of our study was its relatively small sample size, which could limit the generalizability of our results. Myocardial strain and strain rate can be measured in all dimensions (longitudinal, radial, and circumferential) but we only quantified the longitudinal strain and SR. Hence, the RV myocardial ischemia, if present, would affect the strain and other RV functional parameters [11, 15]. Another limitation was our echocardiography system software which was validated for the LV but was not validated for the global longitudinal RV strain. Therefore, RV free wall 2D speckle strain analysis could not be performed.

Our study demonstrated that severe PAH seems to aggravate the RV function more severely compared to PS. However, to better elucidate the role of the RV echocardiography in assessing various types of the RV pressure overload states and its application to discriminate between idiopathic primary PAH and PS patients, further studies with a larger sample size of patients are needed.

Conflict of interest

None of the authors have any conflict of interest to disclose.

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Screening diabetes mellitus patients for tuberculosis in Southern Nigeria: A pilot study

Abstract

Introduction: Diabetes mellitus (DM) and tuberculosis (TB) are of great public health importance globally, especially in Sub-Saharan Africa. Tuberculosis is the third cause of death among subjects with non-communicable diseases. DM increases risk of progressing from latent to active tuberculosis. The study aimed to ascertain yield of TB cases and the number needed to screen (NNS) among DM patients.

Material and methods: A cross-sectional study was conducted at 10 health facilities with high DM patient load and readily accessible DOTS center in 6 states of southern region of Nigeria over a period of 6 months under routine programme conditions. All patients who gave consent were included in the study. Yield and NNS were calculated using an appropriate formula.

Results: 3 457 patients were screened with a mean age (SD) of 59.9 (12.9) years. The majority were male, 2 277 (65.9%). Overall prevalence of TB was 0.8% (800 per 100 000). Sixteen (0.5%) were known TB cases (old cases). There were 221 presumptive cases (6.4%) out of which 184 (83.3%) were sent for Xpert MTB/Rif assay. Eleven (0.3%) new cases of TB were detected, giving additional yield of 40.7% and the number needed to screen (NNS) of 315. All the 11 patients were placed on anti-TB treatment.

Conclusions: The prevalence of TB among DM patients was higher than in the general population. The yield was also good and comparable to other findings. This underscores the need for institute active screening for TB among DM patients. Further studies are recommended to identify associated factors to guide policy makers in planning and development of TB-DM integrated services.

Key words: diabetes, tuberculosis, screening, yield, number needed to be screened, Nigeria

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Introduction

Diabetes mellitus (DM) and tuberculosis (TB) are major lethal diseases of great public health importance globally [1]. This is the most visible in Sub-Saharan Africa (SSA) due to the converging epidemics of both communicable and non-communicable diseases. The World Health Organization (WHO) has identified DM as a global epidemic. The relationship between diabetes and tuberculosis as well as their synergistic role in causing human disease may be the next challenge for global tuberculosis control [2].

Diabetes prevalence is increasing globally, especially in low- and middle-income countries due to ageing, population growth, rapid economic, social, and lifestyle changes [3, 4]. About 422 million people worldwide were living with diabetes in 2014 [5]. The global prevalence of diabetes was estimated to be 8.5% among adults

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aged 18 years and above [5]. In 2012, diabetes was the direct cause of 1.5 million deaths [5]. Eighty percent (80%) of these people live in low- and middle-income countries, including Nigeria where TB prevalence is equally high. This is also where 80% of all deaths due to DM occur [5]. About 10–15% of global TB cases are linked to diabetes [6]. Diabetes mellitus has recently emerged as risk factor for developing active TB [7]. Diabetes triples a person's risk of developing TB [8–11]. The global economic burden of diabetes is enormous. In Africa, the mean annual cost for diabetes care ranges between $2 144 and $11 430 (direct costs $876–1 220) [12].

Tuberculosis ranks as the second leading cause of death from an infectious disease globally next to the human immunodeficiency virus (HIV). DM and TB comorbidities complicate tuberculosis management and negatively influence its treatment outcome [13, 14]. In 2014, 9.6 million people fell ill with TB, 1.5 million died from TB and one in three individuals in the world was infected with latent TB [5]. The World Health Organization (WHO) reported that in 2017, globally there were estimated 10.0 million incident cases of TB (range, 9.0–11.1 million), which translates to 133 cases (range, 120–148) per 100 000 population. Most of these cases in 2017 occurred in Asia (44%) and the African Region (24%) [15]. In Nigeria, tuberculosis is still a grave public health problem. It is associated with huge economic burden just as in other low-income countries [16–18]. In Nigeria, despite the National TB and Leprosy Control Programme (NTBLCP) reporting 94 604 cases in 2012, this number only represents 51% of the cases estimated to have occurred in the country that year [19]. In 2017, the incidence of TB in Nigeria was 418 cases (range 273–594) [15].

The presence of DM alone does not justify screening or treatment of latent TB infection (LTBI). However, when combined with other risk factors for TB, the presence of DM may be sufficient to justify screening and treatment of LTBI, even in a low TB incidence setting [20]. The Sustainable Development Goals (SDGs) among other targets, made ending the global TB epidemic a priority. To achieve this, new strategies need to be employed. Passive case finding which used to be the norm whereby patients present themselves for TB screening seems not yielding desired result. Active case finding (ACF) is believed to contribute to the earlier detection of persons with TB. This will lead to early initiation of treatment, better therapy outcomes for individuals and ultimately, it will reduce transmission in the community [21–23].

The World Health Organization and the Union have launched a new 'Collaborative Framework for the care and control of Diabetes and Tuberculosis'with one of the most important activities being the routine implementation of bi-directional screening of the two diseases [24]. In Nigeria, there are no policies identifying DM patients with TB symptoms, or minimising the time spent by patients with probable DM-TB co-morbidity in the diabetes clinics. In addition, evidence to inform the development of interventions to address the TB burden among DM patients is crucial but lacking. Moreover, the methods of screening, recording and reporting DM and TB co-morbidity in routine health care settings are not well determined, and these knowledge gaps need to be addressed. There is a need for relevant stakeholders, including: WHO, National TB and Leprosy Control Programme and government agencies/departments responsible for non-communicable diseases to review and discuss linkages between DM and TB — hence the need for bidirectional screening and the WHO Union Collaborative Framework. A multicenter, unidirectional study to assess the burden of diabetes mellitus among TB patients was recently completed in 6 selected states in southern Nigeria the results of which have been published [25]. The study seeks to address the second arm, i.e. intensified TB screening among patients with diabetes mellitus. The feasibility of the screening (DM patients for TB), burden and challenges will be evaluated within routine health care services to inform policy change and develop generic protocols for its implementation.

Screening persons with DM for TB could be one of the strategies for early and increased TB case detection in Nigeria. These informed the programme implementation of active case finding through screening to ascertain incidence, yield, number needed to screen (NNS) for a case of TB among DM patients.

Material and methods

Study area

The study was conducted in the southern region of Nigeria spanning through all the 3 geopolitical zones and involving 6 states (two from each geopolitical zone) namely; Ogun, Ondo, Edo, Delta, Enugu and Abia States. Diabetes clinics of selected health facilities with high DM patient load and readily accessible DOTS centre were selected in each state for the study. This region hosts the major oil producing

states. They engage in farming, fishing, mining, trading as well as civil/public services. There are well established health centres, including tertiary, secondary and primary facilities that care for patients, including those with DM and TB. However, 10 health clinics were used for the study. These were the major centres caring for both diseases in the states.

Study design, duration and population

A hospital-based cross-sectional study was done under programme implementation. The study was conducted over 8-month period from February to October 2018. All diagnosed cases of diabetes mellitus who were aged 15 years and above, registered with and attending Diabetes Clinics in selected health facilities within the study period and who gave informed consent were included.

Sampling technique and sample size determination

All diabetic clients attending DM clinics at the selected health facilities who met the inclusion criteria were included in the screening. They were recruited consecutively as they presented at clinic throughout the period of the study. A total of 3 457 patients were included in the study.

Procedure of screening

The subjects were DM patients aged 15 years and above who have been registered in the DM clinic for care. Presumptive and diagnosed TB cases were screened for HIV in line with the national TB guidelines. The screening for TB was carried out at each patient's visit (minimum of one month interval; however, each subject was reported only once during the project period) using a symptom-based standardised checklist.

Referral of identified presumptive TB cases (among DM patients) to TB clinic

Trained research assistants worked in collaboration with the staff at the DM clinics to: conduct a symptomatic TB screening for all eligible DM patients using appropriate tools (checklist), identify presumptive TB cases among those screened for TB; collect 2 sputum specimens from identified presumptive TB cases; send sputum specimens for GeneXpert diagnosis (second sputum specimen was equally processed if the first was negative), refer all diagnosed TB cases to TB clinic for treatment and record necessary data using tools. Good cooperation and collaboration were established between the 2 sets of staff working in the different service areas (DM and TB clinics).

Data collection and analysis

Patient information was extracted from a standard globally used register and analysed. The records were filled by trained health workers to ensure good quality data. Double data entry was done to ensure accuracy. IBM Statistical Package for Social Sciences Version 21 was used for data entry, editing and analysis. Results were presented in tables. Yield [(new TB cases/total number with TB) × 100] and the number needed to screen (number of patients/ /new TB cases) were calculated. Mean, standard deviation, proportion and percentages were used as summary measures, where appropriate.

Ethical consideration

The Ethics and Research Advisory Committee of University of Nigeria Teaching Hospital (UNTH), Enugu approved the study. Approval was also obtained from the State TB Control Programme in six states selected for the project. Permission was equally obtained from heads of the facilities and written informed consent obtained from the patients. Confidentiality of data was ensured in course of the research.

Results

Table 1 shows that a higher proportion of patients were aged ≥ 60 years 2 669 (77.2%) and with their mean age 59.86 years**.** Males were higher in proportion 2 277 (65.9%). They were predominantly civil/public servants — 1 428 (41.3%) and traders — 1 308 (37.8%). The majority had BMI of 25–29.9 kg/m^2 1 340 (38.8%) followed by ≥ 30 kg/m^2 1 019 (29.5%). Only 22 (0.6%) currently smoked cigarettes or tobacco-based products. As well, only 3 (0.1%) tested positive for HIV. Most were type 2 DM 3 328 (96.3%).

Table 2 shows that 6 386 patients attended the clinic within the 6 months of the study. Of this number, 3 457 (54.1%) were new patients or attended the clinic once. These were the patients further studies were based on. Presumptive cases were 221 (6.4%) out of which 184 (83.3%) were sent for Gene Xpert. In all 11 (0.3%) tested positive following screening (new cases), 16 (0.5%) were known cases (old cases), and 27 (0.8%) had TB (old and new cases) among the patients studied. Among the 11 subjects that were newly detected, all were sent for treatment.

Table 3 shows that of the 3 457 patients studied, yield was 40.7% and the number needed to

Table 1. Characteristics of patients

Variables	Frequency (n = 3457)	Percent (%)
Age (years)		
< 60	788	22.8
≥ 60	2669	77.2
Mean (SD)	59.86 (12.86)	
Gender		
Male	2277	65.9
Female	1180	34.1
Occupation		
Civil/public servant	1428	41.3
Trading/business	1309	37.9
Others	722	20.9
BMI		
< 18.5	102	3.0
18.5–24.9	996	28.7
25–29.9	1340	38.8
≥ 30	1019	29.5
Current smoker		
Yes	22	0.6
No	3435	99.4
Type of DM		
1	129	3.7
2	3328	96.3
HIV		
Negative	3454	99.9
Positive	3	0.1

BMI — body mass index; DM — diabetes mellitus; HIV — human immunodeficiency virus

screen (NNS) for the yield was 315 patients. When disaggregated by characteristics, those aged < 60 years had yield of 42.9% and NNS of 263, males had yield of 50.0% and NNS of 326, civil/public servants had yield of 37.5% and NNS of 476, those with BMI of < 18.5 had yield of 60.0% and NNS of 34, smokers had yield of 47.8% and NNS of 313, type 2 DM patients had yield of 55.6% and NNS of 333 and those that were negative for HIV had yield of 38.5% and NNS of 345.

Discussion

The study reported that 11 DM patients or 0.3% of them tested positive following screening (new cases). More findings were that yield of TB cases was 40.7% and the number needed to screen to make diagnosis of a TB case was 315 DM patients. This is revealing and encouraging as these identified cases would have been the foci of spread among unsuspecting public with their consequent effects. The findings can partly be explained by the large population size involved in the study. It also gave credence to innovations aimed at controlling the menace of the diseases. For instance, the Collaborative Framework for the Care and Control of Diabetes and Tuberculosis as launched by WHO and the Union have routine implementation of bi-directional screening of the DM and TB as one of the important activities for control of TB [24]. In Nigeria where the methods of screening, recording and reporting DM and TB co-morbidity in routine health care settings are not well determined, these existing gaps can be addressed by such

Table 2. Distribution of patients studied

Variables	Formula*	Value
A. Total number of DM patient visits over 6 months (including revisit)		6386
B. Number (%) of new DM patients studied (excluding revisit)	[(B/A)×100]	3457 (54.1)
C. Number (%) of presumptive TB cases identified	[(C/B) ×100]	221 (6.4)
D. Number (%) sent for GeneXpert test	[(D/C) ×100]	184 (83.3)
E. Number (%) that with MTB detected (new cases)	[(E/B) ×100]	11 (0.3)
F. Number placed on TB treatment		11
G. Number (%) of previously diagnosed (known) TB cases		16 (0.5)
H. Total number (%) of TB cases	[(E+G)]	27 (0.8)

*What was computed to get value

DM — diabetes mellitus; TB — tuberculosis; MTB — Mycobacterium tuberculosis

Table 3. Distribution of patients yield and number needed to screen disaggregated by patient characteristics

Variables	Number of patients	Total number with TB	Known TB cases	New TB cases	Yield (%)	NNS
	[A]	[B]		[C]	[(C/B)×100]	[A/C]
Overall	3457	27	16	11	40.7	315
Age (years)						
< 60	788	7	4	3	42.9	263
≥ 60	2669	20	12	8	40.0	334
Gender						
Female	1180	13	9	4	30.8	295
Male	2277	14	7	7	50.0	326
Occupation						
Civil/public servant	1426	8	5	3	37.5	476
Trading/business	1309	13	9	4	30.8	328
Others	722	6	2	4	66.7	181
BMI						
< 18.5	102	5	2	3	60.0	34
18.5–24.9	996	10	5	5	50.0	193
25–29.9	1340	6	4	2	30.3	670
≥ 30	1019	4	3	1	25.0	1019
Current smoker						
No	22	4	4	0	0.0	—
Yes	3435	23	12	11	47.8	313
DM type (n)						
1	129	3	3	0	0	—
2	3328	18	8	10	55.6	333
HIV status						
Negative	3454	26	16	10	38.5	345
Positive	3	0	0	0	0	—

BMI — body mass index; DM — diabetes mellitus; NNS — number needed to screen; HIV — human immunodeficiency virus; TB — tuberculosis

activities like this programme implementation screening exercise.

Above all, diagnosis of TB disease is the entry point in the management of TB cases. Consequently, early diagnosis through screening will lead to prompt commencement of chemotherapy; reduced transmission of the disease to unsuspecting populace they come in contact with and ultimately, a positive impact on the control of the disease in the general population.

Other previous studies supported findings from this study. In Taiwan, a screening done for pulmonary tuberculosis among the elderly with type 2 diabetes involving 3 087 patients detected 7 (0.2%) patients who were positive for pulmonary tuberculosis [26]. Similarly, in a symptom screening project in a tertiary care hospital in south India, 12 cases were newly diagnosed of TB among 125 subjects that underwent TB investigation [27]. Another symptom screening research in Mexico detected 38 TB cases in 7 763 diabetes patients [28]. In China, TB was diagnosed in 14 of 4 085 patients with DM following active screening [29, 30]. Findings from previous studies have shown that screening for active TB among diabetics could improve case detection just like in other populations susceptible to TB, including HIV-infected individuals, gold miners, and prisoners in developing countries [31].

The number of diabetics needed to screen to find one extra case of TB is directly related to the TB prevalence among that population. For instance, in areas with TB prevalence less than 25 per 100 000 persons, at least 1 000 diabetic

individuals have to be screened to find one extra case of TB. With increasing prevalence, the number needed to screen to find one additional case of TB ranges from 4 to 442. This implies that the yield of screening increases with the prevalence of TB in that region [31]. Also, the population attributed risk for TB from DM is dependent upon DM prevalence as evidenced in studies which documented that in populations with a higher incidence of TB, DM is a more important risk factor [32]. DM accounts for a small proportion of TB cases in settings such as Australia with a low incidence of TB [33]. This number was 14.8% in India and 25% in a Mexican setting due to higher incidence and prevalence [34].

None of those that tested positive for HIV had TB. This is good as it would be disastrous for a patient to have two recognized major threats to TB diagnosis and treatment outcome. This may be explained by the age distribution of the studied DM patients . Most were aged > 60 years of which most HIV positive subjects may not live as long as that due to either the comorbidities, drug-drug interactions or opportunistic infections as both DM and HIV infection reduce immunity. Human immunodeficiency virus infection is considered as the most potent risk factor for TB. Nevertheless, the high prevalence of DM in the world and its effect on TB burden is greater than that of HIV infection [7]. Even though HIV has been documented to be the strongest risk factor for TB at an individual level, DM is seen as most important at the population level. This indicates that having both will carry far-reaching health and economic implications.

Conclusions

The number of positive cases identified following screening, yield of TB cases and the number needed to screen to make diagnosis of a TB case were encouraging. Active case finding in the form of screening as carried out in this study is needed to end the global TB. Such programme implementation should be encouraged and advanced to reduce scourge of TB and its co-morbidities.

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Conflict of interest

None declared.

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Extracorporeal life support after failure of thrombolysis in pulmonary embolism

Abstract

Introduction: Fulminant pulmonary embolism (PE) may lead to cardiogenic shock or cardiac arrest with high mortality rates (65%) despite treatment with thrombolysis. Patients not responding to this therapy might benefit from extracorporeal life support (ECLS). Only occasional case reports of ECLS in PE patients are available. We studied the use of ECLS after thrombolysis in patients suffering from refractory cardiogenic shock due to PE.

Material and methods: Patients who were admitted to our university intensive care unit (ICU) with PE, not responding to thrombolysis, and who received subsequent ECLS treatment were studied.

Results: 12 patients with severe PE were included. 6 patients were admitted by emergency medical services, 5 patients were transferred to the ICU from other hospitals and one patient presented at the emergency department by herself. 11 of 12 patients suffered from cardiac arrest and needed cardiopulmonary resuscitation (CPR) before ECLS implantation. Three ECLS were implanted during CPR and nine ECLS were implanted during emergency conditions in patients with cardiogenic shock. All patients received thrombolysis before implementation of ECLS. Mean duration of ICU treatment was 22.4 ± 23.0 days. Mean duration of ECLS therapy was 5.6 ± 6.5 days. Bleeding complications occurred in four patients. Complications directly related to the ECLS system occurred in two patients (overall complication rate 42%). Overall, 6 of 12 patients (50%) survived.

Conclusions: ECLS may be considered as a bailout therapy in PE patients not responding to prior definitive treatment such as thrombolysis. ECLS therapy seems to be feasible with an acceptable complication rate even after thrombolysis.

Key words: pulmonary embolism, extracorporeal life support system, cardiopulmonary resuscitation, thrombolysis, right heart failure

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Introduction

Fulminant pulmonary embolism (PE) is a potential hazardous disease. Pulmonary artery occlusion by thromboembolism may lead to oxygenation and/or right heart failure. Patients with PE suffering from cardiogenic shock or cardiac arrest have high mortality rates (65%) [1, 2].

Treatment options range from simple anticoagulation to definitive treatment options such as local or systemic thrombolysis, surgical embolectomy and catheter-based therapies. In cases with severe cardiogenic shock or cardiac arrest, immediate thrombolysis is often performed. Since 1995, only a few cases were reported in which extracorporeal membrane oxygenation (ECMO)/ /extracorporeal life support (ECLS) were applied either in combination with the above mentioned treatment options or alone [3].

However, in some patients who do not respond to the definitive treatment options mentioned above, ECLS might be the only life-saving therapy. In these patients, ECLS can be used as a bridge to right heart recovery. Data on the use of ECLS after treatment of PE with thrombolysis, surgical embolectomy or catheter based techniques are rare [4]. The recently updated ESC (European Society of Cardiology) guidelines from 2019

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for the treatment of PE recommend that "ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest" [5]. This recommendation is classified as class IIb and level C [5]. The use of ECLS in high-risk PE patients as a stand-alone technique with anticoagulation is deemed to be controversial and as such, the ESC guidelines suggest considering additional therapies, such as surgical embolectomy or catheter-directed treatment [5].

We conducted a study in high-risk patients suffering from cardiogenic shock due to PE despite thrombolysis with subsequent need for ECLS therapy.

Material and methods

Our study was performed according to the Declarations of Helsinki. Due to the retrospective nature of the study, a full review by the local Ethics Committee was not required.

We retrospectively enrolled 12 consecutive patients that were admitted to the ICU of the University Hospital of Muenster with fulminant pulmonary embolism who did not respond to thrombolysis and were treated with ECLS.

ECLS was implanted if return of spontaneous circulation (ROSC) could not be achieved during CPR after systemic thrombolysis, if shock symptoms and hypotension did not recede after thrombolysis, and in one patient due to severe shock and progressive lactic acidosis with a rapidly rising need for vasopressors.

For ECLS we used Rotaflow or Cardiohelp systems (Maquet, Rastatt, Germany). Cannulas (Novalung, Heilbronn, Germany and Maquet, Rastatt, Germany) were sized 15F–23F, if appropriate. Cannulas were placed via the femoral vein and femoral artery in most cases. In two cases, the subclavian artery was used via surgically implanted patches.

Thrombolysis was performed using either 8000 IU tenecteplase or 100mg of rtPA with prior application of 5000 IU heparin.

We analyzed demographic parameters of the study cohort as well as the following data: duration of ICU treatment, duration of ECLS treatment, need for cardiopulmonary resuscitation, circumstances of ECLS implantation (during CPR or emergency setting), ECLS associated complications, mode of ICU admission, and survival.

Study cohort characteristics

Our study cohort involved 12 patients (3 females) with a mean age of 44.2 ± 11.9 years (Table 1).

With regard to pre-existing diseases, one patient had a congenital heart defect with a hypoplastic right ventricle, pulmonary valve stenosis and a secundum atrial septal defect which was previously treated with a modified Fontan operation. Another patient suffered from dilative cardiomyopathy. One patient had a factor V Leiden mutation with recurrent deep vein thrombosis and former oral anticoagulation therapy. Lastly, one patient had a myeloproliferative disease.

Table 1. Study cohort characteristics. Summary of study cohort characteristics concerning gender, age, duration of stay on intensive care unit (ICU), duration of extracorporeal life support (ECLS) treatment, need for cardiopulmonary resuscitation (CPR), complications after thrombolysis and ECLS implantation, time point of thrombolysis and survival

Patients (n)	12
Male	9 (75%)
Age (years)	44.2 ± 11.9
ICU duration (days)	22.4 ± 23
ECLS duration (days)	5.6 ± 6.5
CPR before ECLS implantation	11 (92%), 7 in-hospital, 4 out-of-hospital
CPR during ECLS implantation	3 (25%)
ECLS associated complications	5 (42%)
Time of thrombolysis	4 out-of-hospital, 6 in-hospital, 2 local *via* catheter into pulmonary artery
Overall survival	6 (50%)

CPR — cardiopulmonary resuscitation; ECLS — extracorporeal life support; ICU — intensive care unit

Confirmation of diagnosis

Assumed admission diagnosis of all 12 patients was severe pulmonary embolism. In 7 patients, pulmonary embolism was confirmed by contrast-enhanced computed tomography (CT). In the remaining 5 patients, PE was assumed due to clinical presentation and severe right heart dilatation detected by echocardiography.

In one of these five patients, echocardiography detected a large thrombus in the right atrium protruding into the right ventricle.

Circumstances of admission and ECLS implantation

6 patients were admitted to the ICU by the emergency medical service. Further, 5 patients were subsequently transferred to our ICU from other hospitals. One patient presented at our emergency department by herself.

11 of 12 patients suffered from cardiac arrest and received CPR of different duration prior to ECLS implantation (Table 1). Seven of these 11 patients suffered from in-hospital cardiac arrest and four had an out-of-hospital cardiac arrest (OHCA) (Table 1). In one of the four OHCA patients, the emergency medical service team achieved out of hospital return of spontaneous circulation (ROSC). The remaining three OHCA patients were transported under ongoing CPR. In two of these three patients, ECLS was implemented during continuous CPR in our ICU. One of the three patients had intra-hospital ROSC and received ECLS subsequently due to persistent hemodynamic instability.

In total, three of the ECLS systems were implanted during ongoing cardiopulmonary resuscitation and the remaining nine ECLS systems were implanted during emergency conditions in critically hemodynamically unstable patients. Only one patient received ECLS without prior resuscitation due to progressive shock.

ICU and drug treatment

All patients received systemic or local thrombolysis before implementation of ECLS (Table 1). Four patients received systemic thrombolysis out-of-hospital and six patients received systemic thrombolysis intra-hospital. Two patients received local thrombolysis via pulmonary artery catheterization. In addition, two of the 12 patients were additionally treated with pulmonary catheter fragmentation.

During ECLS implantation, 11 patients were intubated and mechanically ventilated. One patient not requiring CPR was awake during ECLS implementation and received analgosedation.

The venous cannula was inserted into the vena femoralis in all patients. The arterial cannula was placed in the arteria femoralis in 10 patients. In 2 patients, the arterial cannula was placed surgically into the arteria subclavia dextra.

ICU course and complications

Mean duration of ICU treatment was 22.4 ± 23.0 days. ECLS therapy was performed with a mean duration of 5.6 ± 6.5 days.

After thrombolysis and subsequent implementation of ECLS, bleeding complications occurred in four patients. One patient showed minor bleeding at the arterial cannula placed in the arteria subclavia. Further, two patients had minor bleedings at the cannulas as well as gastrointestinal bleeding. During ECLS treatment, one patient showed major bleeding with subsequent femoral compartment syndrome. One of these patients also suffered from initially accidental misplacement of the venous cannula into the arteria femoralis during ECLS implantation with need for immediate surgical revision. Additionally, one patient developed an arteriovenous fistula with need for surgical therapy in the further course (Table 1).

In all surviving patients, ECLS was extracted without need for re-implantation.

Outcome

6 of 12 patients (50%) died during treatment. 5 patients died due to multi-organ failure and lactic acidosis after prolonged CPR. Three of these five patients had out-of-hospital cardiac arrest with CPR during transport to the hospital. In addition, one patient died during long-term ICU stay due to sclerosing cholangitis. This patient had presented herself at the emergency department and did not require CPR. The other 6 of 12 patients (50%) were discharged from hospital (Table 1).

Discussion

For prognostic reasons and therapeutic decision making, PE is often classified as high risk, intermediate risk, and low risk PE [5, 6]. Patients with low and intermediate risk PE should receive anticoagulation only. Patients with cardiac arrest

or severe shock due to pulmonary embolism should be treated with thrombolysis with adherence to individual contraindications such as recent intracerebral bleeding. The PEITHO study showed that patients with even an intermediate risk PE had a lower risk of hemodynamic decompensation when treated with thrombolysis. However, they had an elevated risk of major hemorrhage or stroke [7].

Due to advances regarding ECLS therapy (i.e. improved pump technology and coated tubes), ECLS systems have been developed that can be rapidly applied even in patients in severe shock or during CPR via femoral vein and artery access [8]. ECLS has already been reported as a supportive measure in patients undergoing surgical thrombectomy [9]. During the last few years, implementation of ECLS due to refractory cardiac arrest is increasingly used. This procedure is so far called eCPR (extracorporeal cardiopulmonary resuscitation) and is known to increase survival rates in selected patients [10]. Therefore, in patients with massive PE and severe shock despite definitive treatment by thrombolysis and catheter fragmentation, ECLS can be used as a bailout strategy. A review by Yusuff *et al.* reported 43 patients receiving ECLS for refractory cardiac arrest due to PE with an overall survival of 51.2% [3]. In a subgroup of 21 patients treated with ECLS and thrombolysis or catheter embolectomy, survival rate was 43%. Another study reported 17 patients treated with fibrinolysis and ECMO having a 30 day survival rate of 23.5% [11]. In addition, a study by Corsi *et al.* [12] reported thrombolysis in 8 of 17 patients with fulminant PE before ECLS was implemented. Overall, 90 day survival of the 17 PE patients treated with ECLS was 47% [12]. In our study, patients pretreated with thrombolysis and subsequent ECLS therapy had a survival rate of 50% until hospital discharge. In our university hospital, we perform around 50 ECMO/ECLS implantations per year. Around 10 percent of ECMO/ECLS are implanted during ongoing CPR. A trained ECMO/ECLS team for implantation is permanently available. Due to these conditions, the experience of our center might also contribute to the improved survival rate in our study cohort.

In comparison, other studies showed a range of survival rates between 35–52% in patients with PE and cardiogenic shock or cardiac arrest treated with fibrinolysis or embolectomy but without ECLS treatment [1, 2, 11]. When comparing these studies to our study, ECLS therapy may be useful and points to improved survival in a subgroup of patients with high risk PE and failure of thrombolysis and embolectomy.

Further, the review by Yusuff *et al.* found an ECLS related complication rate of 37% (16/43 patients) [3]. Another study with 52 patients being treated with only ECLS therapy or ECLS therapy in combination with thrombolysis and embolectomy found that major bleeding events occurred in 20 patients (38.5%) [11]. In addition, Corsi *et al.* [12] found severe hemorrhages with no impact on survival in 15 of 17 patients (88%) with a median of 4 packed red-cell and 5 fresh -frozen plasma units transfused. Surgical wound infections are reported in 9.6% of PE patients treated with ECLS [11]. In our study, we had a complication rate of 17% directly related to the ECLS (misplacement of one cannula and arteriovenous fistula, 2/12 patients). One of these two patients and an additional three other patients had bleeding complications after thrombolysis and ECLS implantation, which is a typical side effect after thrombolysis. By summarizing the complications due to thrombolysis and ECLS implantation, we observed a complication rate of 42% which is comparable to the reported complication rate by other studies [3, 11, 12]. Therefore, ECLS implantation seems to be feasible in the subgroup of high-risk PE patients pretreated with thrombolysis.

In our study, the mean duration of ICU stay was 22.5 ± 23 days, which is comparable to another study with 19 ± 14.6 days [3]. Duration of ECLS treatment in our patient cohort was relatively short with 5.6 ± 6.5 days and is in a similar range when comparing with other reports (2.5–4.5 days) [3, 11, 12]. Duration of ECLS therapy in patients with severe PE seems to be briefer in relation to patients treated with ECMO due to severe acute respiratory distress syndrome (ARDS) within 9–15 days of ECMO support [13]. This relatively short ECLS treatment duration in PE patients may be due to thrombus dissolution by continuous heparin application together with spontaneous thrombolysis [12].

In our study, as expected, the main cause of death in non-survivors (5/12 patients) was multi -organ failure, which was similarly the cause of death found in other studies [3, 11, 12]. In our study more than half of the patients were resuscitated outside of the hospital, which is a patient subgroup with a known worse outcome.

Conclusions

We therefore postulate that ECLS should be considered as a bailout therapy in PE patients not responding to prior definitive treatment such

as thrombolysis. Further, ECLS therapy seems to be feasible with an acceptable complication rate even after thrombolysis against the background of lacking therapy alternatives in this subgroup of patients. Our results may indicate an improved survival rate in this subgroup of PE patients. Therefore, further studies and randomized controlled trials are required to confirm the usefulness of ECLS therapy in patients with severe PE even without definitive treatment such as thrombolysis but instead, only anticoagulation.

Conflicts of interest

None declared.

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Imaging methods for pulmonary sarcoidosis

Abstract

Sarcoidosis is a chronic systemic granulomatous disease of unknown etiology. In more than 90% of patients with diagnosed sarcoidosis, mediastinal and hilar lymph nodes are affected. The objective of this paper is to discuss the most important chest imaging methods in pulmonary sarcoidosis. A chest X-ray remains the method of choice at both the diagnostic stage and during follow-up of the disease progress. High-resolution computed tomography allows for a more thorough description of lesions in terms of their location. Research demonstrates the superiority of FDG PET over both aforementioned techniques in the assessment of active inflammatory lesions. Magnetic resonance imaging is currently being used in diagnosing cardiac sarcoidosis. Although EBUS constitutes the basic diagnostic tool, the invasiveness of the method results in it not being used when monitoring the activity of the disease.

Key words: X-ray, HRCT, PET/CT, MRI, scintigraphy, pulmonologist point of view

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Introduction

Sarcoidosis is a chronic granulomatous disease of unknown etiology [1]. In more than 90% of patients with diagnosed sarcoidosis, mediastinal and hilar lymph nodes are affected [2, 3]. The diagnosis is based on the evaluation of clinical, radiological, and histopathological features [7]. The objective of this paper is to discuss the most important chest imaging methods in pulmonary sarcoidosis and to determine their role in the process of diagnosing the disease and monitoring its activity.

Conventional X-ray

The method of choice which should be applied in each and every patient with a clinical suspicion of sarcoidosis is a conventional X-ray [8]. Its unquestionable advantages include its wide availability and low cost. Despite the development of other techniques, X-ray imaging remains the first examination recommended in the diagnostic procedure, and a gold standard in monitoring the activity of the already diagnosed disease [8]. It is recommended to apply relevant scales in order to systematise and standardise X-ray images. One of the best-known scales is the one proposed by Scadding/Siltzbach in 1961 in which patients were classified according to one of four groups based on lesions visible in the chest X-ray (i.e. enlarged hilar lymph nodes, the presence of parenchymal infiltrations, and features of fibrosis) [9]. The first group included patients with isolated hilar lymphadenopathy; the second — subjects with accompanying parenchymal infiltrations; the third — subjects without lymphadenopathy, but with lesions in the lung parenchyma; the fourth — patients with fibrotic lesions. On the basis of the group of patients (n = 136), Scadding rated the incidence of individual groups in the population of patients with sarcoidosis and the probability of spontaneous remission in each of them [9]. This scale was accepted and has been widely used to date. Another classification method, which was applied in the analysis of pneumoconiosis and adapted by Muers *et al.*, consists of the division of both lung

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lobes into zones and in the evaluation of the profusion of individual types of lesions in the zones, specifically reticulonodular changes, masses, confluents, and fibrosis [10, 11]. The chest X-ray and the pulmonary function test (PFT) constitute the main tools for monitoring the activity of sarcoidosis. Boros *et al.* retrospectively analyzed the results of functional tests in 830 patients with diagnosed sarcoidosis. They analyzed them based on the stage that they were in determined by the Scadding/Siltzbach classification of chest X-ray [12]. Despite the parenchymal changes visible in the chest X-ray in about three-quarters of patients (stages II–IV), only 7% had a restriction in lung volume. At each stage (according to Scadding/Siltzbach), the lung transfer factor for carbon monoxide was impaired and static lung compliance was reduced [12]. Despite an established position which identifies X-ray imaging as a tool for monitoring the disease, the discussion devoted to decision making with reference to the onset of therapy based exclusively on the basis of radiological changes without accompanying lung function disorders is still ongoing. Pietinalho *et al.*, in their study of patients with recently diagnosed sarcoidosis that had no deviations in the functional tests, applied a 3 months' therapy with prednisone, which was followed by inhaled budesonide for 15 months. They demonstrated that patients, who at the onset of the therapy had stage II/III sarcoidosis and received treatment, experienced specific benefits in terms of FVC and DLCO 5 years after the study. Furthermore, they required glucocorticosteroid therapy much later than when compared to the placebo group [5]. Considering the possible side effects of the therapy, it is recommended to exercise caution when deciding about the beginning and/or continuation of treatment based exclusively on the advancement of the disease as evaluated in the chest X-ray. Figure 1 presents typical conventional chest X-ray picture of stage II sarcoidosis.

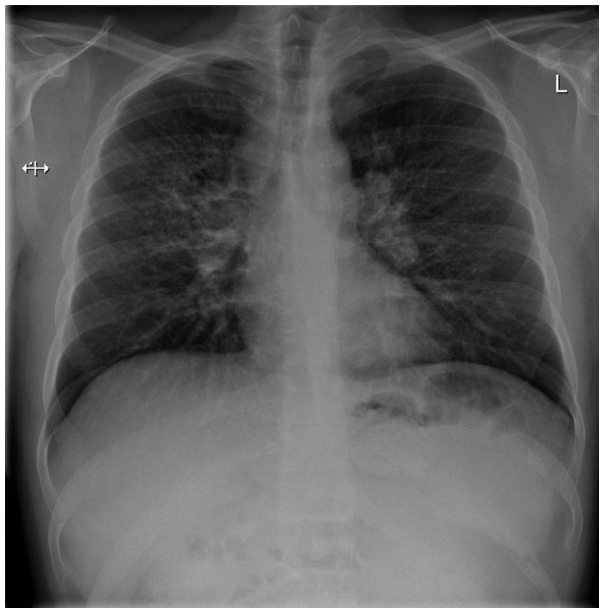

Figure 1. Chest X-ray of the patient with stage II sarcoidosis. Enlarged bilateral hilar lymph nodes, widening of mediastinum and bilateral nodular shadows spreading from perihilar regions to the lung periphery

High resolution computed tomography

A method that has become much more accessible is computed tomography. High-resolution computed tomography (HRCT), which is a method of choice in the evaluation of interstitial diseases, demonstrates a considerable superiority over the CT with contrast in the detection and evaluation of even subtle lesions in lung parenchyma [14]. Routine diagnostic protocols make use of thin-layer scans, from 1 to 1.5–2 mm [15]. In the past, the "so-called" sequential HRCT scans were used where layers were visualized every 10 mm from the apex of the lung to its base at full inspiration. As a result, as much as 90% of the lung was not seen on imaging. Thanks to advanced technical devices (multiple detector computed tomography), the rotation time necessary to generate the image has been shortened to 0.28–0.5 seconds (depending on the type of the apparatus). The use of spiral acquisition enhanced the scan sensitivity and minimised respiratory and pulsatory artefacts [15, 16, 17]. According to the 1999 ATS/ERS/WASOG guidelines which are still valid, there are three indications to perform a CT scan: a) if there are no lesions in the X-ray, but there is a clinical suspicion of sarcoidosis (stage 0); b) if there are atypical clinical or radiological symptoms; and c) in order to diagnose possible complications [1]. There are two typical findings in sarcoidosis in HRCT. Firstly, there is hilar and mediastinal lymphadenopathy which is most frequently bilateral and symmetrical. Secondly, there are nodules (both micronodules [2–4 mm in diameter] and macronodules (diameter ≥ 5 mm)] which can be located along bronchovascular bundles, interlobular septi, interlobar fissures, and in the subpleural region (Figure 2) [18]. In advanced stages, the features of fibrosis are visible and can include honeycombing, architectural distortion, traction bronchiectasis, and/or volume loss. Most frequently, lesions in sarcoidosis demonstrate predilection to the upper and middle fields [18].

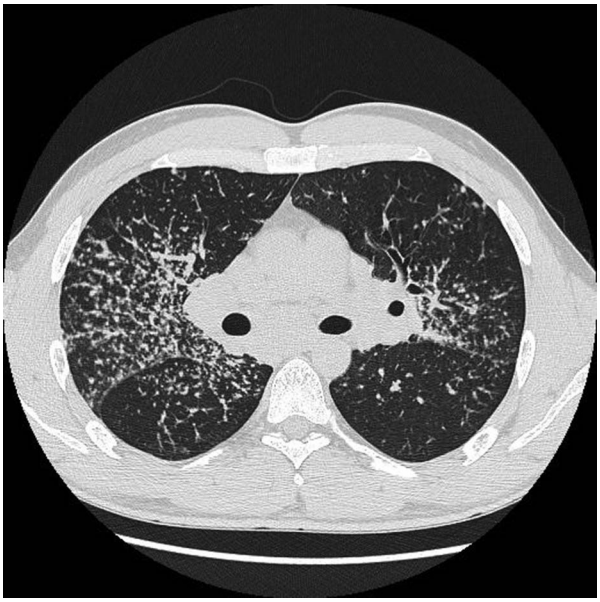

Figure 2. Chest high resolution computed tomography of the patient with stage II sarcoidosis. Enlarged hilar and subcarinal lymph nodes, disseminated high density nodules in both middle lung areas, with peribronchial and subpleural distribution

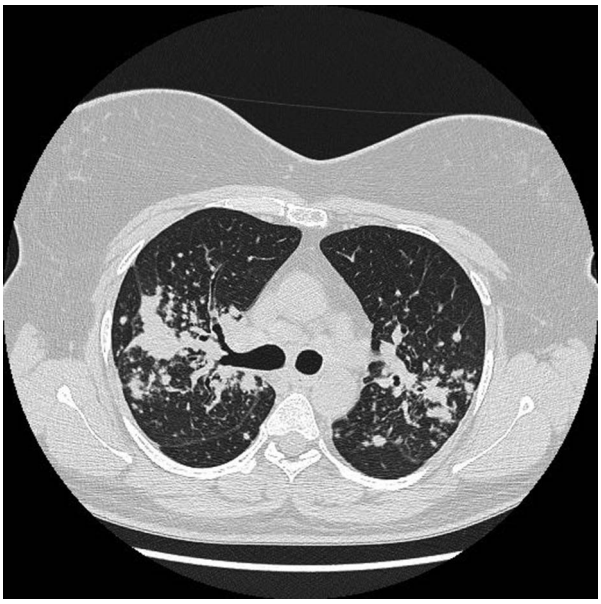

Figure 3. Chest high resolution computed tomography showing coalescent nodules forming larger irregular nodes — "galaxy sign"

The increasingly widespread application of the HRCT scan is associated with better-known radiological characteristics of sarcoidosis. Cases of histopathologically confirmed sarcoidosis with atypical manifestations in the HRCT scan are becoming more and more frequent. Sarcoidosis has been dubbed "the great imitator", just like tuberculosis before it [19, 20]. More and more authors present cases of patients with new CT patterns [21]. Radiological manifestations less frequently encountered in sarcoidosis but seen on HRCT include unilateral or isolated lymphadenopathy, parenchymal infiltrations in the form of conglomerate masses, single nodules larger than 1 cm, confluent alveolar opacities (alveolar sarcoid pattern), and cavernous changes [18]. An interesting symptom is that of granulomatous nodules coalescing together to form larger ones, which was described for the first time by Nakatsu *et al.* [21]. Bigger nodules are surrounded by smaller satellite nodules forming a structure resembling stars forming a galaxy, hence the galaxy symptom mentioned by the authors. In the study, this symptom was found in 16 out of 59 subjects. The 3-mm collimation was used for the evaluation of the larger nodules (instead of conventionally used 1–2 mm layer) which, in the authors' opinion, had a positive effect on the visualisation of peripheral micronodules, bronchioles, and branches thereof [21]. Another relatively new image of sarcoidosis in HRCT is the "sarcoid cluster sign" which was first described by Herráez Ortega. This sign is characterised by the accumulation of small punctiform nodules on the periphery of the lungs [22]. However, both "galaxy" and "cluster" signs can be seen in pulmonary TB and silicosis as well (Figure 3) [23–25].

According to the authors, the majority of such lesions are arranged in circular groups and are not located directly in subpleural peripheral regions of the upper and middle fields of the lungs [22]. Other patterns visible in HRCT have been also described such as "reversed halo" ring-shaped areas of consolidation with a central ground-glass attenuation [26–29]. Besides the precise assessment of the profusion of interstitial lesions, HRCT also indirectly allows to assess the prognosis for patients suffering from sarcoidosis by differentiating between reversible and irreversible lesions [30]. Lesions such as micronodules, nodules, or peribronchovascular thickening can withdraw spontaneously or under treatment. On the other hand, consolidations, ground-glass opacification, or linear opacities are characterised by variable reversibility. Irreversible lesions include architectural distortion, bronchiectasis, honeycombing, and emphysematous bullae (Figure 4) [31]. The role of HRCT in diagnosing sarcoidosis, particularly in cases which are difficult to diagnose, is currently broadly recognised. There is an ongoing discussion regarding the role of computed tomography in the monitoring of the activity of

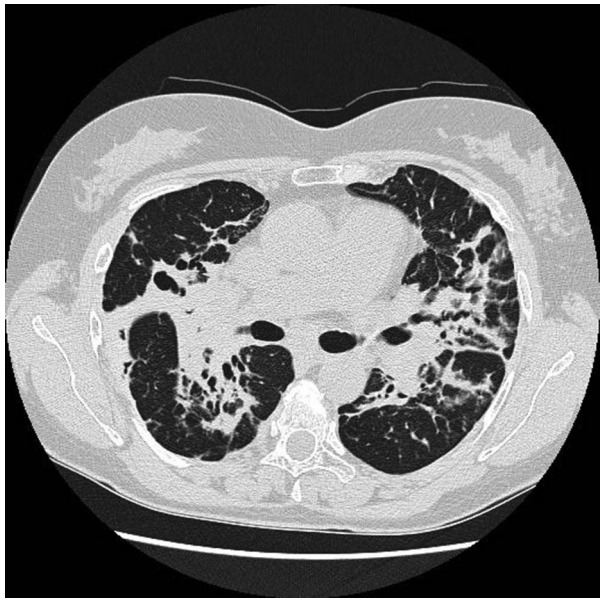

Figure 4. Lung fibrosis in sarcoidosis. Severe architectural distortion

the disease. This discussion is attempting to determine whether it should be repeated routinely in every patient, whether it should be applied only in the case of more advanced lesions visible on an X-ray, and whether it should be used in the presence of functional disorders. Ziora *et al.* analysed a group of patients who would have fallen into group 1 according to the Scadding scale. After examining these patients by HRCT, they assigned them to two separate subgroups: patients with lesions in pulmonary parenchyma, and patients without parenchymal lesions [32]. Both groups underwent regular functional testing and X-ray scans. During a 2-year long observation, no statistically significant difference was observed between the functional test results. Moreover, the share of patients with radiological stabilisation, progression, or improvement was not different in both groups [32]. Numerous studies have demonstrated the superiority of HRCT in detecting lesions corresponding to fibrosis and in diagnosing more advanced stages of the disease. Chest X-ray scans revealed fibrosis in 5–10%, whereas CT scans resulted in such changes being described in as many as 20–50% of patients [33–35]. Currently, there are no clear data which would allow to determine whether repeated HRCT scans in patients suffering from sarcoidosis have any effect on making therapeutic decisions. Levy *et al.* recommend repeated HRCT scans if the clinical image changes or complications are suspected [36 37]. Unlike X-ray scans, some lesions visible in HRCT demonstrate a relationship with pulmonary function disorders [38–40]. Drent *et al.* demonstrated correlations between features visible in HRCT such as thickening of the bronchovascular bundle, intraparenchymal nodules, septal and non-septal lines, or focal pleural thickening on one hand, and results of respiratory functional tests on the other [38]. However, such a relationship has not been demonstrated for consolidations, ground-glass opacifications, or enlargement of lymph nodes. Furthermore, the study also demonstrated the superiority of the HRCT scan over a conventional X-ray scan in terms of their relationship to the respiratory function parameters of the lungs [38].

Gallium-67 scintigraphy

Another imaging method used in sarcoidosis is Gallium-67 scintigraphy (Ga-67), albeit less and less frequently so. Its sensitivity in detecting pulmonary sarcoidosis ranges from 60 to 90% [41, 42]. For patients suffering from sarcoidosis, two gallium uptake patterns are characteristically used known as lambda and panda, and are named as such because of their shapes [43]. The lambda pattern comprises the gallium uptake in the parahilar and infrahilar lymph nodes along with the paratracheal lymph nodes on the right-hand side [43]. The panda pattern is associated with a symmetrical uptake in parotid and lacrimal glands, as well as in submandibular and sublingual salivary glands. The constellation of the lambda and panda pattern uptake is recognised as very characteristic for sarcoidosis [17, 44]. Gallium-67 scintigraphy is more sensitive than an X-ray scan and can be applied for the evaluation of the staging of the disease activity, for the assessment of treatment results, and for the prediction of relapses. However, a more widespread application of this method is limited due to its restricted availability, cost, exposure to radiation, and duration [43].

Scintigraphy with other tracers

It is also possible to use scintigraphy with other tracers. Somatostatin receptor (SR) scintigraphy is based on the uptake of octreotide derivatives, such as 99mTc-octreotide or other somatostatin derivatives, by somatostatin subtype 2 receptors. The application of this method affected therapeutic decisions of Piotrowski *et al.*, who in their study compared the predictive value of scintigraphy with 99mTc-octreotide and biomarkers (SACE, CRP, markers of calcium metabolism, lymphocytes in BALF, 8-isoprostane in exhaled

breath condensate) [45]. The authors observed the uptake in the area of pulmonary parenchyma in patients who had been previously disqualified from treatment. The attempted therapy in such patients was associated with a partial regression of interstitial changes. However, it was decided to terminate the treatment in patients subjected to long-term therapy with glucocorticosteroids who also had a negative scintigraphy result. In relation to the biomarkers, a significantly higher level of EBC 8-IP was demonstrated in patients with a positive uptake in scintigraphy as compared to patients with a negative scintigraphy result. Furthermore, a positive correlation between the uptake ratio and the level of SACE in the group of patients with a positive scintigraphy result was observed [45]. French authors compared gallium scintigraphy with SRS in a group of 18 patients with recognized sarcoidosis. SRS appears to be accurate and contributes to a better evaluation of organ involvement in sarcoidosis patients, especially those treated with corticosteroids [46].

Single-photon emission computed tomography

The image of classical scintigraphy is obtained by projecting a three-dimensional object onto a plane. This technique is extended by the use of several gamma cameras rotating around the patient, which allows to obtain an image of selected layers. This method, referred to as single-photon emission computed tomography (SPECT), was applied by Vis *et al.* [47]. The SPECT/CT scan was performed in a group of 10 patients after the administration of technetium-99m(99mTc) -labelled infliximab. The patients demonstrated a correlation between the radiomarker accumulation in SPECT and the lab parameters (sIL-2R, ACE level in serum, ACE Z-score, CD4/CD8 level in BAL), functional test disorders, as well as the PET scan with fluorodeoxyglucose. The study demonstrated variable selective accumulation of the radiomarker in SPECT, which correlated positively with the lab markers and negatively with the pulmonary function, as well as with the PET scan [47]. A similar result was also obtained by — without limitations — Galli *et al.*, who demonstrated a negative correlation between the uptake of 99mTc-labelled infliximab and the activity measured in the PET scan. The scan with the application of ^{99m}Tc-labelled infliximab with the TNF alpha inhibitor may be used in the future to select groups of patients where this therapy will be effective. However, further research into this subject is required [48].

Positron-emission tomography

Another study in the field of nuclear medicine is positron-emission tomography (PET). Simultaneous use of computed tomography allows to shorten the duration of the scan and additionally improve the accuracy of descriptions of anatomical changes detected (PET/CT) [49]. The most commonly used marker is ^{18}F-FDG, which is a glucose analogue. Transported through the cell membrane inside the cell, it is subjected to phosphorylation by hexokinase. Consequently, a molecule of 18F-FDG-6 phosphate is formed and it is not metabolised any further. The accumulation of macrophages exhibiting increased metabolism in the area of sarcoid granulomas causes an uptake of the administered marker by glucose transporters GLUT-1 and GLUT 3 [50]. The superiority of 18F-FDG PET/CT over Gallium-67 scintigraphy was demonstrated by Braun *et al.* in their study. They confirmed the very high sensitivity of the former in detecting active foci within the chest reaching 100%, as compared to 71% when scintigraphy is applied [49]. In addition, the advantages of FDG-PET include having 3 times lower radiation dose and shorter time of procedure [51].

The research points to a good correlation between an X-ray and PET scan in the case of higher stages of sarcoidosis according to the Scadding scale [52]. A chest X-ray showing no lesion, which stands for stage 0 in this classification, does not exclude a positive result of the PET scan. In the study of Mostard *et al.*, in 27% of patients with no symptoms in the chest X-ray, a marker uptake was detected. In advanced stage 4 patients, activity was also visible in the PET scan for the majority of subjects (88%) [51]. The study also compared HRCT (on the basis of the score proposed by Oberstein) with images obtained in PET scans (occurrence/non-occurrence of changes). In this case, patients with the score 0, according to Oberstein, did not have any changes visible in the PET scan. Conversely, in subjects where HRCT scan revealed features of fibrosis, the activity was frequently visible in the PET scan. This may be indicative of a still active and potentially reversible inflammatory process [52]. The selection of patients in which the inflammatory process is still ongoing despite fibrosis having been found may allow clinicians to choose the optimum treatment in this group of patients. PET can be applied in the diagnostic procedure of the disease; it allows to detect active inflammatory lesions in patients with symptoms,

even if other diagnostic methods give negative results. PET also identifies the best locations for biopsy. It is used for monitoring the activity of the disease, and diffuse parenchymal infiltrations detected in this scan allow to predict further loss of the pulmonary activity [53, 54]. Sobic-Saranovic *et al.* demonstrated that in a group of 90 patients subjected to 18F-FDG PET/CT scans, 81% of them had decisions regarding further treatment made based on the scan result. In the majority of patients in which an increased marker uptake was observed in the PET scan, the previously administered dosage of glucocorticosteroids was increased or a new medication was used. On the other hand, patients with a negative scan result had their dosage reduced or the medications were discontinued altogether [55]. PET can be helpful in deciding whether patients with severe sarcoidosis should receive biological treatment. In the study by Vorselaars *et al.*, a PET scan was performed prior to the onset of therapy and then again after 26 weeks [56]. The second follow-up scan revealed a reduction of the standardised uptake value in the region of mediastinum by 2.97 ($P < 0.0001$), and in the region of lung parenchyma by 3.93 ($p < 0.0001$) as compared to the output SUV values. The higher the SUV values were prior to the administration of infliximab, the greater the improvement was in terms of the FVC values observed after treatment [56].

The role that PET can play in the evaluation of the activity of the disease in the future is pointed to by the study comparing the serological markers of the activity of the disease used so far, such as ACE and soluble interleukin 2 receptor [57]. In a retrospective study, 36 patients with recently diagnosed symptomatic disease had a PET scan performed and their levels of ACE and sIL-2R were measured. F-FDG PET was positive in as many as 34 out of 36 patients (94%), elevated levels of ACE were observed in 13 patients (36%), and increased sIL-2R in 17 (47%) [57].

Additional benefits offered by a PET scan also include the extent of the examination which covers the entire body and can sometimes allow to find sarcoid foci in other organs. This scan can constitute an alternative for patients with suspected cardiac sarcoidosis in whom an MRI scan cannot be performed (e.g. due to the presence of a pacemaker or ICD) [53].

Unfortunately, the uptake of ^{18}F-FDG occurs in sarcoid as well as neoplastic lesions. Therefore, this examination is not suitable for differentiating between sarcoidosis and neoplasms. A group of Japanese researchers raised the subject of using another marker, ^{18}F-FMT (Fluorine-18-α-Methyltyrosine) [58]. The study covered a group of 24 patients with sarcoidosis that also had an additional suspicion of a neoplastic process occurring. The control group included patients with diagnosed lung cancer. In all the subjects from the examined group, the uptake of ^{18}F-FDG in lymph nodes was observed, whereas ^{18}F-FMT was not accumulated in them. In extranodal organs, such as the liver, spleen, and bones, the PET scan result was positive if the former marker was used and negative with the latter. The neoplastic disease was not diagnosed in any of the study subjects [58]. The mean standardised uptake values (SUV) in the examined group for ^{18}F-FDG and ^{18}F-FMT were 5.01 ± 2.15 and 0.77 ± 0.24 respectively, whereas in the control group consisting of patients suffering from the neoplastic disease the values were 6.34 ± 2.52 for ^{18}F-FDG and 1.54 ± 0.82 for ^{18}F-FMT. On the basis of these results, the authors concluded that the additional use of ^{18}F-FMT besides ^{18}F-FDG may facilitate the differentiation between sarcoid and malignant changes [58]. Like is the case with Gallium-67 scintigraphy, the common use of PET and PET/CT scans is limited due to their limited availability and high costs. Figures 5 and 6 present PET results of patients with sarcoidosis.

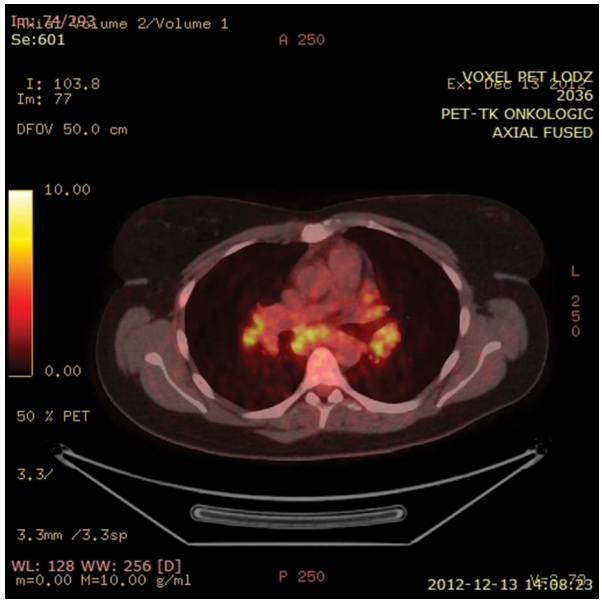

Figure 5. PET-CT axial view showing increased 18F-FDG uptake in both hilar and subcarinal lymph nodes. The patient was suspected of lymphoma, after endobronchial ultrasound (EBUS) transbronchial needle biopsy sarcoidosis was confirmed

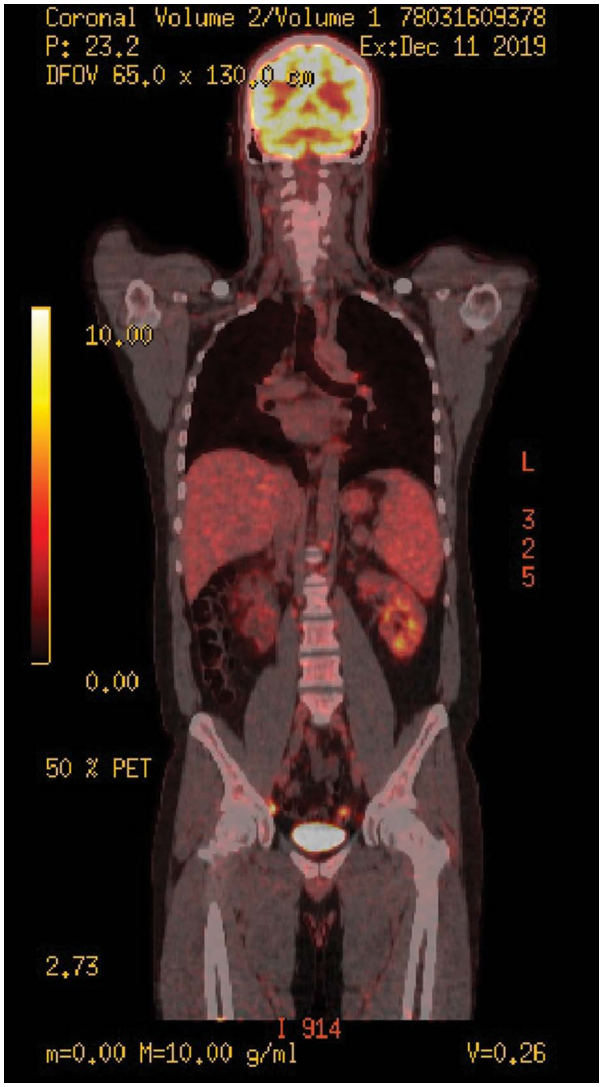

Figure 6. PET-CT coronal view. The patient with chronic sarcoidosis, presenting signs of radiological remission in most recent CT. PET was performed to exclude suspected extrathoracic manifestation of sarcoidosis. Increased uptake of 18F-FDG in cervical, intrathoracic and pelvical lymph nodes

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a recognised imaging method in the diagnostic procedure of cardiac sarcoidosis and in evaluating changes in the structure of bones or in the central nervous system, but it is rarely applied for the evaluation of the lung parenchyma due to the limitations of this method associated with the presence of air in the lung tissue and the physiological motion of the chest (cardiac pulsation, respiration) [17, 59–61]. Most studies have demonstrated the superiority of HRCT over MRI in the evaluation of interstitial lesions [17]. Brady *et al.*, who used the technique of late enhancement in magnetic resonance imaging in their work, obtained comparable results when using HRCT and MRI in the description of lesions suggestive of fibrosis [62]. Consistency between MRI and HRCT in the diagnosis of pulmonary sarcoidosis was also confirmed by Chung *et al.*, who evaluated images in terms of the presence of interstitial changes, reticulations, nodules, and condensations according to a 3-point scale in the division into lobes. Furthermore, they noticed that a better correlation between the scans related to the upper lobes [63]. In relation to lymphadenopathy, MRI is a technique demonstrating a similar value to computed tomography in detecting enlargement of hilar and mediastinal lymph nodes. Nevertheless, MRI facilitates the evaluation of the extent of lymphadenopathy as it is differentiated better from the vascular system of the lungs [64]. Chung *et al.*, referred to above, analysed MRI scans performed in the heart examination protocol and noticed that some patients with sarcoidosis had lymph nodes with a specific appearance: a hypo-intensive signal inside and a hyper-intensive rim. This symptom was called a dark lymph node sign by the authors. Retrospectively, it occurred in 49% of patients from the examined group [65]. New signs being described in MRI scans give hope for better characteristics of sarcoidosis based on MRI and potentially, for a more common use of this method in the future.

Endoscopic ultrasonography

Many studies assessing the possibility of using endoscopic ultrasonography in the evaluation of lymph nodes in patients suffering from sarcoidosis have been conducted in recent years. EBUS/EUS already enjoys an established position in the diagnosis of sarcoidosis [4–6]. EBUS allows to evaluate 2R, 4R lymph nodes on the right-hand side, 2L, 4L lymph nodes on the left-hand side, as well as paratracheal and subcarinal regions (group 7). Additionally, EBUS helps to access hilar lymph nodes (group 10) and the interlobar region of group 11. An EUS scan allows to examine the subcarinal region 7, the paraesophageal region 8, and region 9. It is also possible to access the paratracheal region on the left-hand side (4L), and to partially assess the left hilar region as well (10 L). A meta-analysis covering 14 studies (which covered 2097 subjects in total) demonstrated a high diagnostic efficiency of this method,

reaching 79%. Its sensitivity and specificity were estimated to be 84% and 100%, respectively [66]. The percentage of positive results obtained thanks to the EBUS-TBNA method is higher in patients with stage 1 than 2, which probably results from a higher density of granulomas in stage 1. EBUS allows not only to collect the material, but also to evaluate lymph nodes. In their study, Erol *et al.* compared the image of lymphadenopathy in tuberculosis and sarcoidosis [67]. Lymph nodes in sarcoidosis formed conglomerates more often than in tuberculosis and were also characterised by higher homoechogenicity. In tuberculosis, lymph nodes were more frequently oval in shape and more heterogenous, and their foci of necrosis were bigger as well. Due to the fact that both diseases belong to the group of granulomatous diseases, lymph nodes had a similar vascular pattern [67]. Agrawal *et al.* compared inter alia metastatic lymph nodes with lymph nodes enlarged due to sarcoidosis. In this case, features that differentiated lymph nodes in the course of proliferative diseases from sarcoid ones were predominantly heterogenicity, clear margins, signs of coagulative necrosis, and the presence of the central hilar structure (CHS) [68]. Regrettably, due to the invasiveness of this method, it cannot be practically used in the monitoring of the activity of the disease [69].

Transthoracic ultrasound scan

Nowadays, advanced high-resolution ultrasound apparatuses with facultative employment of colour Doppler allow to examine the mediastinum and the heart region. In their study, Hirche *et al.* compared the application of a transthoracic ultrasound scan with a conventional X-ray scan [70]. The use of an ultrasound scan in the evaluation of mediastinal lymph nodes proved to be up to 90% effective. Lymph nodes in patients who on the basis of a chest X-ray had been assigned to groups 1–3 according to the Scadding score were particularly well visible. This is in contrast to group 4, in which the ultrasound visualisation of lymph nodes turned out to be insufficient. A benefit stemming from this method is the fact it allows for a morphological assessment of the lymph nodes, which is not possible based on an X-ray scan. In the study summary, however, the authors emphasise that the sensitivity of this method in detecting lymphadenopathy is highly dependent on the experience and skills of the operator and the class of the device [70].

Conclusion

Currently, we have observed constant progress in the field of imaging. Thanks to the development of advanced techniques, it is possible to understand sarcoidosis better, to grasp its natural course and the effect of treatment onto the activity of the changes. A chest X-ray scan remains the basic examination at the stage of diagnosis, as well as in the subsequent monitoring of the disease. High-resolution computed tomography allows for a more precise description of lesions with reference to their location. Studies point to the superiority of FDG PET over both methods in the evaluation of active inflammatory changes. The use of other markers in PET, such as FAMPT for example, may be helpful in differentiating between sarcoid and malignant changes in the future. Ultimately, deciding which diagnostic method is best for each individual patient is the responsibility of the clinician. The decision should be made on the basis of an analysis of possible profits and losses considering the repeatability of the results, availability of the method, its invasiveness, radiation exposure, cost, and possible influence on therapeutic decisions. It is worth emphasizing, that the average radiation dose in the case of X-ray imaging (PA and lateral view) ranged from 0,05–0,25 mSv, in the case of HRCT from 2,1–3,5 mSv, and in the case of PET from 7–11,5 mSv. Bearing in mind that most of the patients with sarcoidosis are between the ages 20 and 40 years old and will never require treatment, the decision about repeated studies involving a high dose of radiation should be made prudently [72].

Conflict of interest

None declared.

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Treatment of persistent air leak with endobronchial valves

Abstract

Persistent pulmonary air leaks are usually treated conservatively with prolonged thoracostomy tube drainage. In case this approach fails, surgical revision used to be the only option. This case report describes the successful treatment of a 66-year old patient who developped a pulmonary air leak after cardiothoracic surgery that persisted despite attempted surgical repair and talc pleurodesis. The treatment was successfully completed with endobronchial valves thereby demonstrating that treatment with endobronchial valves doesn't only represent an alternative to surgery, but that it can also be successful in case surgical intervention fails.

Key words: pulmonary air leak, endobronchial valve

Adv Respir Med. 2020; 88: 28–30

Introduction

A 66-year old man developed an air leak on the left side after minimally invasive direct coronary artery bypass surgery which was performed via anterolateral thoracotomy along the fourth intercostal space. He had a history of chronic obstructive pulmonary disease with bullous emphysema, and had a smoking history of 50 pack years. Because the air leak persisted on the sixteenth postoperative day, the patient underwent surgical revision where stapling of the lung at the suspected location of the leak was performed, followed by talc pleurodesis. Nonetheless, a significant leak was still observed on the sixth day after surgical revision. Consequently, it was decided to attempt to reduce the air leak by placing Zephyr endobronchial valves (EBV's) using rigid bronchoscopy while the patient was under general anaesthesia. First, a balloon-tipped catheter was inserted into the left upper lobe bronchus and the balloon was inflated to block the airflow. The chest drain was observed and a complete cessation of the air leak was noted. Subsequently, the balloon catheter was deflated and sequentially repositioned into the segmental bronchi of the upper lobe. However, occlusion of both of them did not result in a decrease of the air leak. A valve was therefore placed in each of the segmental bronchi (Figure 1) of the upper lobe bringing the total number of valves used to three (the patient only had two upper division segmental bronchi, besides the lingular bronchus). Approximately five minutes after the third valve was deploy-

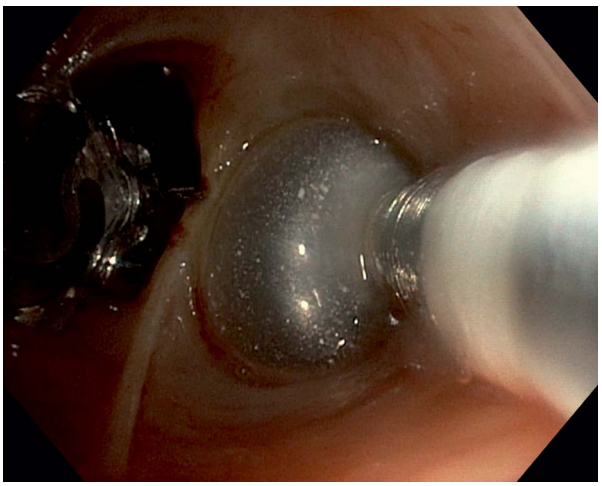

Figure 1. Endoscopic image demonstrating one valve in the medial upper lobe bronchus and the placement of a second valve in the lateral upper lobe bronchus

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ed, a decrease of the air leak to 0–10 mL/min was observed. The first day after the procedure, the patient developed respiratory insufficiency, which was quickly resolved after treatment with bronchodilators, systemic corticoisteroids and a short period of bilevel non-invasive ventilation. A chest radiograph showed elevation of the left diaphragm suggesting atelectasis of part of the left lung, but no pneumothorax. The chest tube was successfully removed on the fifth day after EBV placement and the patient was discharged home one week later with supplemental oxygen (4 L/ /min). The valves were removed 15 weeks after their placement using rigid bronchoscopy. The patient was last seen at follow-up three weeks after valve removal. His respiratory condition remained stable. His chest radiograph continued to show elevation of the left diaphragm. The patient still needed supplemental oxygen, but the flow rate was now reduced to 2 L/min.

Discussion

Pulmonary air leaks arise when there is an abnormal communication between the bronchial or alveolar spaces and the pleura through a bronchopleural or alveolar-pleural fistula [1]. A pulmonary air leak is deemed persistent when it lasts for more than 5 to 7 days postoperatively [2]. Persistent air leaks occur after 15% of thoracic procedures [3]. Of the air leaks still existing on the fourth postoperative day, 83% will still be present on the seventh postoperative day [2]. They often lead to increased morbidity resulting in prolonged hospital stays and increased healthcare costs [4].

Persistent air leaks are usually treated conservatively with prolonged thoracostomy tube drainage [1, 2, 5]. In case this approach fails, surgical revision used to be the only option. It is important to note that the patients who suffer from a persistent air leak also frequently suffer from an underlying lung disease with low FEV_1 and decreased functional status. This makes surgical intervention challenging. In addition, several other factors in this population contribute to poor wound healing such as malnutrition, diabetes, steroid use *etc.* [1]. Consequently, during the past few decades, numerous minimally invasive techniques have been developed ranging from pleurodesis with chemicals or blood components, to bronchoscopic techniques using coils, stents, antibiotics, ethanol and several other glues or adhesives [5]. However, controlled studies showing consistent efficacy are lacking.

EBVs were originally developed as a minimally invasive alternative for lung volume reduction surgery in severe emphysema [6]. EBVs are one-way valves that inhibit air-entry into a segmental bronchus, but allow for drainage of air and secretions [4]. Snell and colleagues were the first to report on the succes of EBVs for the treatment of a broncho-cutaneous fistula in 2005 [7]. Since then, several case reports and case series on the use of endobronchial valves for treatment of persistent air leaks have been published. One of the largest studies using endobronchial valves was published by Traveline and colleagues [4]. They reported a complete resolution of air leak in 47.5% of patients and a reduction of air leak in 45% of patients. In 2016, Gilbert and colleagues [8] reported data on 75 patients who recieved intrabronchial valves for a persistent air leak. Air leak resolution occured in 56% of these patients within one day or less from intrabronchial valve placement. In 37% of patients, the air leak still persisted one week after valve placement. Generally, it is recommended that the valves are removed 4 to 6 weeks after placement, but in a considerable number of cases the valves were left in place without apparent significant impairment [1, 4, 8, 9]. The number of reported adverse events is low. These include pneumonia, bacterial colonization, empyema, decrease in FEV1 and valve migration or expectoration [1, 4, 9]. Furthermore, if respiratory insufficiency occurs, the valves can be removed again.

Overall, the results indicate that endobronchial valves represent an effective treatment for persistent air leaks, especially in patients who are unfit for surgery. Furthermore, our case demonstrates that treatment with EBVs not only represents an alternative to surgery, but that it can also be succesful in case surgical intervention fails. Still, the current knowledge is largely based on case reports and retrospective case studies with a limited number of patients. Accordingly, prospective randomized controlled trials are needed.

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Double or nothing: old chest X-ray as a clue to lung mass

ABSTRACT

Mucoepidermoid carcinoma is a young person's lung cancer with no apparent causal connection to smoking. It exhibits slow growth, which can make it challenging to detect changes in size on serial chest imaging. Another way of describing its growth pattern is that mucoepidermoid carcinoma has an unusually long volume doubling time. We describe a case of an incidental lung nodule diagnosed as mucoepidermoid carcinoma in which a prior chest radiograph provided a clue to the indolent nature of the abnormality and therefore argued against typical lung cancer. In the same context, we underscore the value of volumetric analysis in improving the accuracy of nodule growth determinations, which further strengthens the argument that the importance of locating prior imaging has not diminished in contemporary pulmonary practice.

Key words: mucoepidermoid carcinoma, lung cancer, lung mass, volume doubling time, volumetric analysis

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Introduction

The incidental pulmonary nodule is a common reason for pulmonology consultation in the current era of abundant medical imaging. While in an active or former smoker conventional smoking-related lung cancer is the dominant clinical concern, diagnostic considerations are more diverse in the never-smoker. In the evaluation of such patients, especially as imaging has become increasingly sophisticated, the importance of comparison films — something basic and cost-free — is nowadays easily overlooked. We present a case of mucoepidermoid carcinoma of the lung in a young never-smoker, which illustrates that the value of prior images has not diminished even in today's pulmonary practice. Besides discussing this rare indolent lung malignancy, we also address the concept of volumetric analysis — a modern technique that has made comparison imaging all the more relevant.

Case report

A 49-year-old man presented to the emergency department (ED) of our trauma center after a motor vehicle collision in which he sustained a minor leg injury. On further questioning, he reported intermittent nonproductive cough and night sweats over the past 3 months as well as unintentional weight loss of approximately 7 kg during the same period. His medical history included hypertension and diabetes mellitus. He had no personal history of lung disease or malignancy, although approximately 11 months earlier he had been diagnosed with pneumonia at another hospital and treated with outpatient antibiotics. No post-treatment follow-up took place. He had never smoked but had experienced significant second-hand smoke exposure in his youth.

Upon examination in the ED, he was hemodynamically stable and afebrile. Cardiopulmonary auscultation was unremarkable. There were no palpable lymph nodes or masses. Routine laboratory evaluation was notable for normocytic anemia

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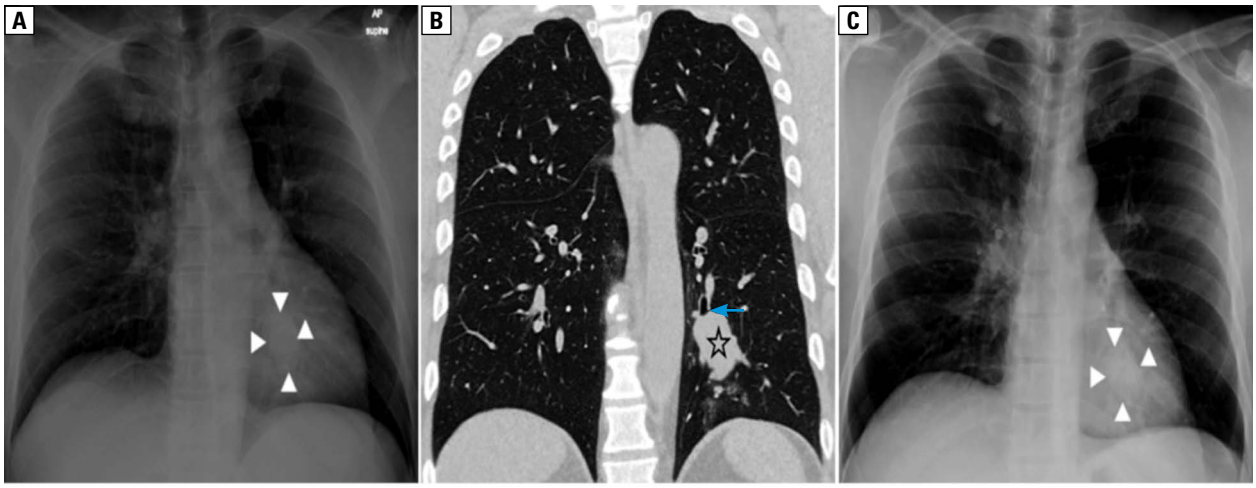

Figure 1. A. Frontal chest radiograph performed in the emergency department of our institution showed an ovoid, mass-like density in the retrocardiac region of the left hemithorax (arrowheads); **B.** Computed tomography of the chest (coronal reconstruction) performed without administration of intravenous contrast confirmed the presence of a lung mass in the posterior basal segment of the left lower lobe (star) with associated obstruction of the segmental bronchus (blue arrow); **C.** Comparison frontal chest radiograph performed at an outside institution approximately 11 months prior illustrated minimal interval growth of the lesion (arrowheads)

(hemoglobin 10.9 g/dL, normal range 14.0–18.0 g/dL). Blood interferon-gamma release assay testing was negative. Plain frontal chest radiograph (CXR) performed as part of the trauma protocol revealed an approximately 4 cm ovoid density in the retrocardiac region of the left hemithorax (Figure 1A). Subsequent computed tomography (CT) of the chest performed without intravenous contrast administration confirmed the presence of a lobular mass in the posterior basal segment of the left lower lobe (LLL) measuring approximately 3.8 cm in the greatest dimension (Figure 1B). Prior CXR taken 11 months earlier for the reported pneumonia demonstrated the same lesion (Figure 1C) with interval change in diameter of only 8 mm.

On bronchoscopy, an endobronchial mass occupying the posterior basal segment bronchus of the LLL (LB10) was noted. Biopsy revealed clusters of mucinous cells interspersed among intermediate and squamoid cells with conspicuous absence of cellular atypia and mitotic activity consistent with low-grade mucoepidermoid carcinoma (Figure 2).

Upon establishing the diagnosis of low-grade MEC, the patient was discharged from our hospital with instructions for evaluation by the thoracic oncology team of a cancer center located closer to his residence. He has not been seen in our institution since the time of discharge but reportedly has undergone resection of the MEC.

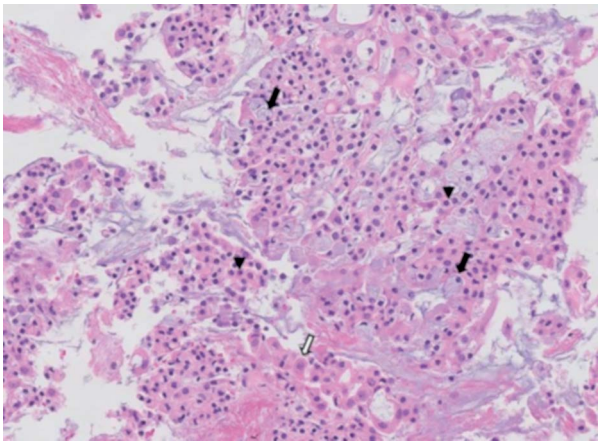

Figure 2. Microscopic section of the lung tumor showing mucinous cells (black arrows), intermediate cells (black arrowheads), and a rare squamoid cell (white arrow) (Hematoxylin & eosin, original magnification × 200). Cellular atypia and mitotic figures are not observed (Ki67 index = 2%). These findings are consistent with low-grade mucoepidermoid carcinoma of the lung. Immunohistochemical stains were performed to exclude competing histologies and were confirmatory

Discussion

In a relatively young never-smoker with an incidentally detected lung mass, cell types other than the most common smoking-related histologies, which are small-cell carcinoma, squamous cell carcinoma, and lung adenocarcinoma, should merit serious consideration. There is a category of indolent lung malignancies not directly linked to smoking that deserves attention in such a scenario (Table 1).

Support for the presence of one of these low-grade tumors would be provided by demonstrating that the so-called "volume doubling time" of the mass in question is very long. The volume doubling time (VDT) of a spherical tumor is a lo-

Table 1. List of examples of slow-growing malignant primary lung tumor histologies

Histological cell type	Remarks
Carcinoid	Spherical, vascularized, usually endobronchial
Mucoepidermoid carcinoma	Current case
Adenoid cystic carcinoma	Like MEC arises from submucosal salivary glands
Granular cell tumor	Extremely rare
BALT lymphoma	Indolent lymphoproliferative disorder

BALT — bronchus-associated lymphoid tissue; MEC — mucoepidermoid carcinoma

garithmic function that can be solved — assuming a constant growth rate — by measuring its diameter on two different CXRs separated by a known period of time. According to the theory of exponential tumor growth, the more rapidly dividing the neoplasm, the shorter will be its VDT in an exponential manner [1]. For example, using diameter measurements on CXR, it has been determined that lung adenocarcinoma has a mean VDT of about 220 days, whereas the much more active small cell carcinoma has a VDT of about 86 days, with squamous cell carcinoma falling in between at about 115 days [2]. Limitations of the planar approach (CXR or CT) for extrapolating change in volume based on change in diameter include the assumption that the lesion is perfectly spherical, that it grows symmetrically, and that its diameter can be reliably determined — something that is subject to significant interobserver variability [3]. Additionally, because the volume of a sphere is related to the cube of its diameter, a simple comparison of diameters underestimates the degree of volume change. For example, a 10-fold increase in diameter from 1 mm to 1 cm (10 mm) corresponds to a 1000-fold (10^3) increase in volume. In the modern era of CT scanning, it has become possible to generate spatial reconstructions of lung nodules for volumetric analysis, which overcomes the deficiencies of two-dimensional methods and allows for direct volume calculations and comparisons (Figure 3). The expectation is that volumetry therefore results in more accurate determinations of VDT [4].

With the above principles in mind, it was felt that the most important initial diagnostic maneuver would be something fundamental and cost-free: obtaining the outside CXR performed 11 months earlier for pneumonia, which indeed demonstrated the same lesion (Figure 1C) with interval change in diameter of only 8 mm, corresponding to a doubling time of 359 days. Although compatible with some estimates for more indolent lung adenocarcinomas and even squamous cell carcinomas, such slow growth prompted consideration of unusual cell types such as MEC: the eventual diagnosis.

MEC is a malignant salivary gland neoplasm that can rarely arise from the minor salivary glands of the bronchial submucosa. It accounts for < 1% of all lung cancers and is often diagnosed at an unusually young age: nearly a third of patients are under 40 [5]. There is no definitive etiological link to cigarette smoking, which likely accounts for its early presentation [6]. The usual gross appearance is that of a polypoid mass confined to the airway lumen and frequently associated with post-obstructive infection or mucus plugging [7]. MEC can be classified as low-grade or high-grade based on the degree of cellular atypia. With rare exceptions, low-grade tumors remain localized and therefore manifest 5-year survival rates exceeding 90% [5]. High-grade MEC, on the other hand, is an aggressive malignancy with a propensity for local invasion and distant spread; its survival figures are far inferior to those of low-grade MEC [5]. Surgical resection is considered the primary management strategy for this uncommon lung cancer and is feasible in the vast majority of cases.

This case illustrates how something as basic as a comparison with a prior CXR can help assess the growth pattern of a lung mass and thereby categorize its aggressiveness. Strikingly indolent behavior increases clinical suspicion of unusual lung malignancies, among them MEC. In hindsight, it is apparent that what was diagnosed as pneumonia 11 months prior to our encounter with this patient was actually lung cancer in a young never-smoker, which highlights another important use of comparison chest imaging: documentation of pneumonia resolution following treatment.

Conflict of interest

None declared.

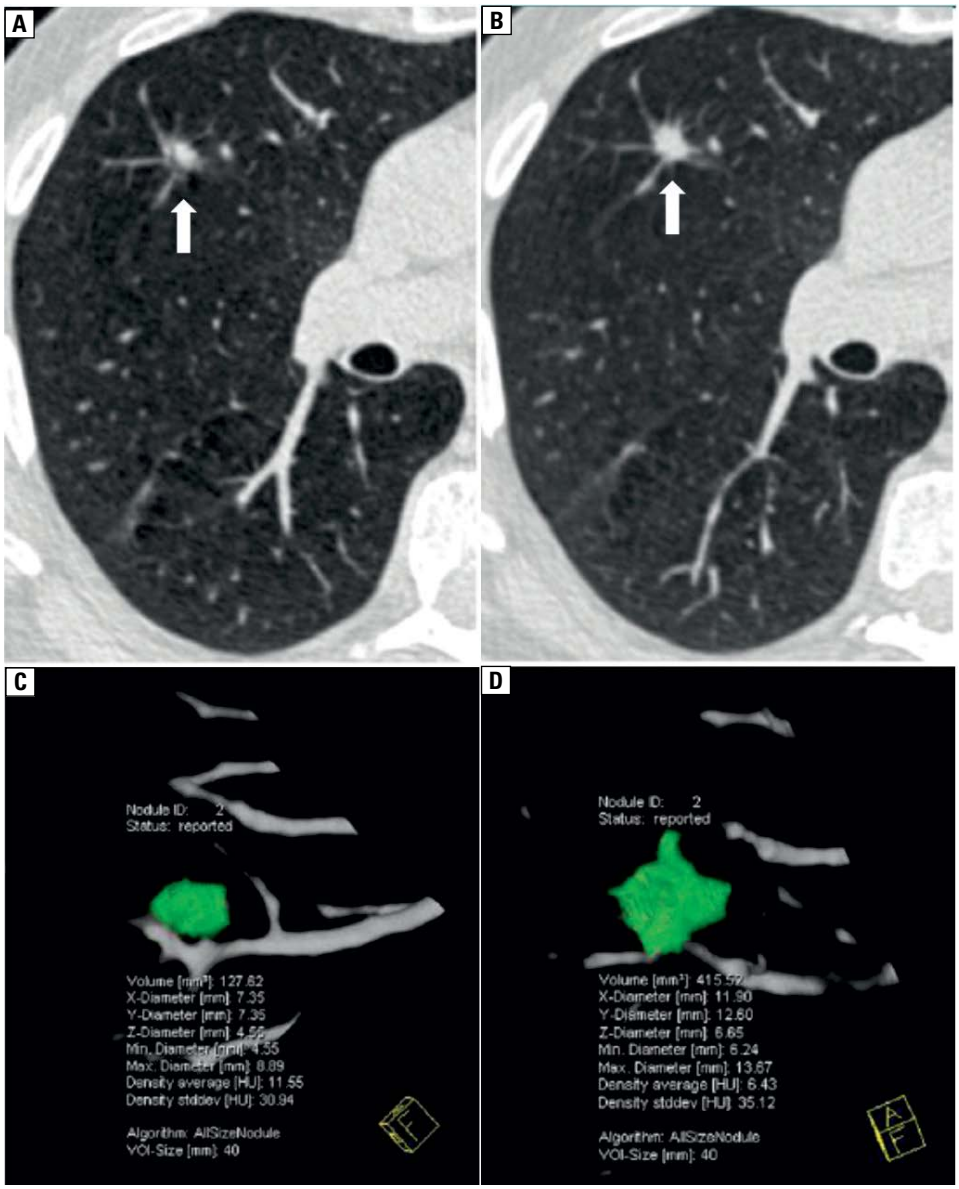

Figure 3. Example of volumetric analysis applied to a solitary pulmonary nodule (white arrow) detected on an initial (**A.**) and 12-month follow-up (**B.**) chest computed tomography. The corresponding spatial reconstructions used for volumetric calculations are shaded in green in panels **C.** and **D.** The interval increase in nodule diameter of 13 mm amounted to a 15% change, whereas the corresponding increase in volume of 288 mm^3 amounted to a 325% change. The volume doubling time (VDT) extrapolated from the change in diameter was 580 days, an excessively long duration for usual lung cancer histologies. The VDT derived from volume measurements was 214 days, entirely consistent with typical lung cancer [4]. This patient turned out to have adenocarcinoma of the lung (Image reused, with permission, from Radiology 2017 ©RSNA [4])

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Hemoptysis with lung cavity — triple whammy

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A 37-year male presented with cough and dyspnoea for 9 months that had worsened over the past 7 days and was complicated by haemoptysis. Haemoptysis was moderate in amount with 3–4 episodes per day consisting of fresh red blood and was not associated with bleeding from any other site. There was no history of fever or weight loss. Dyspnoea was persistent and progressive to dyspnoea at rest on presentation. Two years ago, the patient had undergone 6 months of anti-tubercular therapy for sputum positive pulmonary tuberculosis.

On examination, the patient was conscious and oriented. His blood pressure was 110/70 mm Hg, pulse was 120/minute and respiratory rate was 34/min. Pallor was present but without any icterus, pedal oedema or lymphadenopathy. Respiratory system examination revealed vesicular breath sounds with bilateral crackles.

Investigations revealed Haemoglobin 9 gram% with normal organ function tests and hypoxemic respiratory failure. Chest X-ray and a CT examination of the chest are provided below (Figure 1 A–E).

Flexible bronchoscopy was essentially normal. Sequential bronchoalveolar lavage (BAL) fluid instillation became progressively bloodier upon aspiration and contained hemosiderin-laden macrophages confirming diffuse alveolar haemorrhage (DAH). BAL was negative for acid-fast bacilli (AFB), pneumocystis pneumonia (PCP), fungal mount, malignant cytology, and pyogenic/mycobacterial culture.

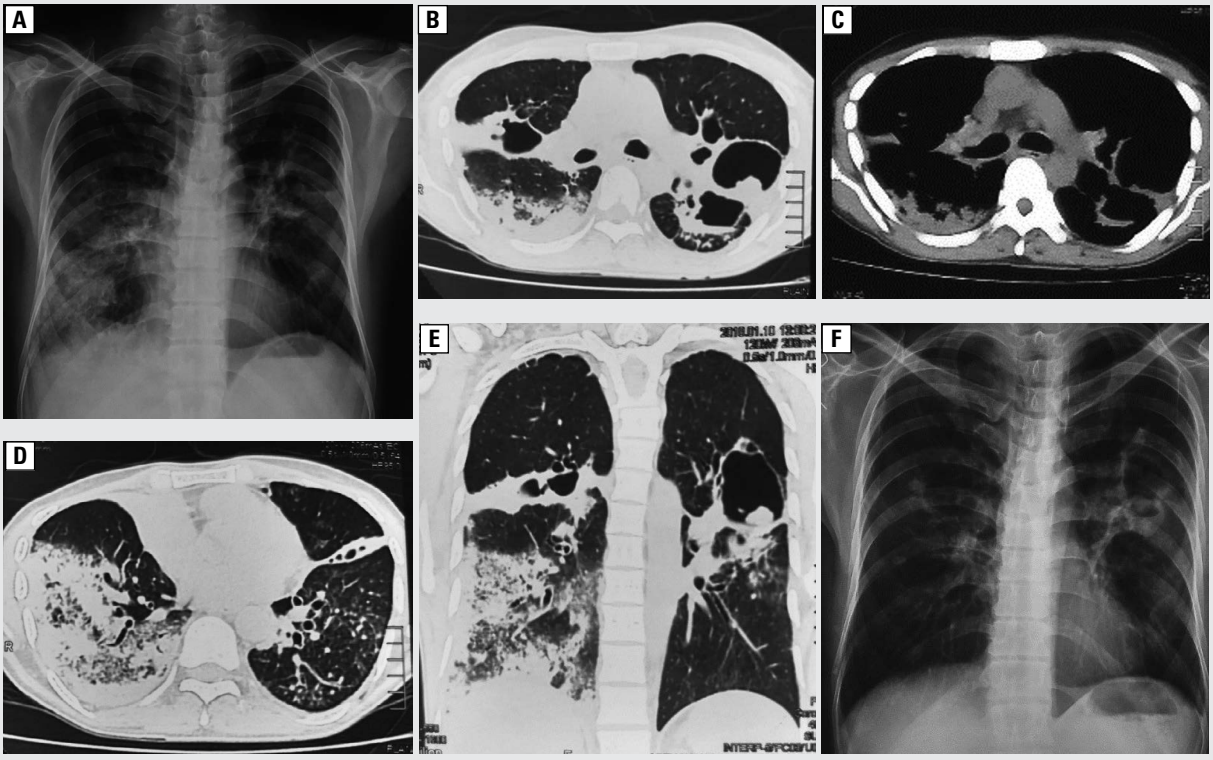

Figure 1. A. Chest X-ray showing bilateral cavitary lesions with right lower zone opacities; **B–E.** CECT chest suggestive of bilateral cavities with a fungal ball in the left upper lobe cavity. Also, bilateral dense alveolar opacities are present and are more prevalent in the right lower lobe; **F.** Chest X-ray showing resolution

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Serum precipitins and IgG against aspergillus were positive. Further probing revealed a history of intermittent episodes of epistaxis for 4 years which had spontaneously resolved. Further laboratory investigations revealed a positive c-ANCA by ELISA and anti-PR3 antibodies. Urine investigations were suggestive of 10–12 RBC with 24-hour protein of 400 mg%.

The American College of Rheumatology (ACR) 1990 classification criteria [1] for GPA was fulfilled by three out of four criteria (bloody nasal discharge, lung cavity, and ≥ 5 RBC in urine analysis). The 2017 proposed ACR/EULAR criteria require 5 points for a diagnosis; our patient satisfied 10 points (5 points for ANCA, 2 for lung cavity and 3 for epistaxis). This criterion is, however, suggested for clinical trials and the ACR suggests not to use it for diagnosis. Diffuse alveolar haemorrhage (DAH) presents with haemoptysis, anaemia or falling haematocrit, diffuse lung infiltration, and acute respiratory failure [2]. Our patient had all these features of DAH. It is difficult to diagnose DAH early because of its abrupt onset and rapid progression as well as because of its non-specific clinical symptoms and radiographic findings. The alveolar infiltrates can be unilateral, and a drop in hematocrit can be difficult to document [3].

The patient needed steroids and immunosuppressants, but also had CPA. The diagnosis of CPA requires consistent appearance in thoracic imaging (preferably by CT), direct evidence of Aspergillus infection or an immunological response to Aspergillus spp, and exclusion of some alternative diagnoses. In addition, at least 3 months of duration of disease are needed, even if inferred from or based on symptoms, or visualized on progressive radiological abnormalities [4]. Our patient had a lung cavity with positive serology to Aspergillus. Thus, the patient had a diagnosis of old treated pulmonary tuberculosis with GPA presenting as DAH with CPA. A cut-off of 10 mg prednisolone daily (or its equivalent) is arbitrarily considered to cause immunosuppression during clinical management. Intermittent higher levels of immunosuppression may accelerate progression of CPA if not controlled with antifungal therapy [4].

A case series found that seven ANCA-associated vasculitis patients developed invasive pulmonary aspergillosis when treated with steroids and immunosuppressants [5]. Therefore, they recommend that prophylactic antifungals should be given to high risk patients, especially those who are on immunosuppression.

The patient was given parenteral cyclophosphamide 750 mg for 1 day and methylprednisolone 1 g for 3 days under cover of intravenous voriconazole 200 mg every 12 hours.

Haemoptysis of the patient resolved in 2 to 3 days and room air saturation became 99%. The patient was discharged on oral prednisolone 1 mg/kg and oral voriconazole 200 mg twice daily and asked to follow up for subsequent pulses with cyclophosphamide. Chest X-ray at discharge (Figure 1F) showed resolution.

To conclude, cavitating lung diseases have varied etiologies and more than one apparent cause may be present simultaneously. Early diagnosis and treatment of diffuse alveolar hemorrhage can reduce mortality. Prophylactic antifungal treatment may be warranted in patients with an Aspergillosis infection who are put on immunosuppressant therapy.

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Defying the paradigm — rescue thrombolysis in a postoaperative patient with pulmonary embolism

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Parenteral anticoagulation is recommended for patients of pulmonary embolism with intermediate to high early mortality risk. Rescue reperfusion is considered if signs of hemodynamic decompensation appear. Recent surgery within last 3 weeks is considered to be an absolute contraindication to thrombolytic therapy [1]. Percutaneous catheter-directed thrombolysis and surgical embolectomy can be done in such patients. However, they are not readily available. We hereby report a case of rescue thrombolysis in a post lower segment caesarean section (LSCS) patient with pulmonary thromboembolism. We successfully achieved thrombolysis in our patient with improvement in clinical and hemodynamic parameters and with no major bleeding from any site.

A 21-year-old married female was admitted to the intensive care unit with complaints of sudden shortness of breath and dizziness since last 6 hours. She had 2 episodes of syncope followed by spontaneous regaining of consciousness within 10 minutes. The patient had undergone LSCS 2 weeks back and had reduced mobility since then. On admission, she had tachypnea, tachycardia, was normotensive and hypoxic on room air. There were no signs of deep venous thrombosis. Arterial blood gases on ambient air revealed respiratory alkalosis with hypoxemia. Chest radiograph did not disclose any significant abnormality. Electrocardiogram showed right axis deviation and RV strain pattern. Her Wells and Revised Geneva scores were suggestive of intermediate risk of pulmonary embolism and as D-dimer was raised, urgent CT pulmonary angiography was performed which revealed a thrombus in both right and left pulmonary arteries and infarction involving the right middle lobe and posterior basal segment of the left lower lobe (Figure 1). 2D- Echocardiogram revealed dilatation of the right atrium and ventricle, positive McConnels sign with raised pulmonary artery systolic pressure of 60 mm Hg. NT-ProBNP was elevated (4054 pg/mL). Compression venous ultrasonography of bilateral lower limbs showed deep vein thrombosis of the right saphenous--femoral vein and popliteal vein. Her simplified pulmonary embolism severity index (sPESI) was 2. As she had intermediate high early mortality risk, she was started on initial parenteral anticoagulation with unfractionated heparin. However, after few hours, she developed hypotension which was nonresponsive

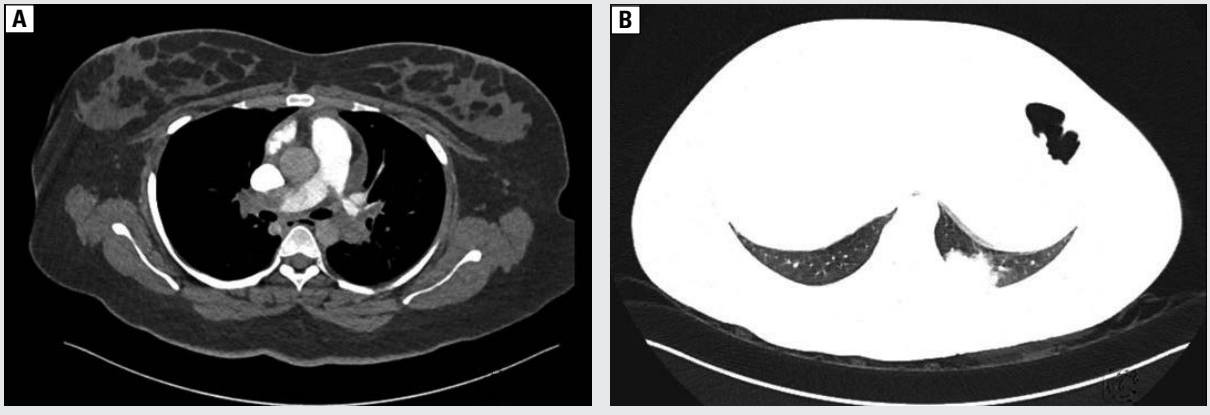

Figure 1. A. CTPA image showing a thrombus in both right and left pulmonary arteries; **B.** Lung window showing wedge-shaped infarct in the left lower lobe

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Table 1. Case reports and studies of successful thrombolysis in patients of pulmonary embolism in the presence of contraindications

	Author	Type of study	Year	Reason of contraindication	Agent used
1.	Cable DG *et al.* [2]	Case report	2003	Abdominal aortic aneurysm repair	Alteplase
2.	Koroneos A *et al.* [3]	Case report	2007	Intracerebral haemorrhage	Alteplase
3.	Han S *et al.* [4]	Case report	2006	Intracranial tumour	Alteplase
4.	Allport *et al.* [5]	Case report	2008	Stroke	Alteplase
5.	Zhang *et al.* [6]	Retrospective study (n = 17)	2013	Postoperative status	Urokinase
6.	Bottinor *et al.* [7]	Case report	2014	Haemorrhagic CVA	Alteplase

CVA — cerebrovascular accident

to crystalloid bolus infusion and sPESI deteriorated to 3. Repeated 2D-echo revealed bowing of the interventricular septum to the left in addition to previous findings.

Recent surgery within 3 weeks is considered as an absolute contraindication to systemic thrombolysis. A retrospective study and several case reports of patients with pulmonary embolism with various contraindications have shown that successful thrombolysis is possible in these patients [2–5] (Table 1).

In view of high mortality risk, and as catheter-directed thrombolysis was not immediately available, a decision to initiate rescue thrombolysis with streptokinase was taken. Risks and benefits of thrombolysis were discussed with the patient and her family members. After obtaining written informed consent, the woman was thrombolysed with streptokinase. After 24 hours, tachycardia and tachypnea resolved, she became normotensive and was weaned off oxygen. Repeated 2D-Echo revealed normal right heart chamber dimensions and SPAP reduced to 30 mm Hg. The patient did not develop any vaginal bleeding. Ultrasound of pelvis did not disclose any intrauterine or pelvic collection.

Our report highlights the fact that in cases of high-risk pulmonary embolism, an absolute contraindication to thrombolysis might become a relative contraindication. Systemic thrombolysis can be lifesaving in such patients.

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COPD 2020 Guidelines — what is new and why?

To the editor

The new year dawns with new guidelines. Global Initiative for Obstructive Lung Disease (GOLD 2020) has some major and few minor changes to offer for the management of COPD. The significant changes include defining the role of inhaled corticosteroids (ICS) and vitamin D levels [1].

Definition — the definition remains the same. "Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases". However, there may be significant lung pathology (emphysema) in the absence of airflow obstruction, which warrants a detailed assessment. This stems from the ancient concept of GOLD 0, where there were structural changes but no obstruction. Being a clinically common scenario, the entity of emphysema without obstruction has been re-introduced.

Epidemiology — the predicted mortality by 2030 of 4.5 million deaths annually from COPD and related conditions has been extrapolated to over 5.4 million deaths annually by 2060 [2]. Among risk factors, documented Pseudomonas infection is a new addition. The rationale is a large observational study which documented that *Pseudomonas aeruginosa* colonization independently predicted an increased risk of hospitalization for exacerbation and all-cause mortality [3]. The utility of biomarkers in COPD has a new comment. The guidelines advocate the use of serum C-reactive protein (CRP) and procalcitonin in restricting antibiotic usage during exacerbations [1]. However, the observed sputum color remains highly sensitive and specific for a high bacterial load during such episodes. The SUMMIT trial failed to show the benefit of using CRP, SPD, s RAGE, CC-16, and fibrinogen to predict forced expiratory volume in 1st second (FEV_1) decline, hospitalization, or exacerbation [4]. Continued cautious and realistic interpretation of the role of biomarkers in the management of identified clinical traits is needed.

A caution on the use of e-cigarettes has been mentioned in the new guidelines citing a lack of safety data. Eosinophilic pneumonias, acute lung injury, diffuse alveolar hemorrhage and respiratory bronchiolitis have been linked to their use [5]. The CDC and FDA are investigating this, around 1604 illnesses and 34 deaths have been reported up to October 2019. Certain countries including India have recently banned the use of e-cigarettes citing unproven safety profile.

Diagnosis and treatment plan — the treatment algorithm emphasizes on using the ABCD assessment to determine initial treatment only. The follow-up treatment utilizes the management cycle changes as per dyspnea or exacerbation, similar to 2019 guidelines. The management of persistent dyspnoea with add-on bronchodilators and recurrent exacerbation with add-on inhaled steroids is identical to the GOLD 2019 guidelines [1].

The role of inhaled steroids (ICS) in the GOLD 2020 guidelines has been clarified. The history of ≥ 2 moderate exacerbations or hospitalization(s) attributable to exacerbation, serum

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eosinophilia (> 300 cells/μL) or concomitant asthma are factors that strongly support the use of ICS. The factors unfavorable to ICS use are recurrent pneumonia, history of mycobacterial infection, and eosinophils (<100 cells/μL) [6]. The new guidelines do mention that recent trials using triple therapy, showing a mortality benefit. However, as mortality was not the primary endpoint of any of the studies, hence, the mortality benefit warrants further evaluation [6, 7].

GOLD 2020 guidelines recommend all patients hospitalized for exacerbations should be assessed and investigated for the severe Vitamin D deficiency (< 10 ng/mL or < 25 nM), followed by supplementation if required. The rationale is similar to all chronic diseases; vitamin D levels are lower in COPD than in health. A recent meta-analysis showed that vitamin D supplementation reduced exacerbation rates in patients with low baseline vitamin D levels [8]. However, in unselected patients, the decline is not documented. Theophylline use in COPD has an unchanged recommendation. A trial in 2018, using low dose theophylline found no benefit in reducing exacerbation rates, and hence efficacy for the same remains doubtful [9].

The guidelines draw on the importance of phenotyping COPD patients. Four phase 3 studies evaluated the efficacy of mepolizumab and benralizumab in patients with severe COPD. The inclusion criteria were recurrent exacerbations and peripheral blood evidence of eosinophilic inflammation despite high intensity inhaled therapy. There was a 15–20% reduction in the rate of severe exacerbations, but, it was variable between studies and doses. There was no effect on FEV_1 or quality of life scores and no consistent relationship between the response to treatment and the peripheral blood eosinophil count. A posthoc analysis of the mepolizumab trial showed a more significant benefit against oral corticosteroid treated exacerbations [10, 11]. Thus, raising the possibility of this treatment might gain a role in a highly selected subgroup of patients with eosinophilic COPD and frequent requirement for oral corticosteroids. Further studies are required to investigate this.

Non-medical management — interventional procedures like endobronchial valves recommended according to appropriate indication. The rationale stemmed from the EMPROVE trial reporting a significant benefit in FEV_1, hyperinflation, dyspnoea, and health status [12]. However, the possibility of considerable pneumothorax warrants the need for the procedure performed at expert centers only. The current guidelines document the additional role of pulmonary rehabilitation in the reduction of anxiety and depression.

Acute exacerbation — the classification and management protocol of acute exacerbation episodes is unchanged. The clinical suspicion and investigative workup of the differential diagnosis of an exacerbation are listed in present guidelines. Thus, stress on systemic disease evaluation and comorbidities in diagnosis are explicit.

Clinical impact and future directives — the GOLD 2020 document presents a global resource as an evidence-based review and guide for the diagnosis, management, and prevention of COPD. The importance of COPD is magnified by the increasing global burden of this disease with estimated increased mortality by 2060. The new guidelines recognize the role of ICS as an individualized decision with a detailed evaluation of risks and benefits. The position of triple inhaled therapy, biologics, lung volume reduction, need for biomarkers, and assessment of vitamin D deficiency have been explicitly stated. Even though these differences are subtle, they provide the future directive of research.

Certain limitations include the specification that persistent symptoms are required to make the diagnosis which leaves outpatients with varying day-to-day traits. Additional updates regarding novel pharmacotherapeutic options, asthma-COPD overlap phenotype, recommendations around e-cigarette use, and further guidance for referral for lung transplantation are the need of the future.

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Guidelines of the Polish Respiratory Society for diagnosis and treatment of idiopathic pulmonary fibrosis

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Abstract

Introduction: This document presents the guidelines of the Polish Respiratory Society (PTChP, *Polskie Towarzystwo Chorób Płuc*) for diagnosis and treatment of idiopathic pulmonary fibrosis (IPF), developed by a group of Polish experts.

Material and methods: The recommendations were developed in the form of answers to previously formulated questions concerning everyday diagnostic and therapeutic challenges. They were developed based on a current literature review using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: We formulated 28 recommendations for diagnosis (8), pharmacological treatment (12) as well as non-pharmacological and palliative therapy (8). The experts suggest that surgical lung biopsy (SLB) not be performed in patients with the probable usual interstitial pneumonia (UIP) pattern, with an appropriate clinical context and unanimous opinion of a multidisciplinary team. The experts recommend using antifibrotic agents in IPF patients and suggest their use irrespective of the degree of functional impairment. As regards non-pharmacological and palliative treatment, strong recommendations were formulated regarding pulmonary rehabilitation, oxygen therapy (in patients with chronic respiratory failure), preventive vaccinations as well as referring IPF patients to transplant centres. Table 1 presents an aggregate list of recommendations.

Conclusions: The Polish Respiratory Society Working Group developed guidelines for IPF diagnosis and treatment.

Key words: diagnosis, idiopathic pulmonary fibrosis, treatment, differentiation, usual interstitial pneumonia

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Table 1. An aggregate list of recommendations

Module	No	Question	Recommendation
Diagnosis	1	Can IPF be diagnosed without lung biopsy in a patient with "probable UIP" HRCT pattern (without honeycombing, but with peripheral traction bronchiectasis or bronchiolectasis)?	We suggest that a "probable UIP" HRCT pattern, if it contains no changes suggestive of an alternative diagnosis, in an appropriate clinical context (e.g. male sex, smoking history, age > 60) and after excluding other causes of such changes, should be a sufficient basis for a multidisciplinary team to diagnose IPF with no need for diagnostic lung biopsy
	2	Can a UIP pattern confirmed by pathomorphological examination of material collected through cryobiopsy be considered equivalent to a diagnosis made based on surgical biopsy?	We suggest that material collected for pathomorphological examination through cryobiopsy, sufficient to diagnose UIP, should be considered equivalent to material from surgical lung biopsy
	3	What respiratory function examinations should be performed to assess the risk of lung biopsy complications?	We recommend that qualification for elective lung biopsy include arterial blood gas analysis, spirometry and assessment of transfer factor for carbon monoxide
	4	Is it necessary to perform serological tests for autoimmune diseases in every patient with suspected IPF without clinical signs of connective tissue disease?	We recommend that every patient with suspected IPF undergo serological tests for autoimmune diseases
	5	Is it necessary to determine serum concentrations of specific immunoglobulins (precipitins) in order to diagnose hypersensitivity pneumonitis (allergic alveolitis) in every patient with suspected IPF?	We recommend that a test for the presence of specific immunoglobulins in the serum (precipitins) NOT be performed in all patients with suspected IPF
	6	Should BAL be performed in every patient with suspected IPF?	We suggest that BAL NOT be performed in every patient with suspected IPF. The examination is not necessary in patients with a radiographic UIP pattern if the clinical context raises no doubt, but it can be helpful in differential diagnosis of ambiguous clinical or radiographic picture
	7	What is the role of a multidisciplinary team in diagnosing IPF and who should be part of such a team?	We recommend establishing the diagnosis in all patients diagnosed with signs of fibrosis due to ILD through a multidisciplinary discussion We recommend that a multidisciplinary team include at least a clinician (pulmonologist) and radiologist as well as pathologist (if lung biopsy has been performed). All team members should be experienced in the diagnosis of ILD
	8	How to define disease progression?	We suggest that FVC decline rate be recognized as the basic measure of IPF progression. A loss ≥ 10% of predicted value within 12 months or less is considered clinically relevant
Pharmacological treatment	9	Should IPF patients be treated with pirfenidone?	We recommend the use of pirfenidone in IPF patients
	10	Should IPF patients be treated with nintedanib?	We recommend the use of nintedanib in IPF patients
	11	Can IPF patients be treated simultaneously with pirfenidone and nintedanib?	Currently, we DO NOT recommend simultaneous use of pirfenidone and nintedanib in IPF patients
	12	Should patients diagnosed with IPF based on the clinical context and the "probable UIP" pattern in lung HRCT be treated with antifibrotic agents?	We suggest that patients with IPF diagnosis established by a multidisciplinary team based on the clinical context and the "probable UIP" pattern in lung HRCT be started on antifibrotic agents
	13	Should IPF patients with mildly decreased or normal pulmonary function parameters be treated with antifibrotic agents?	We suggest that antifibrotic treatment be proposed to IPF patients with mildly decreased or normal pulmonary function parameters

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Table 1 cont. An aggregate list of recommendations

Module	No	Question	Recommendation
Pharmacological treatment	14	Should IPF patients with severe lung function impairment (FVC < 50% of predicted, $T_{L,CO}$ < 30% of predicted) be treated with antifibrotic agents?	We suggest that antifibrotic treatment following IPF diagnosis be proposed to all patients without contraindications for this treatment, irrespective of the degree of lung function impairment
	15	Is disease progression an indication for discontinuation of antifibrotic treatment?	We suggest that disease progression NOT be an indication for discontinuation of antifibrotic treatment
	16	In what situations should one consider switching from one antifibrotic agent to the other?	We suggest switching from one antifibrotic agent to the other in case of significant lack of tolerance or adverse effects
	17	Should all IPF patients be treated with anti-acid agents?	We suggest that anti-acid agents in IPF patients NOT be used in absence of other indications for such treatment
	18	Should N-acetylcysteine be used in IPF treatment?	We recommend that N-acetylcysteine NOT be used in the treatment of IPF patients, either as monotherapy or in combination with other agents.
	19	Should IPF patients receive immunosuppressive treatment?	We recommend that NO type of immunosuppressive treatment be used in IPF patients
	20	Should agents dedicated to treating pulmonary hypertension be used in IPF patients?	We suggest that agents dedicated to treating pulmonary hypertension NOT be used in IPF patients
Non-pharmacological and palliative treatment	21	Should pulmonary rehabilitation be used in IPF patients?	We recommend the use of pulmonary rehabilitation in IPF patients
	22	Should LTOT be used in patients with respiratory failure in the course of IPF?	We recommend using LTOT in patients with chronic respiratory failure in the course of IPF
	23	Should oxygen be used during exercise in IPF patients?	We suggest using oxygen during exercise in IPF patients with dyspnoea and exertional desaturation
	24	Should preventive vaccinations be used in IPF patients?	We recommend use of pneumococcal and flu vaccinations in IPF patients
	25	Should patients with advanced IPF be referred to palliative care centres?	We suggest that patients with advanced IPF be referred to palliative care centres
	26	Should morphine be used in palliative treatment?	We suggest using oral morphine in patients with severe IPF in palliative treatment of persisting dyspnoe
	27	Should invasive ventilation be used in IPF patients with acute respiratory failure?	We suggest that invasive ventilation NOT be used in IPF patients with acute respiratory failure
	28	Should IPF patients be referred to lung transplant centres and if so, when?	We recommend referring to lung transplant centres all IPF patients without contraindications for the procedure
			We suggest referring IPF patients to lung transplant centres immediately after the disease is diagnosed

BAL — bronchoalveoar lavage; FVC — forced vital capacity; HRCT — high-resolution computed tomography; IPF — idiopathic pulmonary fibrosis; ILD — interstitial lung disease; LTOT — long-therm oxygen therapy; $T_{L,CO}$ — transfer factor of the lung for carbon monoxide; UIP — usual interstitial pneumonia

INTRODUCTION

Definition, epidemiology, aetiopathogenesis

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease (ILD) limited to the lungs, associated with progressive fibrosis and consequentially with disturbances in diffusion of respiratory gases through the alveolar-capillary membrane, most commonly restrictive ventilation impairment, respiratory failure and premature death. The disease affects the elderly, more frequently males, and individuals with a history of tobacco smoking.

The aetiology is unknown and the diagnosis is conditional upon identifying the so-called radiographic or histopathological pattern of usual interstitial pneumonia (UIP) in a patient in whom other causes of ILD have been excluded, such as extrinsic factors damaging the respiratory system or comorbidities that could be associated with lung changes of a similar nature.

Idiopathic pulmonary fibrosis belongs to a group of diseases called idiopathic interstitial pneumonias (IIP) and is the most frequent condition in this group (accounting for 50–60% of IIP cases) [1]. It is one of the most common interstitial diseases, accounting for 20% of all diagnoses in patients diagnosed and treated in reference centres [2]. The disease is rare (affecting < 50 patients per a population of 100, 000). Its incidence, based on data from New Mexico (US), is estimated at 10.7 per 100, 000/year for men and 7.4 per 100, 000/year for women [3]. British data suggest an incidence of 4.6 per 100,

000/year in the general population [4]. Prevalence based on data from an American registry of medical services from 1996–2000 is estimated at 14–47 per 100, 000 [5]. In Poland, no systematic epidemiological studies of IPF have been performed. Szafrański [6] estimated the incidence of interstitial lung disease at 5.0 per 100, 000/year when coded as J84 and at 2.5 per 100, 000/year when coded as J84.1. He compiled this data based on an admission registry of one of non-academic lung disease centres which admitted 554 patients with interstitial diseases in 2000–2009. Of those patients, 55.7% were individuals with a diagnosis coded as J84. In a publication called the Polish IPF White Book (*Polska Biała Księga IPF*) [7], the calculations of the estimated number of IPF patients in Poland were based on mean values from different countries: for incidence it was 4.7 and for prevalence 17.1 per 100, 000. This way, the number of patients diagnosed with IPF was estimated at 6585 and the number of annual new cases at 1809. However, one should remember that the accuracy of disease coding around the world is low, and imprecise diagnostic criteria can render an especially significant bias in coding. Another problem may be introduced by non-specific symptoms, which result in the time from onset to diagnosis of up to several years and misdiagnosis of many IPF patients [8]. Furthermore, the reliability of epidemiological data is undoubtedly affected by the fact that the first systematic criteria for IPF were published only in 2000 [9] and radically redefined in 2011 [10], while most of the cited epidemiological data come from before these publications. The authors of the epidemiological report from the United Kingdom point to an increase in incidence observed in recent years [4]. Szafrański also suggests a possible upward trend [6].

Age, the male sex and tobacco smoking are named as risk factors for IPF. Studies examine the effects of chronic, mostly viral infections (among others, Epstein-Barr virus, other Herpes viruses, hepatitis C), although their role in aetiopathogenesis remains controversial [11–15]. The relationship between IPF and gastroesophageal reflux (GER) is also unclear. The latter promotes microaspirations of gastric content into the respiratory system and can potentially be a factor directly injuring the alveolar epithelium. We still lack an answer to the question whether this phenomenon causes the disease process or rather is a consequence of pulmonary fibrosis, which is associated with changes in the anatomy and pressure distribution within the chest, promoting regurgitation of the gastrointestinal content [16, 17]. Not without significance is the impact of genetic factors [18]. Mutations within the telomerase complex genes and genes encoding surfactant proteins C and A2 as well as MUC5B gene polymorphism are known to increase the risk of pulmonary fibrosis [19, 20]. Mutations promoting the development of the disease are more frequent in familial interstitial pneumonia (FIP) [21]. Findings of UIP features can be an element of the rare Hermansky-Pudlak syndrome, an autosomal recessive hereditary disease, in which lung changes are additionally accompanied by such features as oculocutaneous albinism and platelet function disorders caused by lack of delta granules [22].

In light of the current studies, IPF is a consequence of repeated microinjuries of the alveolar epithelium caused by factors such as tobacco smoke components, environmental pollutants, viruses, occupational factors or gastric content microaspirations. The development of fibrosis is conditional upon alveolar epithelial dysfunction (acquired or genetically determined), making the epithelium incapable of physiological regeneration [23]. Cell-level abnormalities are known as "accelerated ageing" or "cellular senescence". Features indicative of this process include, among others, shortened telomeres. In IPF patients, both with the sporadic and familial forms, shorter telomeres have been identified in peripheral blood lymphocytes and alveolar epithelial cells [24–26], and shorter telomere length in IPF patients is correlated with shorter life spans [25, 27]. Another important phenomenon observed in epithelial cells is intracellular accumulation of abnormal proteins (unfolded protein response), associated with impairment of the autophagy process. These phenomena lead to an endoplasmic reticulum [ER] stress response and in consequence to the activation of proapoptotic signals and shortening of the epithelial cells' lives [28]. Fibrosis requires an appropriate environment to develop, one which depends on cell-secreted cytokines. The main role is played here by growth factors i.e. transforming growth factor-ß, TGF-ß; fibroblastic growth factor, FGF; platelet-derived growth factor, PDGF; vascular endothelial growth factor, VEGF; connective tissue growth factor, CTGF; and cytokines e.g. interleukin (IL)-1, IL-4, IL-13. This results in the deposition of collagen and other components of extracellular matrix produced directly by stimulated fibroblasts (myofibroblasts). The accumulation of these substances in lungs is a result of epithelial-mesenchymal transition (EMT) during which epithelial cells undergo morphological

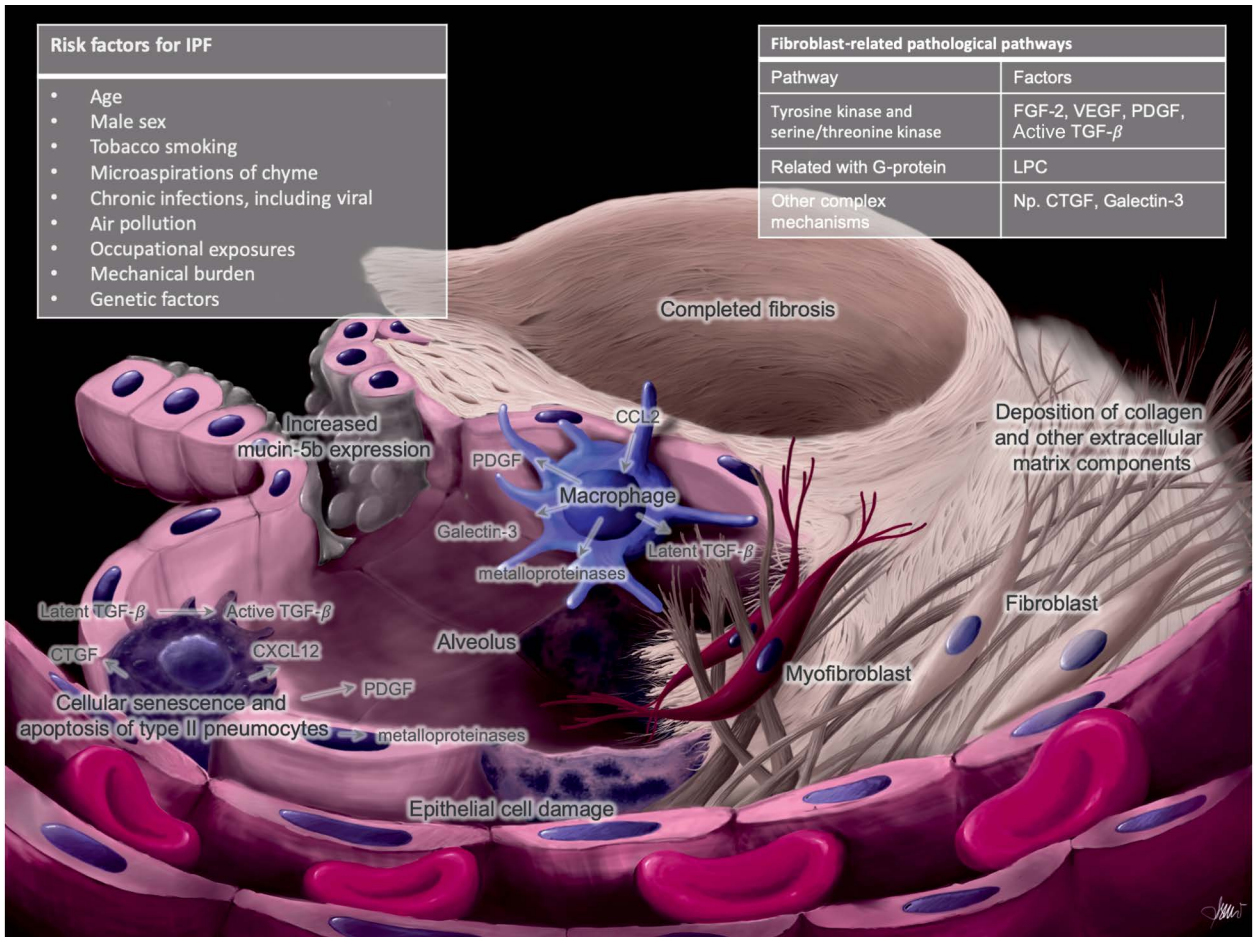

Figure 1. Selected mechanisms leading to pulmonary fibrosis in IPF (author: AJB)

CCL — chemokine (C-C motif) ligand; CXCL C-X-C motif chemokine ligand; CTGF — connective tissue growth factor; FGF — fibroblastic growth factor; LPC — lysophosphatidylcholine; PDGF — platelet-derived growth factor; TGF — transforming growth factor; VEGF — vascular endothelial growth factor

and functional transformation into mesenchymal cells. Another source of fibroblasts in lungs are fibrocytes, cells originating from bone marrow, which acquire mesenchymal features after they are released to the blood stream. When they reach the lungs, they transform into fibroblasts, and then myofibroblasts. Selected mechanisms leading to pulmonary fibrosis in IPF are summarised in Figure 1.

The radiographic pattern of usual interstitial pneumonia (UIP)

UIP pattern

The definition of the UIP pattern in high-resolution computed tomography (HRCT) includes reticulation with a predominantly subpleural (occasionally diffuse) and basal distribution. Changes of crucial importance for UIP diagnosis by CT are those of "honeycombing", with or without peripheral bronchiectasis or bronchiolectasis, without findings indicative for alternative diagnoses (Table 2). Honeycomb-type changes manifest as clusters of well-defined, thick-walled, usually subpleural, cyst-like air spaces with a diameter of several millimetres to several centimetres (usually 3–10 mm) [10, 29] (Figure 2).

Bronchiectasis or bronchiolectasis are peripherally located in the areas of reticulation (traction bronchiectasis). A characteristic feature for UIP is heterogeneity of lesions, meaning that areas with architectural distortion are found next to areas of relatively normal parenchymal structure. The UIP pattern is characteristic of IPF but can also be present in other disease entities. After known causes of UIP are excluded, it is possible to diagnose IPF without invasive approach [10, 29].

The probable UIP pattern

Lack of honeycombing in the HRCT image, with the presence of reticular changes predominantly in the subpleural and basal lung areas,

Table 2. Criteria for identifying a UIP pattern based on high-resolution computed tomography (Adapted from [29], with modifications)

UIP	Probable UIP	Indeterminate	Findings suggestive of a different diagnosis
Subpleural and basal predominant	Subpleural and basal predominant	Subpleural and basal predominant	Cysts
The distribution is often heterogeneous, in many cases asymmetrical	The distribution is often heterogeneous, in many cases asymmetrical	Subtle reticulation, possible presence of mild ground glass opacifications and architectural distortion (the "early UIP" pattern)	Marked mosaic attenuation
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis	No honeycombing	CT features of interstitial fibrosis or the nature or distribution of changes not suggestive of any specific aetiology (truly indeterminate)	Prevalence of ground glass
Reticular changes	Reticular changes with peripheral traction bronchiectasis or bronchiolectasis		Profuse micronodules
Possible presence of mild ground glass opacifications as well as isolated calcified nodules (ossifications) in fibrotic areas	Possible presence of mild ground glass opacifications		Centrilobular nodules
			Other nodules
			Consolidation
			Peribronchovascular, perilymphatic distribution
			Changes in the upper or mid-lung fields
			Pleural plaques
			Dilated oesophagus
			Distal clavicular erosions
			Extensive lymph node enlargement
			Pleural effusion, pleural thickening

UIP — usual interstitial pneumonia; CT — computed tomography

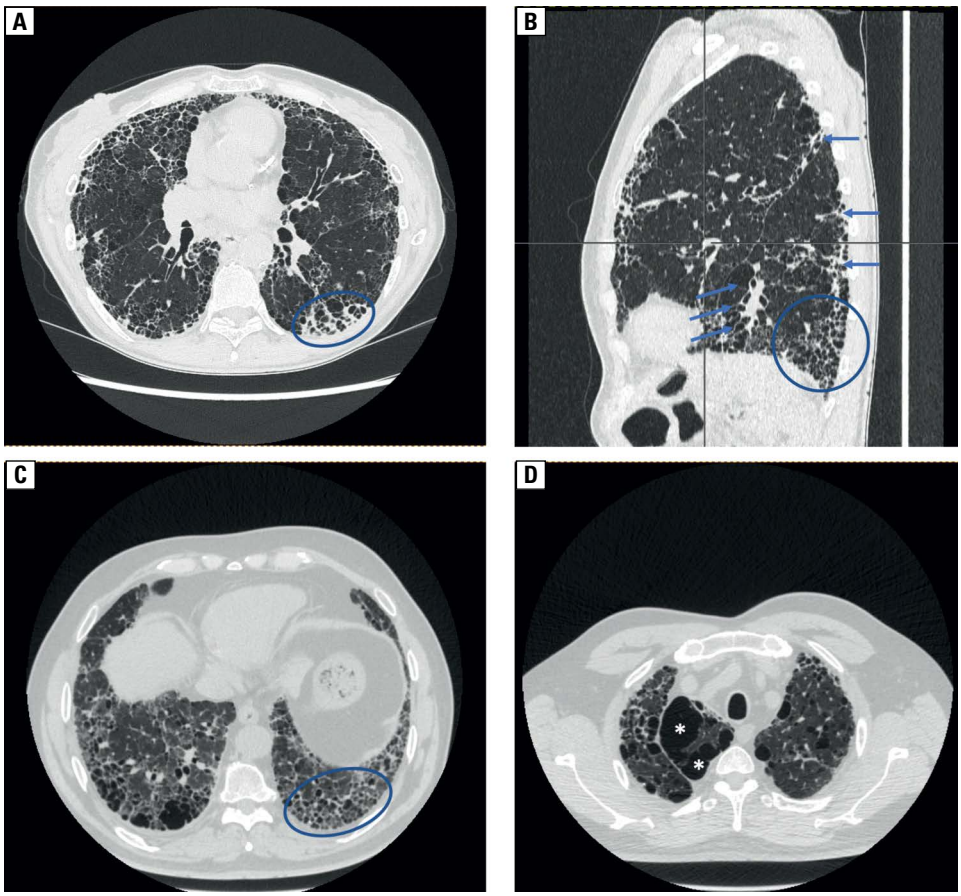

Figure 2. High-resolution computed tomography images depicting: **A** and **B** — usual interstitial pneumonia; **C** and **D** — usual interstitial pneumonia concomitant to emphysema (from Radiology Department, N. Barlicki University Teaching Hospital Nº 1 in Lodz). Honeycoming located subpleurally at lung bases (blue ovals), traction bronchiectasis (blue arrows), concomitant emphysema (white asterisks)

with peripheral traction bronchiectasis or bronchiolectasis warrants the diagnosis of probable UIP. Differentiation of bronchiectasis from honeycombing can be difficult. Traction bronchiectasis

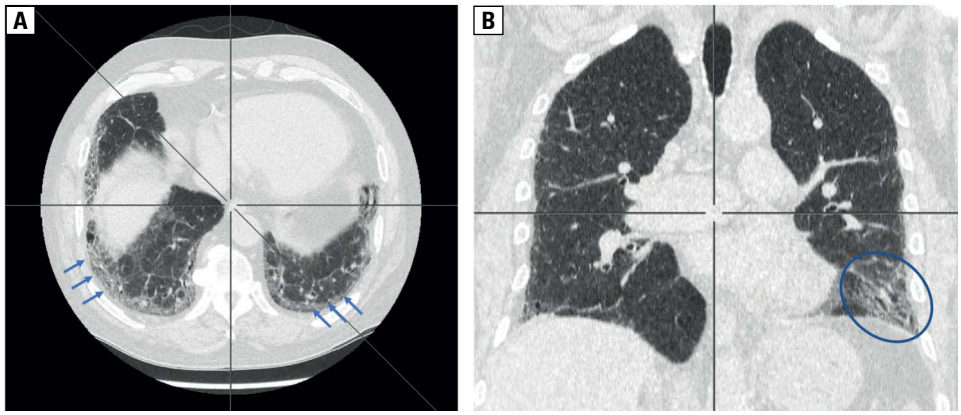

Figure 3. High-resolution computed tomography images illustrating the probable UIP pattern (from the Radiology Department, N. Barlicki University Teaching Hospital Nº 1 in Lodz). A — axial view; B — coronal view. Subpleural reticulation located at the lung bases (blue arrows), traction peripheral bronchiectases (blue oval)

is irregular, deformed widening of bronchi and bronchioles caused by fibrosis of the surrounding lung parenchyma. Unlike bronchiectasis of different origin, it is located in the area of reticular changes and associated with signs of lobular destruction and architectural distortion of the lung parenchyma. A conglomerate of peripheral traction bronchiolectasis located in the basal lung parts can resemble a honeycombing. Features differentiating traction bronchiectasis from honeycombing include: lack of bronchiectasis or bronchiolectasis directly below the pleura (honeycomb cysts are usually located subpleurally) and distribution of cysts. In bronchiolectasis the cysts are separated from each other whereas in a honeycombing area they are close together and share walls [30, 31]. An example HRCT image illustrating probable UIP is presented in Figure 3.

Indeterminate pattern

An indeterminate pattern is one in which no honeycombing or traction bronchiectasis or bronchiolectasis is seen but at the same time no features are observed that would allow a specific diagnosis. This category includes patients with slight, limited reticular changes, often with concomitant ground glass opacifications or architectural distortions distributed in subpleural and basal regions of the lung (the "early UIP" pattern). An example of such an HRCT image is presented in Figure 4. If the nature of lung changes distribution does not suggest any specific aetiology, we call it a truly indeterminate pattern. Such patients should undergo supplementary HRCT examinations in the prone position in order to discreetly differentiate early fibrosis from changes caused by the gravitational effect.

An indeterminate pattern does not preclude IPF diagnosis but requires pathomorphological examination to confirm the UIP pattern.

Pathomorphological UIP pattern

Morphological changes appearing in the course of IPF are identified in microscopic examination, similarly to radiographic examination, as UIP. The international ATS/ERS/JRS/ALAT recommendations (2018) [29] for diagnosis of IPF as well as recommendations contained in the Fleischner Society White Paper [31] point to benefits of making IPF diagnosis based on SLB, which remains the gold standard of microscopic diagnosis of IPF/UIP, in spite of growing experience with other material collection techniques, such as cryobiopsy.

Microscopic changes characteristic of UIP:

- intensive collagenous fibrosis, leading to remodelling of the lung parenchyma, with complete honeycomb-type destruction;
- disseminated fibroblastic foci, usually located at the periphery of remodelling areas;
- areas of fibrosis separated by fragments of less affected lung parenchyma (the characteristic mosaicism reflecting different times of change formation);
- changes located below the pleura, along the interlobular septa, at the periphery of the lobules;
- lack of morphological changes indicative of alternative diagnosis (e.g. granulomas, organising pneumonia, diffuse alveolar damage) or fibrosis located in other areas than those characteristic of UIP (e.g. around the bronchioles).

A microscopic image with signs of usual interstitial pneumonia is presented in Figure 5.

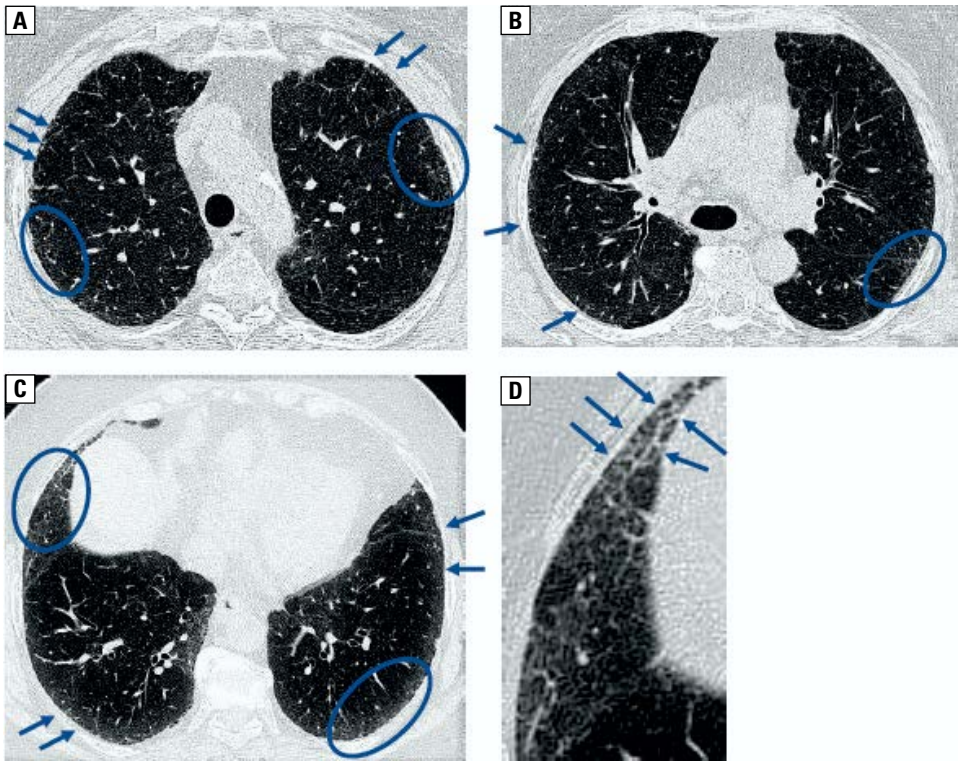

Figure 4. HRCT images illustrating an indeterminate pattern. The radiographic image corresponds to the early UIP pattern (from the Division of Imaging Diagnostics, Voivodeship Hospital in Opole). Axial views: **A** — at the aortic arch level; **B** — of the main bronchi; **C** — supradiaphragmatic; **D** — a magnified fragment of the middle lobe. Ground glass areas (blue ovals), mild reticular thickening of septal lines (arrows) which are predominant in the subpleural and supradiaphragmatic (basal) areas. Changes are also visible in the middle lobe, near the anterolateral wall, which indicates they are not associated with hydrostatic effect. Pathomorphological examination confirmed UIP

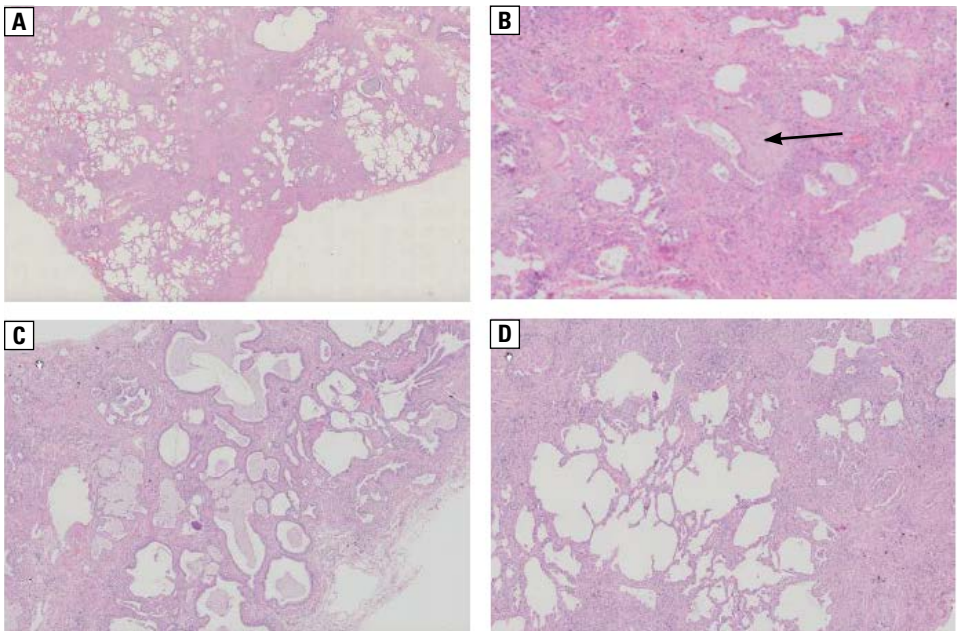

Figure 5. Pathomorphological UIP patterns (Department of Pathology, National Tuberculosis and Lung Diseases Research Institute, Warsaw). **A.** A fragment of lung parenchyma with visible diffuse fibrosis affecting the subpleural parenchyma, interlobular spaces, with a region of less affected lung parenchyma. Low magnification; **B.** A fragment of lung parenchyma with diffuse fibrosis, with a focus of fibroblastic fibrosis (fibroblastic focus) visible in the central part (arrow). High magnification; **C.** Lung parenchyma with areas of cystic remodelling of air spaces with creation of honeycomb-type areas. Medium magnification; **D.** Fields of completed fibrosis distorting the lung structure are separated by small fragments of aerial parenchyma (mosaicism). Medium magnification

Table 3. The histopathological criteria for UIP diagnosis (Adapted from [29])

Definite UIP	Probable UIP	Indeterminate	Morphological changes indicative of a different diagnosis
Dense fibrosis with architectural distortion of the lung parenchyma and/or honeycombing	Some features described in column 1 are present, but to an extent that precludes a definite diagnosis of UIP/IPF	Fibrosis with or without architectural distortion of the parenchyma with morphological features suggestive of a different diagnosis than UIP, or with features indicative of secondary UIP associated with a different cause*	Features typical of other interstitial fibrosis types (e.g. absent fibroblastic foci, loose connective tissue fibrosis covering the entire area of the examined specimen)
— Predominant subpleural and/or paraseptal distribution of fibrosis — Patchy involvement of lung parenchyma by fibrosis — Fibroblastic foci — Absence of morphological features suggestive of an alternate diagnosis	— Absence of morphological features suggestive of an alternative diagnosis or — Presence of honeycombing only	Certain changes present in column 1 are present but with morphological features suggestive of an alternative diagnosis**	Morphological changes indicative of a different diagnosis (e.g. HP, LAM, Langerhans cell histiocytosis)

*Granulomas, hyaline membranes (except for acute exacerbation of IPF), pronounced peribronchiolar location, diffuse areas of intensive inflammatory infiltration in the stroma without fibrosis, intensive chronic fibrosis of the pleura, organising pneumonia
**Diffuse inflammatory infiltration in areas away from remodelling fields, intensive hyperplasia of lymphoid tissue with the presence of lymph nodules and germinal centres, peribronchiolar location with peribronchiolar metaplasia (bronchiolisation)
HP — hypersensitivity pneumonitis; IPF — idiopathic pulmonary fibrosis; LAM — lymphangioleiomyomatosis; UIP —usual interstitial pneumonia

Microscopic diagnosis requires not only an experienced pathologist, but also adequate fixation and preparation of material for pathomorphological examination. The collected material should be fixed in a 10% solution of neutral buffered formalin. Lung fragments collected during SLB should be decompressed by injecting the lung parenchyma with a 10% formalin solution and placed in a vessel containing 10 times more fixing solution in relation to the specimen size.

The histopathological criteria for UIP diagnosis are presented in Table 3.

Microscopic diagnosis of UIP/IPF requires multidisciplinary cooperation. The pathologist must have access to detailed clinical data, information on previous treatment and an up-to-date chest HRCT report. Referral for microscopic examination is completed by a clinician.

Clinical picture

The most typical and common symptoms of this progressive disease include dyspnoea and non-productive, tiring cough. The symptoms usually appear insidiously, and many patients are unable to pinpoint the date of their appearance. Very often, deteriorating exercise tolerance fails to alarm patients at early stages as they explain the symptoms by the ageing or treat them as a consequence of long-term tobacco smoking. Other, less common and non-specific, complaints which are usually present in addition to exertional dyspnoea include general fatigue, dizziness, chest discomfort or pain and anxiety [32]. An acute exacerbation is a rare first manifestation of the disease. In such a case, the symptoms appear unexpectedly and intensify in a short time [33].

Most frequently, a patient diagnosed with IPF is male (approximately 70% of patients), a former or, less frequently, current tobacco smoker (50–70% of patients), aged above 60 years [32, 34]. In very rare case the diagnosis is made in patients under the age of 50. In 2–20% of patients the disease runs in the family. If this is the case, the first symptoms can develop even before the age of 40 [21, 35, 36].

Bilateral, basal crepitations (so called "Velcro-type" cracles) identified during physical examination, especially with concomitant digital clubbing, increases the likelihood of the diagnosis [32, 37]. Crepitations, although not pathognomonic, are present in about 90% of IPF patients. Digital clubbing is observed in < 30% of patients [32].

The clinical symptoms accompanying IPF are not characteristic of this condition only. Therefore, the condition is often misdiagnosed as another dyspnoea-associated disease (e.g. chronic obstructive pulmonary disease — due to tobacco smoking history) or heart failure (due to the presence of auscultatory crepitations in the lower

lung fields). In one study the mean time from the first symptoms to diagnosis was assessed at 3–4 years. At least 50% of patients are previously diagnosed with COPD, asthma, other interstitial disease or heart failure. At least 50% of patients consult 3 or more specialists before receiving the correct diagnosis [8].

IPF is a progressive disease. Progression pattern can be various, from slow loss of lung function parameters slightly above the loss associated with natural ageing, in which cases survival often exceeds 10 years, to violent progression leading to death sometimes in under 1 year. Additionally, the disease course can be complicated with an acute exacerbation. According to a new definition [38], an acute exacerbation of IPF (AE-IPF) is a deterioration of the patient's general condition with developing or worsening of dyspnoea, typically intensifying in a period shorter than 30 days, associated with the appearance of new parenchymal consolidations or areas of ground glass overlapping existing sings of fibrosis characteristic of the UIP pattern. In most patients the cause of AE-IPF is never discovered. In others, the symptoms can result from known triggers, such as infection, air pollution, microaspirations or drugs. These events are associated with high mortality (early mortality of around 50%, exceeding 90% in intubated and mechanically ventilated patients). Those who survive such an episode experience a chronic, irreversible worsening of lung function. The risk of AE-IPF is higher in patients with more advanced disease and lower baseline lung function parameters [38].

The clinical picture of IPF also involves comorbidities. Conditions which are more frequent in IPF patients than in the general population include gastroesophageal reflux disease (GERD) [39–41], lung cancer [42, 43], emphysema [42, 44], pulmonary hypertension [38, 45, 46] and obstructive sleep apnoea [47]. Other common diseases characteristic of this age group include hypertension, ischaemic heart disease, cardiac arrhythmias, stroke, other forms of arterial atherosclerosis, depression, venous thromboembolism and diabetes [48, 49]. Many of these diseases negatively affect survival [48, 49] and quality of life [50].

IPF patients have a poor prognosis. Median survival before the introduction of antifibrotic agents was assessed at approximately 3.5 years, while the percentage of patients surviving 5 years after diagnosis was slightly above 30% [51]. This means that the prognosis can be poorer than in the case of many neoplastic diseases [52].

The prognosis in IPF patients can fundamentally improve as a result of a wider use of antifibrotic agents [53–55].

One of commonly used methods for the assessment of risk of death is the GAP score (gender, age, physiology — Table 4) [56].

After summing all points, an appropriate category should be assigned according to the Table 4B attached.

Table 4A. The GAP score, used to assess the risk of death

Category	Characteristic	Number of points
G — gender	Female	0
	Male	1
A — age	≤ 60	0
	61–65	1
	> 65	2
P — physiology (functional examinations — FVC, $T_{L,CO}$ in reference to predicted normal values)	FVC > 75%	0
	FVC 50–75%	1
	FVC < 50%	2
	$T_{L,CO}$ > 55%	0
	$T_{L,CO}$ 30–55%	1
	$T_{L,CO}$ < 30%	2

FVC — foced vital capacity; $T_{L,CO}$ — transfer factor of the lung for carbon monoxide

Table 4B. The table presents how the GAP score should be interpreted, with estimated risk of death in 3 consecutive years [57]

Number of points	Grade GAP	Mortality at 1 year [%]	Mortality at 2 years [%]	Mortality at 3 years [%]
0–3	I	5.6	10.9	16.3
4–5	II	16.2	29.9	42.1
6–8	III	39.2	62.1	76.8

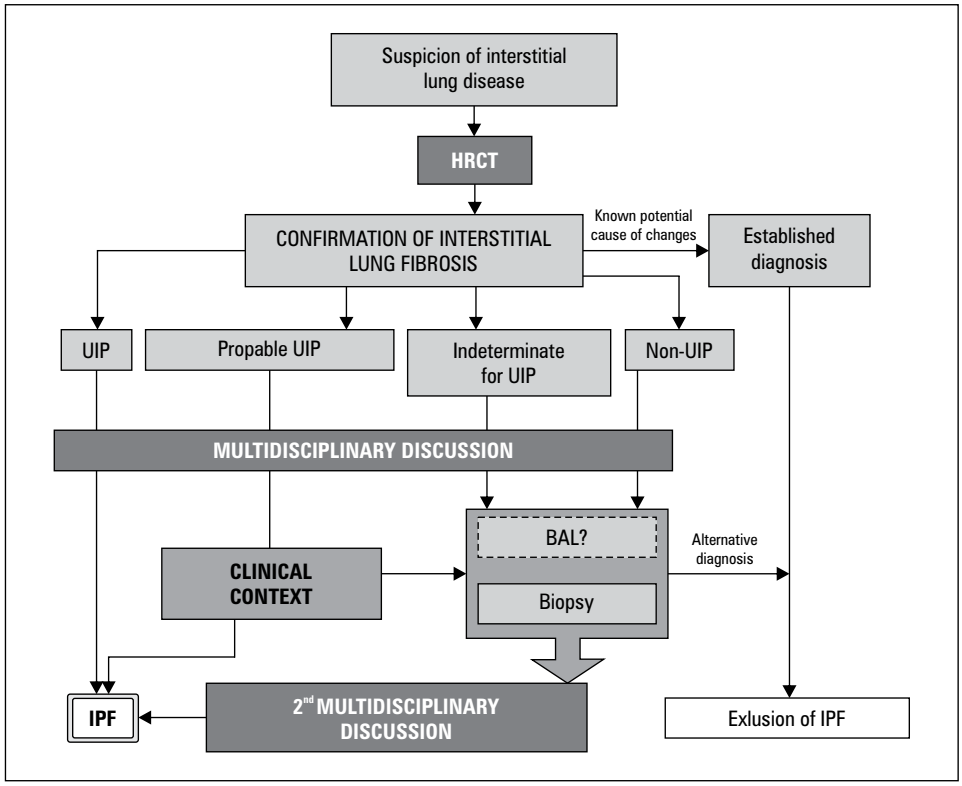

Figure 6. The proposed diagnostic algorithm for IPF (authors: AJB, WJP)

HRCT — high-resolution computed tomography; UIP — usual interstitial pneumonia; BAL — bronchoalveolar lavage; IPF — idiopathic pulmonary fibrosis

Basic rules for diagnosis

In order to diagnose IPF, one should:

— exclude known causes of ILD;

— confirm the presence of the UIP pattern in HRCT or, if the radiographic image is ambiguous, of the UIP pattern in pathomorphological examination of lung biopsy [29].

Another important factor is the so-called clinical context, i.e. taking into account the fact that IPF is more frequent in men, tobacco smokers and people after the age of 60.

The proposed diagnostic algorithm for IPF is presented in Figure 6.

Medical history taking and physical examination

The absolute condition for establishing a diagnosis is exclusion of known causes of interstitial fibrosis. Thorough history taking plays the most important role in this process. It must take into account possible exposure to bioaerosols and toxic substances at workplace, at home, in the immediate neighborhood or in places frequently visited by the patient [29]. The history taking should take into account whether the patient's current or past occupation (this pertains also to distant pass) has been associated with a marked risk of developing lung changes, especially if it has involved exposure to asbestos, silica-containing dusts, metal dusts and other harmful substances. Medical history should include comorbidities and symptoms associated with other organs (e.g. musculoskeletal or other suggestive of autoimmune causes). The question of using pneumotoxic drugs — currently and in the future — is of special importance. The risk of causal relationship can be assessed based on information gathered in medical databases such as Medline or Pneumotox.com.

It is extremely important to collect a detailed family history, aimed at determining the presence of ILDs in members of the immediate and more distant family.

Radiological examinations

A routine chest radiograph is usually the first stage of imaging diagnostics. It can be used to exclude other causes of abnormalities observed (e.g. heart failure, lung tumour). In some patients it is possible to identify changes suggestive of interstitial pulmonary fibrosis without significant clinical manifestation, which warrants further diagnosis.

Table 5. The recommended computed tomography protocol in the diagnosis of ILD (Adapted from [29])

1. Non-contrast examinantion
2. Volumetric acquisition: — collimation < 1 mm — the shortest possible rotation time — the highest possible pitch factor — voltage and current appropriate for the patient's size: • typically 120 kVp and ≤ 240 mAs • lower tube potentials (e.g. 100 kVp), with adjustment of tube current for slim patients — utilisation of available techniques limiting unnecessary radiation (e.g. tube current modulation)
3. Reconstructions of thin-slice images (≤ 1.5 mm): — continuous or overlapping — using a high spatial frequency algorithm — using an iterative reconstruction algorithm, if validated on the CT unit (if not — filtered back projection should be used)
4. Number of acquisitions: — in the supine position: inspiratory (volumetric acquisition) — obligatory — in the supine position: expiratory (volumetric or sequential acquisition) — optional — in the prone position: only inspiratory scans (volumetric or sequential) — optional, can include only the lower lobes
5. The recommended radiation dose for volumetric acquisitions on inspiration: — 1–3 mSv (e.g. "reduced" dose) — strong recommendation to avoid < 1 mSv (ultra-low doses)

An imaging examination of key importance for IPF diagnosis is HRCT. An experienced radiologist can use its results to diagnose UIP pattern as well as indicate possible changes requiring differential diagnosis [29]. The recommended technique is a multi-detector CT based on volumetric acquisition, which allows multiplanar reconstructions and more thorough radiographic assessment of the nature of lung changes. The standard method is to perform the examination at deep sustained inspiration in the supine position, although in an early fibrosis stage, in order to differentiate from the so-called gravitational effect, an additional examination in the prone position is recommended. Additional scans in the expiration phase can be helpful in differential diagnosis to identify areas of so-called air trapping. Table 5 summarises the technical requirements for HRCT used in the diagnosis of ILDs.

Lung biopsy

Currently, a common tendency is observed to limit the indications for SLB due to a significant risk of complications in this patient population. There is an ongoing discussion on cases when lung biopsy is indispensable, which is reflected in the disagreement between the Fleischner Society experts [31] and the current version of the international guidelines for IPF diagnosis [29]. The objective of SLB should be arriving at a diagnosis of a disease that can be treated in a specific way based on a pathomorphological diagnosis. A procedure suggestion must be based on an analysis of potential benefits and risks, and should take into account the patient's general condition and comorbidities. Cryobiopsy may be considered a safer alternative for SLB.

The multidisciplinary nature of diagnosis

The international guidelines for IPF diagnosis stress the role of a multidisciplinary discussion (MDD) in making decisions regarding necessary diagnostic procedures (e.g. lung biopsy) as well as establishing the final diagnosis [29]. The basic composition of the multidisciplinary team should include a clinician (pulmonologist) and radiologist as well as pathologist in cases where lung biopsy has been performed. Specialists involved in the work of such a team should have extensive experience in diagnosing ILD, although a method to measure this experience has not been specifically defined. Many publications recommend extending the team, if possible, to include a rheumatologist, thoracic surgeon (who should take part in assessing indications for SLB and choosing an optimum biopsy site), occupational medicine specialist (potential environmental exposure), cardiologist and other specialists depending on comorbidities, psychologist, ILD nurse as well as palliative care specialist. In spite of unequivocal international guidelines, a survey

conducted among Polish pulmonologists before antifibrotic agents were commonly available demonstrated that only 55% of respondents establish IPF diagnosis in cooperation with a radiologist and only 40% of diagnoses in patients following lung biopsy were discussed directly with a pathologist [58].

The final diagnosis should be clearly formulated. One should also verify whether the diagnosis meets the required formal criteria or rather is a "working" diagnosis (one that does not fulfil the required formal criteria). In the latter case, one should specify whether the diagnosis is "definite" or "provisional/preliminary with high or low likelihood" [31, 59]. Sometimes even if the radiographic and pathomorphological criteria of UIP are met, the diagnosis has a working nature. This can stem, for instance, from inability to exclude in a reliable way the impact of environmental factors or the risk of developing a systemic disease (in a dozen or so per cent of patients with connective tissue diseases (CTDs), lung changes precede the complete presentation of symptoms which allows the diagnosis of CTDs). Every patient with a working diagnosis of IPF should undergo periodic and systematic assessment for a possible change of diagnosis.

Table 6 presents the rules for diagnosing IPF if both HRCT and lung biopsy are available.

Diagnosis of IPF without lung biopsy

If during the diagnostic process (irrespective of the reason), no diagnostic pathomorphological material has been obtained, then the diagnosis should be made through a MDD taking into account all clinical factors (such as age, gender, history of tobacco smoking, course of the disease) and the available results of additional tests and examinations (BAL, serological tests and other deemed necessary based on a clinician's suggestion). On this basis one can decide to make either a final or "working" IPF diagnosis [31].

Other diagnostic investigations

Other diagnostic investigations include tests of autoantibody titres performed in all patients with lung interstitial changes (antinuclear antibodies — ANA, rheumatoid factor — RF) to identify those who require further assessments for connective tissue disease. Bronchoalveolar lavage (BAL) with cellular composition assessment can be used in differential diagnosis of ILDs. In certain cases, determination of serum concentrations of precipitating antibodies makes it possible to confirm environmental exposure, which can be important in establishing the cause of ILD.

In all patients, a full physical examination should be performed as it can be helpful in determining a potential known cause of interstitial changes as well as diagnosing comorbidities. If needed, other specialists should be consulted. Another element of assessment are laboratory tests, such as complete blood count, urea, creatinine and electrolyte concentrations, urinalysis or liver function tests.

Table 6. Idiopathic pulmonary fibrosis diagnosis based upon HRCT and lung biopsy patterns (Adapted from [29, 60], with modifications)

		Biopsy				No biopsy
		UIP	Probable UIP	Indeterminate	Inconsistent with the UIP pattern	
HRCT	UIP	IPF	IPF	IPF	A different diagnosis	IPF
	Probable UIP	IPF	IPF	IPF likely*	A different diagnosis	IPF likely*
	Indeterminate	IPF	IPF likely*	Indeterminate**	A different diagnosis	Indeterminate**
	Inconsistent with the UIP pattern	IPF likely*	A different diagnosis	A different diagnosis	A different diagnosis	A different diagnosis

*The final diagnosis can be made through a multidisciplinary discussion. The following configurations of demographic and clinical characteristics increase the likelihood of IPF diagnosis: a) moderate to serious traction bronchiectasis/bronchiolectasis (of mild intensity in more than 4 lobes including the lingula or intensive in 2 or more lobes) in males > 50 years of age or females > 60 years of age; b) reticular changes affecting > 30% of the lung area in HRCT in a person > 70 years of age; c) an increased neutrophil percentage or absence of lymphocytosis in BAL

**If biopsy has provided no signs excluding UIP, no biopsy has been performed or the material's quality is insufficient for diagnosis while medical history and other examinations have excluded the influence of external pneumotoxic factors or diseases associated with interstitial changes in the lungs, the current classification of interstitial diseases states that a diagnosis of unclassifiable interstitial lung fibrosis should be made [1]

IPF — idiopathic pulmonary fibrosis; HRCT — high-resolution computed tomography; UIP — usual interstitial pneumonia

Table 7. Basic features facilitating differentiation of IPF from selected ILDs leading to fibrosis

	cHP	CTD-ILD	Pneumoconioses	Interstitial changes associated with the use of pneumotoxic drugs
Medical history	In some patients it is possible to identify potential exposure.	Most patients present with extrapulmonary symptoms	A history of exposure to dusts	Interstitial fibrosis can result from long-term exposure to a drug, often lasting many years
HRCT	The UIP pattern may be observed in a chronic, fibrotic form of HP. Extensive areas of ground glass appearance, mosaic attenuation, air trapping, centrilobular nodules. Predominantly upper-zone distribution (although predominantly lower -zone distribution is also possible), predilection for affecting areas surrounding bronchovascular bundles. Common coexistence of changes typical for the acute form	The UIP pattern is observed most commonly in RA. The most typical feature of lung changes in the course of CTD is the NSIP pattern. More extensive ground glass areas can suggest CTD-ILD. Coexistence of exudative pleuritis can be suggestive of CTD-ILD	The UIP pattern can be present in asbestosis. Local thickenings of the pleura called pleural plaques may suggest asbestosis. Pleural effusion or pleural mesothelioma can coexist with the picture of asbestosis	The typical UIP pattern is a rare manifestation of drug--induced lung changes. More frequently observed patterns include HP, NSIP or OP
BAL	Severe lymphocytosis, more often in patients with active exposure. Patients with a fibrotic form, when the exposure occurred in a distant past, can have a normal differential cell counts	Possible lymphocytosis	Possible lymphocytosis, presence of asbestos bodies	Possible lymphocytosis and eosinophilia
Laboratory tests	Precipitins can be positive, but they document exposure rather than prove the disease diagnosis	Increased titres of ANA, RF, aCCP and other autoantibodies are suggestive of a CTD-ILD diagnosis. The diagnosis should be confirmed by a rheumatologist	No specific studies confirming diagnosis	No specific studies confirming diagnosis
Clinical picture	Although, in most cases chronic fibrosing HP develops in more advanced age, disease onset at a young age, sometimes in childhood, is also possible	An interstitial disease can precede the full picture of a CTD. Usually symptoms characteristic of a specific disease entity are present	Usually progressive dyspnoea and cough in an individual with long-term occupational exposure. Clinical symptoms and radiographic changes are present during or after the exposure	Exposure to a harmful drug is associated with the treatment of comorbidities
Lung biopsy	Peribronchial distribution of changes, loosely formed granulomas, lymphocytic infiltrations, empty spaces left by washing away cholesterol crystals	Presence of abundant lymphocytic infiltrations with visible germinal centres	Asbestos bodies	HP, OP, NSIP

ILD — interstitial lund diseases; cHP — chronic hypersensitivity pneumonitis; CTD-ILD — connective tissue disease-associated interstitial lung disease; HRCT — high-resolution computed tomography, UIP — usual interstitial pneumonia, RA — rheumatoid arthritis; NSIP — non-specific interstitial pneumonia; OP — organizing pneumonia; ANA — antinuclear antibodies; RF — rheumatoid factor; aCCP — anti-cyclic citrullinated peptide autoantibodies

Differential diagnosis

Differentiation should include above all those disease entities which can be associated with a radiographic or histopathological pattern of UIP. First and foremost, differentiation should pertain to chronic hypersensitivity pneumonitis (cHP) [61], ILD in the course of CTD (CTD-ILD) (especially in the course of rheumatoid arthritis, RA) [62], pneumoconioses (especially asbestosis) [63] or drug-induced changes [22]. Table 7 presents the basic features of other diseases facilitating such differentiation.

The features useful in the differential diagnosis listed in Table 7 should be understood as typical for individual disease entities, but their absence does not preclude a given diagnosis. In addition to the above disease entities, one should take into account very rare causes of the radiographic UIP pattern, such as sarcoidosis [64] and other rare ILDs [65].

Table 8. Selected forms of pharmacotherapy not recommended in IPF treatment based on the results of randomised trials

Name of the drug	Recommendation in the international guidelines	Acronym	References
Interferon gamma-1b	Strongly against [10]	INSPIRE	[71]
Colchicine	Strongly against [10]		[72]
Cyclosporine	Strongly against [10]		[73]
TNF-alpha antagonist (etanercept)	Strongly against [10]		[74]
Oral anticoagulants (warfarin)	Strongly against [75]	ACE-IPF	[68]
Triple therapy (prednisone + azathioprine + NAC)	Strongly against [75]	PANTHER-IPF	[67]
Selective endothelin-1 receptor antagonist (ambrisentan)	Strongly against [75]	ARTEMIS-IPF	[70]
Dual endothelin receptor antagonist (bosentan, macitentan)	Conditionally against [75]	BUILD-3 MUSIC	[76, 77]
Phosphodiesterase-5 inhibitor (sildenafil)	Conditionally against [75]	STEP-IPF	[78]
Single-target tyrosine kinase inhibitor (imatinib)	Strongly against [75]	IMATINIB-IPF	[79]
LOXL-2 inhibitor (simtuzumab)	Not considered	RAINIER	[80]

Differentiation of the UIP pattern from a fibrotic form of non-specific interstitial pneumonia (NSIP) can be another issue. Problems can arise from overlapping of radiographic features. For instance, IPF patients can present with limited ground glass areas (one of the radiographic features of NSIP). On the other hand, traction bronchiectasis is also often observed in NSIP patients. The presence of honeycombing areas in NSIP is also possible, although rare, and changes in both patterns are predominantly located in the lower lung zones. In addition, coexistence of both histopathological patterns may be observed in one lung biopsy [66].

Idiopathic pulmonary fibrosis treatment

Idiopathic pulmonary fibrosis treatment approaches have drastically changed in the last 20 years. Furthermore, new reports are continuously emerging on the molecular pathomechanisms and options of pharmacological interventions. In the guidelines for the diagnosis and treatment of IPF of 2000, the only recommended pharmacotherapy methods were glucocorticosteroids and immunosuppressants [9]. As new evidence arose indicating a secondary role of inflammation and a primary role of fibrosis in the pathogenesis of IPF, a search for new IPF treatment options began. Numerous randomised clinical trials have been conducted, proving lack of efficacy or even harmful effects of many treatment regimens used. For instance, we currently have access to unequivocal data documenting harmful effects of glucocorticosteroids and immunosuppressants [67]. Despite this fact, the aforementioned survey demonstrated that in 2016 23% of IPF patients in Poland received glucocorticosteroids [58]. Negative results were obtained also in the ACE-IPF study, which demonstrated detrimental effects of warfarin use [68] in spite of encouraging results from earlier studies [69].

Negative results were also achieved in studies of an endothelin-1-receptor antagonist (ARTEMIS-IPF) [70]. Endothelin-1 is a cytokine involved in the pathogenesis of both IPF and pulmonary hypertension. Table 8 summarizes drugs which according to the current state of knowledge should not be used in the treatment of IPF patients.

The breakthrough in IPF treatment was possible thanks to studies demonstrating the efficacy of pirfenidone [81, 82] and nintedanib [83]. These drugs, currently called antifibrotic agents, slow down the rate of fibrosis progression.

AE-IPF significantly worsen the prognosis. Most centres use high-dose glucocorticosteroids, often in combination with an immunosuppressant. This treatment is recognised as the standard of care, although evidence supporting its efficacy is very limited [38]. For this reason, this document omits the problem of the pharmacological treatment of IPF exacerbations.

Non-pharmacological treatment is an important element of therapy. This mostly pertains to the treatment of chronic respiratory failure. In this document we discuss problems associated with the use of oxygen in individuals with respiratory failure and with the use of ventilation

support in AE-IPF and in patients with end-stage respiratory failure. Pulmonary rehabilitation is another important and underestimated element of non-pharmacological treatment. Given the progressive nature of the disease, sooner or later every IPF patient requires palliative care.

MATERIAL AND METHODS

The Polish recommendations for diagnostic and therapeutic management were developed by a team of Polish experts in ILDs. The initiative of developing national guidelines arose in a group of specialists in ILDs. It was sparked by nonunanimous opinions on IPF diagnosis, qualification for treatment, management using antifibrotics, supportive and palliative treatment as well as methods for monitoring of the disease course. The initiative gained support by the General Board of the Polish Respiratory Society (PTChP, *Polskie Towarzystwo Chorób Płuc*) and the Head of the Interstitial Lung Diseases Section of the society.

The guidelines were created following two important publications: the Fleischner Society expert opinion published in February 2018 [31], which contained suggested changes to the international guidelines for IPF diagnosis of 2011 [10], and the final version of the updated international guidelines published in September 2018 [29]. This publication was based on a systematic review of global literature, taking into account local factors resulting from the uniqueness of the Polish healthcare system and the rules of the IPF treatment programme currently in place. The literature review was completed on 30th June 2019.

Objectives of the guidelines:

— improving the quality and reliability of IPF diagnoses;
— increasing antifibrotic treatment accessibility by popularising the diagnostic and treatment qualification criteria in Poland;
— creating conditions for optimal utilisation of Poland's existing IPF treatment programme;
— identification of shortcomings and health needs in terms of IPF patient care.

The patient population to which the guidelines pertain are patients with suspected or diagnosed IPF. The audience for whom the guidelines have been developed are doctors dealing with the subject matter of ILDs, especially pulmonologists, radiologists, pathologists, thoracic surgeons, pulmonary rehabilitation specialists, healthcare organisation specialists, representatives of the Polish National Health Fund (*Narodowy Fundusz Zdrowia*) or other institutions shaping the healthcare politics in Poland.

Working team members: The working team comprises doctors specialising in ILDs, representative of various expert centres: pulmonologists (AJB, PWB, EJ, DJ, JK, KL, SM, MMM-B, WJP, EP, AS, MS, EW, DZ), radiologists (IB, PG, KO), pathologists (RL, MSz), as well as patients (DK, GW). The literature review regarding specific issues was prepared independently by authors assigned to a given task and by the author assigned to act as a librarian (AJB). WJP and AJB supervised the methodological consistency of the guidelines.

The methodology was adapted from the document "Ramy metodyczne opracowywania zaleceń diagnostyczno-terapeutycznych" (Methodological framework for developing diagnostic and therapeutic recommendations) published by the Agency for Health Technology Assessment and Pricing (*Agencja Oceny Technologii Medycznych i Taryfikacji*) [84]. The guidelines were developed according to the GRADE methodology (Grading of Recommendations Assessment, Development, and Evaluation) in a form similar to one used in the American Thoracic Society's position [85]. Contentious issues were resolved using the Delphi method. At every development stage, the criteria described in the document "Narzędzie oceny wytycznych AGREE II" (A tool to assess the AGREE II guidelines) were also taken into account [86].

The recommendations were divided into three parts: 1. Diagnosis; 2. Pharmacological treatment; 3. Non-pharmacological and palliative treatment. The experts presented clinical problem suggestions in the form of a list of questions. The suggested questions were sent to all Editorial Board members, and the formulated clinical questions, after initial revisions and proofreading, were assessed in terms of their relevance. The score proposed by the authors of the Swiss Lung Disease Society consensus was used [87]. The importance of individual questions was evaluated in a 9-point score and grouped into the following categories: very important questions (8–9 points), important questions (6–7 points), unimportant questions (below 6 points). Questions considered by a majority as very important and important were subjected to further process.

Subsequently, a working team was established with an aim to develop individual guidelines: MMM-B, WJP — diagnosis; KL, SM, MS — pharmacological treatment; EP, AJB, AS, WJP — non-pharmacological treatment and palliative care.

The review of available literature was performed in the Medline and Cochrane databases. Existing systematic reviews were used as well as *de novo* reviews were made if a given systematic review was not available. The quality of evidence was determined as high, moderate, poor or very poor. The strength of recommendation was assessed as strong or conditional [29].

The authors of respective sections developed the initial version of a response to a given question, accompanied by a short commentary. Subsequent versions were developed following discussions via electronic means and face-to-face meetings. A preliminary version was sent out to all guideline authors for internal review.

The final version was sent for external review. After introducing final revisions, the work was sent to print. The English-language version was assumed as the original one.

The recommendations will undergo planned revision every five years or earlier if new evidence emerges affecting in a significant way the state of knowledge on the diagnosis and/or treatment of IPF and an expert panel decides that it changes significantly the meaning of the previously published recommendations, thus necessitating an earlier than planned update.

RECOMMENDATIONS

DIAGNOSIS

Question 1. Can IPF be diagnosed without lung biopsy in a patient with "probable UIP" HRCT pattern (without honeycombing, but with peripheral traction bronchiectasis or bronchiolectasis)?

Introduction

Analyses of patient populations meeting the "probable UIP" criteria in high-resolution computed tomography (HRCT) indicate that lack of honeycombing should not exclude IPF diagnosis if all remaining radiographic features of the UIP pattern are present (especially predominantly subpleural and basal distribution of changes as well as the presence of bronchiectasis) [30, 88–98]. The extent of reticular changes is of great importance. This is because if they exceed 1/3 of the total lung volume (in a person above 60), the probability of IPF diagnosis exceeds 80%, with a 96% specificity [99]. The "probable UIP" pattern in HRCT co-exists with changes typical of definite or probable UIP in pathomorphological examination of SLB material in 82–94% of patients [88–90]. A recently published meta-analysis demonstrated that IPF diagnosis can be made in as many as 94% (87–99%) of patients with a radiographic pattern corresponding to "probable UIP" [100]. The probability of IPF diagnosis increases in an appropriate clinical context, comprising the following: age above 60 years, a positive history of tobacco smoking (currently or in the past) and lack of other identifiable causes that could lead to interstitial fibrosis (especially lack of significant environmental exposure, chronic use of potentially pneumotoxic drugs or signs of CTD) [31, 97, 99, 101, 102]. In the group of patients with "probable UIP" (who had not undergone lung biopsy), an annual FVC decline was observed as well as a response to antifibrotic treatment (with nintedanib) reducing the rate of this decline, comparable with outcomes observed in the "definite UIP" group (based on radiographic or pathomorphological presentation) [103].

Recommendation 1.

We suggest that a "probable UIP" HRCT pattern, if it contains no changes suggestive of an alternative diagnosis, in an appropriate clinical context (e.g. male sex, smoking history, age above 60) and after excluding other causes of such changes, should be a sufficient basis for a multidisciplinary team to diagnose IPF with no need for diagnostic lung biopsy.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (IPF diagnosis in the case of probable UIP with no need for diagnostic lung biopsy) — 6; conditionally for — 14; strongly against — 1; conditionally against — 0; abstained — 0

Commentary

This recommendation is in line with the Fleischner Society's position presented as a consensus of an international group of experts in ILDs (including eight pulmonologists, six radiologists and three pathologists), which was developed based on a systematic literature review [31]. Ad-

ditionally, this position is not inconsistent with the international ATS/ERS/JRS/ALAT recommendations (2018), which suggests to consider invasive diagnosis (BAL or even SLB) in patients with the "probable UIP" HRCT pattern. However, the guidelines also allow the possibility of establishing IPF diagnosis without any invasive procedures, taking into account the clinical context (presented in the above discussion) through a multidisciplinary discussion (MDD) [29, 104]. A group of experts, including the co-authors of both documents, stress the fact that the recommendation to perform lung biopsy in case of "probable UIP" is conditional (with a poor strength of evidence) and in a situation when the only missing element of the radiographic UIP pattern is lack of honeycombing while the other criteria are met and the clinical picture is highly suggestive of IPF, such a final diagnosis is highly likely. Surgical lung biopsy is an invasive, costly procedure associated with possible complications, while it does not guarantee diagnosis [105–109].

Question 2. Can a UIP pattern confirmed by pathomorphological examination of material collected through cryobiopsy be considered equivalent to a diagnosis made based on surgical biopsy?

Introduction

Surgical lung biopsy remains the gold standard in invasive diagnosis of ILD, including UIP/IPF [29, 31]. In most situations, video-assisted thoracoscopic surgery (VATS) is preferred over open lung biopsy (OLB). Video-assisted thoracoscopic surgery, like OLB, allows a controlled and precise choice of the biopsy site as well as achieving adequately sized (even several centimetres) diagnostic material for examinations, which is especially important for appropriate pathomorphological assessment [110, 111]. The optimal management involves collecting material in the form of numerous specimens, from different lobes, with a margin extending 1–2 cm away from the pleura [112–114]. Surgical lung biopsy is a procedure associated with risk that encompasses standard periprocedural complications (pneumothorax, bleedings), infections as well as, in the case of UIP/IPF patients, a higher risk of AE-IPF and also death [115, 116]. SLB-associated mortality depends on the advancement of disease, the need for mechanical ventilation, comorbidities, immunosuppressive treatment and the centre's experience [117–119]. In specialist centres of the United States and England, the mean intrahospital mortality due to this diagnostic procedure only was 1.7%, with mortality within 30 days after biopsy of 2.4% and within 90 days of 3.9% [120, 121]. Transbronchial lung cryobiopsy (TBLC) is a new diagnostic technique [92, 122–126]. Its diagnostic effectiveness and complication rates are varied and depend on the experience of the person performing the procedure [123, 125, 127–139]. The mean mortality due to this diagnostic procedure only has been estimated at 0.2%, with less frequent sudden exacerbations than in the case of SLB (1.2% *vs* 6.1%). However, there are frequent complications of pneumothorax (0% *vs* 26% with TBLC; in the case of SLB, the rates of pneumothorax or persistent air leak are lower) and bleeding (on average, 5.3% *vs* 0.8% with SLB) [111, 123, 128, 133, 135–145].

Recommendation 2.

We suggest that material collected for pathomorphological examination through cryobiopsy, sufficient to diagnose UIP, should be considered equivalent to material from surgical lung biopsy.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (accepting a UIP-confirming result based on material from cryobiopsy) — 8; conditionally for — 11; strongly against — 0; conditionally against — 1; abstained — 1

Commentary

The international ATS/ERS/JRS/ALAT recommendations (2018) on IPF diagnosis do not take into account a situation where the patient is unable or unwilling to undergo SLB [29]. Observational studies based on IPF patient registries indicate that material for lung pathomorphological examination is ever-more often collected using the TBLC method [146]. At present, the procedure is not commonly available or practiced, although there are ongoing attempts at its standardisation [147–149]. Material collected with this method is usually smaller than in surgical biopsy, with no possibility of choosing the precise biopsy site — it usually comes from the more centrally located areas [122]. The percentage of TBLC-based diagnoses is up to 80–85% *vs* more than 95% in the case of diagnoses based on SLB [122–124].

The classical transbronchial lung biopsy (TBLB), given its low clinical effectiveness,

is not a recommended method for confirming the UIP pattern in pathomorphological examination. However, sometimes (in over one third of IPF patients) it is possible to use TBLB material to demonstrate changes corresponding to elements of the UIP pattern (such as fibroblastic foci) [91, 127, 128, 138, 140, 150, 151]. Although TBLB can be useful in certain situations, e.g. differential diagnosis (if changes inconsistent with UIP are present, in order to confirm an alternative diagnosis) [117], prospective studies that would reliably determine the place of this method in UIP/IPF diagnosis are still lacking [29, 130].

Question 3. What respiratory function examinations should be performed to assess the risk of lung biopsy complications?

Introduction

In light of the current clinical practice and international guidelines for IPF diagnosis, in cases where non-invasive methods do not make it possible to establish diagnosis with a satisfactory level of confidence, it is recommended to perform pathomorphological examination of lung biopsy material [29]. At present, the recommended diagnostic procedure is SLB [29]. The invasiveness of this method is associated with a risk of complications (including disease exacerbations and even death) [152]. The identified risk factors for complications include: the male sex, non-elective or open procedure, requirement of mechanical ventilation following the procedure, preliminary diagnosis of IPF or connective tissue disease-associated ILD (CTD -ILD), immunosuppressive treatment or $T_{L,CO}$ < 50% of predicted [105, 121, 153]. Another method providing tissue material of acceptable sizes is TBLC. This method is associated with a lower risk of death but also characterised by lower diagnostic effectiveness [123]. The nature of its complications is also different (with more frequent bleedings and pneumothorax). The recognised risk factors for cryobiopsy complications include, among others, forced vital capacity (FVC) < 50% of predicted and carbon monoxide lung transfer ($T_{L,CO}$) < 35% of predicted, serious hypoxaemia (PaO_2 < 50–60 mm Hg when breathing atmospheric air at rest), suspected pulmonary hypertension with > 40 mm Hg in echocardiographic examination. These factors are sometimes considered relative contraindications for the procedure [147, 148].

Recommendation 3.

We recommend that qualification for elective lung biopsy include arterial blood gas analysis, spirometry and assessment of transfer factor for carbon monoxide.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (performing examinations to assess the degree of respiratory dysfunction before elective biopsy) — 11; conditionally for — 6; strongly against — 0; conditionally against — 0; abstained — 4

Commentary

In the case of biopsy, loss of lung parenchyma is small, and this element is not important for risk analysis. The suggested threshold values of lung function parameters to be used in qualification for diagnostic lung biopsy in patients with suspected IPF are arbitrary and have been chosen based on retrospective analyses and observational studies. In such *a-priori* studies, patients with very low values of functional parameters (FVC, $T_{L,CO}$) and with respiratory failure, were excluded — that is why it is impossible to perform an assessment of the procedure safety with consideration of a wide range of FVC and $T_{L,CO}$ values. On the other hand, there is a safety analysis performed in 699 patients with ILDs. The analysis revealed that complications were not more frequent in patients with FVC < 50% of predicted and $T_{L,CO}$ < 35% of predicted compared with individuals with higher values of these parameters [154]. Pneumothorax was more frequent in patients with a higher radiographic fibrosis index and pathomorphological UIP diagnosis, irrespective of FVC < 50% of predicted or $T_{L,CO}$ < 35% of predicted [154]. In light of the above, no definite recommendation can be given regarding threshold values defining an absolute contraindication for the procedure.

A separate problem associated with biopsy is an increased risk of AE-IPF. It is believed that when mechanical ventilation is used during any surgical procedure, intraoperative exposure to high oxygen concentrations (hyperoxia) and high pressures (barotrauma) or respiratory volumes (volutrauma) can increase recruitment of circulating proinflammatory cells and mediators, thus intensifying the fibrotic process [155]. The recognised factors predisposing for an exacerbation in the periprocedural period include reduced FVC and $T_{L,CO}$ values, although it is impossible to name any specific factors that would constitute contraindications for biopsy [156].

Question 4. Is it necessary to perform serological tests for autoimmune diseases in every patient with suspected IPF without clinical signs of connective tissue disease?

Introduction

Increased titres of ANA and RF are present in many IPF patients with no signs of CTD [157–161]. Many studies point to lack of significant differences in the clinical course and prognosis of IPF patients with high antibody titres compared with IPF patients without antibodies [158, 161, 162], although the most recent meta-analysis of 9 studies (a total of 4602 IPF patients) indicates a higher risk of developing autoimmune disorders by patients with high titres of ANA and myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies (MPO-ANCA) [163, 164]. Interstitial lung disease can be the first symptom of CTD in more than ten per cent of patients [165]. The UIP pattern is the most common pulmonary presentation of rheumatoid arthritis (RA) [166], but it can also occur in patients with systemic scleroderma [167, 168] and, much less frequently, in the course of other CTDs [169]. Similarly to IPF, lung changes among RA patients are more frequent in males and older patients and exhibit a relationship with tobacco smoking [166, 170–174]. Differentiation can be especially difficult in such cases if no extrapulmonary RA symptoms are present.

Recommendation 4.

We recommend that every patient with suspected IPF undergo serological tests for autoimmune diseases.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (performing serological tests for autoimmune diseases in all patients with suspected IPF) — 14; conditionally for — 6; strongly against — 0; conditionally against — 0; abstained — 1

Commentary

The current international guideline for IPF diagnosis recommends performing serological tests in all patients with suspected IPF. This is a motherhood statement, i.e. a recommendation adopted *a priori* and not subjected to voting [29]. However, the guidelines fail to specify the exact tests that should be performed. It has been agreed that the basic serological tests include tests for antinuclear antibodies (ANA), rheumatoid factor (RF) and antibodies against cyclic citrullinated peptide (aCCP). Experts recommend that the panel be extended to include tests for other specific antibodies (e.g. a dermatomyositis-specific profile) depending on the clinical situation and diagnostic capabilities of a given facility [10, 29]. Patients with positive titres of ANA, RF, aCCP or other autoantibodies should be consulted by a rheumatologist and if connective tissue disease is preliminarily excluded, they should undergo periodic assessment for the development of an autoimmune disease. In patients with increased autoantibody titres (ANA > 1:320, RF > 60 U/L) but without other signs of autoimmune diseases and meeting other diagnostic criteria, a working IPF diagnosis should be established through a MDD and scrupulously monitored.

Question 5. Is it necessary to determine serum concentrations of specific immunoglobulins (precipitins) in order to diagnose hypersensitivity pneumonitis (allergic alveolitis) in every patient with suspected IPF?

Introduction

Radiographic changes in lung HRCT in patients with chronic hypersensitivity pneumonitis (cHP) can correspond to the radiographic UIP pattern. It was demonstrated that in as many as 40% of patients with an initial IPF diagnosis, the diagnosis was changed to cHP after more thorough examinations [175]. This makes it the most important disease entity that needs to be excluded in differential diagnosis of patients with suspected IPF. The identification of the antigen cause and source is of crucial importance for prognosis [176]. In everyday practice, the element of key importance is a scrupulously collected, systematic medical history of possible exposures in the occupational and domestic environments as well as in the immediate neighborhood and frequently visited places [177, 178]. Unfortunately, it is estimated that in 50% of cHP cases the causative antigen remains unidentified [178–180]. A suggestion was made to name this form a cryptogenic hypersensitivity pneumonitis [178].

One of recently published studies revealed positive results of a precipitin test for farmer's lung in 78% of patients with an acute form, but only in 48% of patients with a chronic form [181]. Specific antibodies were detected only in 52% of pigeon breeders with a chronic form of lung disease [182]. In a group of 86 bird breeders with

lung disease, the presence of specific immunoglobulins was identified in 92% of patients (only in 2 radiographic signs of UIP were observed), while in the control group comprising healthy pigeon breeders specific antibodies were detected in as many as 87% of subjects [183]. By contrast, in the case of many patients with signs of cHP with positive results for specific antibodies, these antigens are not detected in the patients' domestic environments [184]. The value of positive precipitins in differentiation of cHP from other ILDs associated with pulmonary fibrosis was considered low (sensitivity: 72%, specificity: 68%) *vs* diagnosis made based on a MDD [185].

Recommendation 5.

We recommend that a test for the presence of specific immunoglobulins in the serum (precipitins) NOT be performed in all patients with suspected IPF.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (performing a test for the presence of precipitins in the serum in all patients with suspected IPF) — 0; conditionally for — 0; strongly against — 11; conditionally against — 9; abstained — 1

Commentary

There is no need for assessing precipitins in all patients with a radiographic pattern corresponding to UIP. It is especially unjustifiable to perform a wide panel of all available tests (for instance, performing a test for farmer's lung in someone who has never had any contact with rural environment is aimless). In HP a potential role is played by antigens present in the domestic environment: avian antigens contained in bedding [180], nontuberculous mycobacteria [180] and fungal antigens [186]. For this reason, in justified cases, the domestic environment examination as well as choice of antibodies to test should above all take into account these antigen groups. However, detailed history taking is the most important element. It is justified to test for selected antibodies in the following situations: historical data pointing to possible exposure to antigens; presence of radiographic signs in HRCT suspicious of HP, such as ground glass, mosaic attenuation, air trapping; changes distributed predominantly in the upper and middle fields; young age of the patient; high lymphocyte percentage in BAL fluid [175, 177, 178, 187].

Question 6. Should bronchoalveolar lavage (BAL) be performed in every patient with suspected IPF?

Introduction

The cellular composition of BAL fluid in IPF patients does not have any characteristic features that would distinguish this disease entity from other ILDs [188]. Most patients are identified with an increased total cell count [189], increased neutrophil percentage > 5% [188, 190], increased eosinophil percentage > 2% [188], while the lymphocyte percentage is normal or slightly increased [188, 190]. Many authors point to a high lymphocyte percentage in BAL fluid (BALF) as a feature differentiating IPF from cHP [190, 191]. In a group of patients with ILDs it was observed that no IPF patient had a BALF lymphocyte percentage higher than 25% [190]. Another study demonstrated that a BALF lymphocyte percentage > 30% was the cause of changing the diagnosis from IPF to non-specific interstitial pneumonia (NSIP) or chronic cHP [191]. However, the BALF lymphocyte percentage in patients with chronic (fibrotic) HP can be normal, especially when exposure that caused the (now completed) disease occurred in the past. Other authors state that the BALF lymphocyte percentage in IPF patients can be increased and does not differentiate IPF patients from those with cHP. For instance, in one study 18% of patients with the final diagnosis of IPF (biopsy-confirmed) the BALF lymphocyte percentage was above 40% [188]. In studies by Vasakova *et al.*, the BALF lymphocyte percentage did not differentiate IPF patients from those with cHP — in both disease entities the median was 22–23% [192]. The lack of differences in the lymphocyte percentage between patients with IPF and cHP is also referred to by the authors of the current international IPF guidelines who support it with meta-analysis results [29].

Recommendation 6.

We suggest that bronchoalveolar lavage (BAL) NOT be performed in every patient with suspected IPF.

The examination is not necessary in patients with a radiographic UIP pattern if the clinical context raises no doubt, but it can be helpful in differential diagnosis of ambiguous clinical or radiographic picture.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (performing BAL in all patients with suspected IPF) — 0; conditionally for — 2; strongly against — 6; conditionally against — 13; abstained — 0

Commentary

If known causes of ILDs have been excluded and the radiographic image indicates UIP, the analysis of BALF cellular composition usually contributes little to the diagnosis. Even though an increased lymphocyte percentage decreases the likelihood of IPF diagnosis, it does not preclude it [188, 192]. On the other hand, in cHP patients the likelihood of increased lymphocyte percentages in BALF decreases with fibrosis progression [190]. An increased lymphocyte percentage may, however, suggest an alternative diagnosis [in the context of IPF diagnosis this is usually cHP, NSIP (idiopathic or associated with CTD), much less frequently sarcoidosis, drug-induced changes or pneumoconioses]. If cHP is suspected, it is important to identify a potential antigen since its elimination from the environment can significantly alter the prognosis [176]. That is why patients with an increased lymphocyte percentage should undergo thorough assessment for environmental exposure.

The threshold value for lymphocytosis in BALF, which when exceeded should suggest a different diagnosis than IPF, is 25% according to the ATS/ERS guidelines dedicated to assessing the cellular composition of the BALF [193]. The current guidelines for IPF diagnosis of 2018 do not specify any cut-off value [29]. Exceeding the BALF eosinophil percentage above 25% can suggest acute or chronic eosinophilic pneumonia [193].

Question 7. What is the role of a multidisciplinary team in diagnosing IPF and who should be part of such a team?

Introduction

The current ATS/ERS/JRS/ALAT guidelines (2018) on IPF diagnosis attribute a very important role to a multidisciplinary discussion (MDD), which is suggested in case of every patient diagnosed for ILD of elusive aetiology, with a clinical suspicion of IPF [29]. The agreement between a single discipline decision (SDD) and one made through a MDD is assessed at 70% (47–87%) [194–198]. A MDD can prevent the initiation of inappropriate treatment, delay of the correct therapy or redundant but potentially dangerous diagnostic procedures [29, 199, 200].

A multidisciplinary team involved in IPF diagnosis should always include a clinician (pulmonologist) and radiologist as well as pathologist (in case of lung biopsy has been performed) — all should be experienced in ILD diagnosis, and if needed, also a rheumatologist (possibility of CTD), occupational medicine specialist (potential environmental exposure), specialist in respiratory physiology, cardiologist (both helpful, for instance, in assessing the risk associated with invasive diagnosis) or another specialist whose assessment can be helpful in making diagnostic or therapeutic decisions [29, 87, 201–203]. A MDD in IPF diagnosis is of greatest importance when there is no unequivocal radiographic diagnosis of UIP (in HRCT) [29, 31, 204].

Recommendation 7A.

We recommended establishing the diagnosis in all patients diagnosed with signs of fibrosis due to ILD through a multidisciplinary discussion.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (arriving at ILD diagnosis through a multidisciplinary discussion) — 13; conditionally for — 7; strongly against — 0; conditionally against — 0; abstained — 1

Recommendation 7B.

We recommend that a multidisciplinary team include at least a clinician (pulmonologist) and radiologist as well as pathologist (if lung biopsy has been performed). All team members should be experienced in the diagnosis of ILD.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (the recommended make-up of a multidisciplinary team) — 11; conditionally for — 8; strongly against — 0; conditionally against — 0; abstained — 2

Commentary

The involvement of a MDD is considered the gold standard in the diagnostic process for IPF, especially in differentiation from other ILDs associated with fibrosis [1, 29, 31, 87, 201]. An appropriate assessment of the HRCT image forms the basis of IPF diagnosis. However, the

consistency of change assessment in reference to the UIP pattern is moderate even among experienced radiologists (especially at an early stage of the disease). That is why patients diagnosed due to suspected IPF should be referred to reference centres capable of providing diagnosis by an experienced team of doctors and organising a MDD, which facilitates establishing an adequate management approach [200, 205–208]. Sometimes a discussion of this type, offering a broader perspective on the disease contexts, leads to changing a previously made diagnosis [195, 197]. In cases where the radiographic image does not meet all the UIP criteria but corresponds to the "probable UIP" pattern, with an appropriate clinical context and lack of other lung changes, a MDD can be helpful in arriving at a diagnosis with no need for invasive diagnostic methods [31, 104]. In other cases, IPF can be diagnosed based on a combination of specific HRCT patterns in relation to the pathomorphological picture and clinical context. In such situations, the involvement of a multidisciplinary team is also recommended [29]. If biopsy cannot be performed or the patient does not consent to it (in spite of existing indications), the diagnosis should be made through a MDD taking into account any clinical factors and available results of additional tests and examinations (BAL, serological tests and other deemed necessary). On this basis, depending on the likelihood of correct diagnosis, a decision can be taken to establish a final IPF diagnosis (if it is definite) or a temporary, "working" one (if not all formal requirements have been met) [59]. A MDD should occur both before making a decision to use invasive diagnosis and after receiving pathomorphological examination results for a lung fragment (if biopsy has been performed) in order to agree the most likely diagnosis and further management. The seemingly best way to conduct a MDD is direct confrontation of opinions, but a discussion through electronic means (telemedicine) is also acceptable [31, 59].

Question 8. How to define disease progression?

Introduction

Idiopathic pulmonary fibrosis is a disease characterised by progressive interstitial fibrosis [10]. Progression rate clearly affects the prognosis. The course of disease is difficult to predict and can range from slow worsening of lung function parameters in a span of many years to a dramatically fast progression, leading to death within several months of diagnosis [209–211]. In addition, the course can be complicated with an acute exacerbation, which is associated with an approximately 50% mortality rate [38]. There are many ways to monitor progression, from assessment of symptom severity and quality of life through questionnaires [209], to evaluation of fibrosis progression in imaging examinations (assessment of variations in the nature and extent of changes visible in HRCT at different intervals) [179, 212, 213], to objective measurements of exercise capacity (e.g. changes of distance in the six minute walking test, 6MWT) [209], changes in the transfer factor of the lung for carbon monoxide ($T_{L,CO}$) and changes in vital capacity (usually forced vital capacity, FVC) [214, 215] within 6–12 months intervals. An absolute decline in FVC within 6 or 12 months expressed in % of predicted is the most commonly used measure of progression. The reasons include the ease of measurement, repeatability of results and a documented relationship with prognosis [179, 214–219]. An absolute FVC decline during the study is the primary endpoint in all major clinical trials of antifibrotics [82, 83, 217, 218, 220, 221]. A decline in FVC ≥ 10% is a component of a composite endpoint (FVC decline or death) defining lack of treatment response [82, 222, 223], and a lower rate of patients with a FVC decline ≥ 10% in the actively treated group compared with the placebo group proves the efficacy of a treatment [222–224].

Recommendation 8.

We suggest that forced vital capacity (FVC) decline rate be recognised as the basic measure of IPF progression. A loss ≥ 10% of predicted value within 12 months or less is considered clinically relevant.

Quality of evidence: poor
Strength of recommendation: conditional
Votes: strongly for (recognising the FVC decline rate as the basic measure of IPF progression) — 8; conditionally for — 9; strongly against — 0; conditionally against — 0; abstained — 4

Commentary

There is no single ideal indicator that would define clinically relevant IPF progression. An absolute decline in FVC ≥ 10% from the baseline is the most commonly used, arbitrary measure of clinically relevant progression (which should not be confused with a clinically perceptible change) and is associated with a significantly higher risk of acute exacerbations and death. A comparison

of two methods for calculating FVC decline (absolute decline, for instance from 80% to 70% of predicted *vs* relative decline by 10%, for instance from 4.0 L to 3.6 L, which with a predicted normal of 5.0 translates into a decline from 80% to 72% of predicted) indicates greater sensitivity of the relative index [225]. This means that thus defined number of patients with progression in a studied patient population will be higher, but there is also a risk of overestimating the percentage of patients with clinically relevant progression. Both methods are characterised by a comparable predictive value of progression-free survival, progression being defined as requirement of transplant or death [225]. Many authors point to the fact that a decline in the range from ≥ 5% to below 10% is also associated with a poorer distant prognosis [226, 227]. Another frequently used measure of progression is a decrease in $T_{L,CO}$ ≥ 15% or shortening of distance in the 6MWT by ≥ 50 m [224, 228]. A possible alternative to individual functional indices is the composite physiologic index (CPI), which takes into account the FVC, FEV_1 and $T_{L,CO}$ values [222, 224, 229]. However, given the common use of spirometers, the ease of measurement, good repeatability as well as a well-documented relationship with prognosis, an absolute decline in FVC ≥ 10% within 12 months or less should be considered the basic measure of clinically relevant progression [230]. When assessing progression based on pulmonary function tests, it is important to use the same reference values. Currently, it is recommended to use the Global Lung Function Initiative (GLI) reference values [231, 232].

PHARMACOLOGICAL TREATMENT

Question 9. Should IPF patients be treated with pirfenidone?

Introduction

Pirfenidone is the first agent of antifibrotic agents to have been approved for IPF treatment. It's main mode of action is inhibition of fibroblast activity and type I collagen production by affecting TGF-β. The antifibrotic effects of this agent were initially demonstrated in non-randomised studies in the 1990s [233] and later confirmed in randomised, double-blind, placebo-controlled trials. The first studies performed in Japan demonstrated deceleration of FVC decline in treated patients compared with the placebo group. A decreased rate of AE-IPF was also observed in the treatment group, which however was not confirmed in further studies [234, 235]. The agent was approved based on the results of three international multi-centre, randomised studies, CAPACITY 1 and 2 and ASCEND, involving close to 1300 patients. The results of the CAPACITY 2 and ASCEND studies as well as a pooled analysis of all three trials confirmed the efficacy of the drug in patients with mild-to-moderate IPF. Patients with a severe form of the disease (FVC < 50% of predicted) were excluded from these trials. Deceleration of FVC decline rate of approximately 50% was demonstrated *vs* the placebo group, while a pooled analysis of patients in all three clinical trials demonstrated a reduction in the risk of death in the treatment group by almost 50% [81, 82]. Furthermore, post-hoc analyses of these trials in pirfenidone-treated patients revealed a reduced number of hospitalisations due to respiratory causes and a lower number of post-discharge deaths [236]. Pirfenidone also reduced worsening of dyspnoea, especially in patients with stages GAP II and GAP III, as well as severity of cough, one of the most bothersome symptoms experienced by IPF patients [223]. The proven benefits and safety of pirfenidone-based antifibrotic treatment allowed its approval for the treatment of IPF patients in 2011 in Europe and in 2014 in the US. The drug has received a conditional recommendation in the international IPF treatment guidelines, supporting its use in the treatment of IPF patients [75].

Recommendation 9.

We recommend the use of pirfenidone in IPF patients.

Quality of evidence: moderate
Strength of recommendation: strong
Votes: strongly for (the use of pirfenidone in IPF patients) — 13; conditionally for — 6; strongly against — 0; conditionally against — 0; abstained — 2

Commentary

The results of randomised, placebo-controlled studies as well as a pooled analysis of data gathered in these studies indicate that pirfenidone effectively slows down fibrosis progression in IPF patients [81, 82]. Pirfenidone is a safe drug, but one that can cause adverse effects. The most frequent ones include gastrointestinal symptoms (nausea, vomiting, lack of appetite, bodyweight loss) in approximately 20–40% of patients and

skin changes, especially rash associated with exposure to sunlight (in approximately 10%). An important but much less common treatment complication is elevated liver enzyme activity (approx. 3.5% of treated patients). In most cases, these effects are observed within the first six months of treatment. Their severity can be reduced through appropriate patient education as well as using preventive means and symptomatic treatment. If necessary, it is possible to reduce the pirfenidone dose or transiently interrupt the treatment, with no negative effects on its efficacy [237]. PASSPORT, a study designed to assess long-term safety of pirfenidone, failed to reveal any new adverse effects of the drug in addition to those already observed in randomised trials [238]. Contraindications include individuals diagnosed with hypersensitivity to the active substance or to any of the excipients; patients with a history of angioedema following pirfenidone administration; cases where simultaneous use of fluvoxamine is necessary; serious hepatic dysfunction or end-stage liver disease; and serious renal dysfunction with endogenous creatinine clearance < 30 mL/min or requiring dialysis therapy. The initiation of pirfenidone treatment should always be preceded by a discussion with the patient, explaining the benefits of the treatment but also the risk of adverse effects. A decision to start the treatment should be made jointly by the doctor and the patient.

Question 10. Should IPF patients be treated with nintedanib?

Introduction

Nintedanib is a non-selective tyrosine kinase receptor inhibitor. It acts by simultaneously inhibiting three growth factor receptor families involved in fibrogenesis and angiogenesis. These factors include platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) [239]. A clinical trial programme assessing the efficacy and safety of nintedanib in IPF treatment includes a phase 2 trial, TOMORROW [240], and two replicated phase 3 clinical trials — INPULSIS-1 and 2 [83], which collectively enrolled nearly 1,500 patients who were treated for 12 months. The INPULSIS studies confirmed the efficacy of the drug in reducing the rate of FVC decline in patients, irrespective of their baseline clinical characteristics or degree of lung dysfunction (FVC > *vs* < 70% of predicted). The FVC loss observed during follow-up in the nintedanib-treated group was lower by approximately 50% than in the placebo group [241]. A pooled analysis of data, complemented with a meta-analysis of the above three randomised trials of nintedanib in the treatment of IPF patients, additionally demonstrated that nintedanib treatment was associated with a reduction in the risk of an acute exacerbation of the disease (AE-IPF) by 47% compared to placebo, a trend towards reduced all-cause mortality and mortality due to respiratory causes as well as a significant reduction in mortality during treatment [221]. At the same time, an acceptable safety profile of the treatment was observed. Long-term observational studies confirm the efficacy and safety of nintedanib treatment in IPF patients [242]. The proven benefits and safety of nintedanib-based antifibrotic treatment allowed its approval for the treatment of IPF patients in 2014 in the US and in 2015 in Europe. The drug has received a conditional recommendation in the international IPF treatment guidelines, supporting its use in the treatment of IPF patients [75].

Recommendation 10.

We recommend the use of nintedanib in IPF patients.

Quality of evidence: moderate
Strength of recommendation: strong
Votes: strongly for (the use of nintedanib in IPF patients) — 13; conditionally for — 6; strongly against — 0; conditionally against — 0; abstained — 2

Commentary

A programme of randomised, placebo-controlled clinical studies [83, 221, 240] as well as long-term observational studies [242] confirms the beneficial effects of nintedanib on slowing down IPF progression and an acceptable safety profile of the treatment. The beneficial effect of the drug is comparable across all analysed subgroups of studied subjects [241]. Nintedanib reduces the risk of AE-IPF, at the same time demonstrating a trend towards reduction of the risk of death [221]. This data supports the use of nintedanib in antifibrotic treatment of IPF patients. The main adverse effects reported by patients during nintedanib treatment include diarrhoea, nausea, abdominal pain and vomiting [83, 240, 242]. Diarrhoea observed during treatment responds well to symptomatic treatment (loperamide), a temporary interruption of treatment or dose reduction. Liver function should be assessed before starting nintedanib and monitored during the treatment. The drug

should not be used in patients with liver injury (Child-Pugh classes B and C) and severe kidney failure. Since the drug's mode of action involves the VEGF receptor, caution is recommended when treating patients with a history of cardiovascular diseases or increased risk of bleedings. Patients with a history of myocardial infarction or unstable angina pectoris in the last six months, and those receiving intensive antiplatelet treatment (> 325 mg/day of acetylsalicylic acid or > 75 mg/ /day of clopidogrel) or full anticoagulation therapy were not enrolled into randomised clinical studies of nintedanib. Nevertheless, no contraindication for nintedanib treatment in this patient population has been formulated, and a decision to start this treatment should be based on an analysis of the benefit-risk balance [243]. The initiation of nintedanib treatment should always be preceded by a discussion with the patient, explaining the benefits of the treatment but also the risk of adverse effects. A decision to start the treatment should be made jointly by the doctor and the patient.

Question 11. Can IPF patients be treated simultaneously with pirfenidone and nintedanib?

Introduction

The necessity of exerting pharmacological action on different profibrotic signalling pathways as a result of the multifactorial and complex pathogenesis of IPF suggest that better outcomes could be achieved with combination therapy. In recent years, several studies have been published assessing the safety, tolerability and pharmacokinetics of combination therapy with pirfenidone and nintedanib in IPF patients [244–247]. In a randomised, double-blind phase 2 study conducted in a small group of 50 IPF patients, Ogura *et al.* [30, 57] demonstrated that combination therapy with pirfenidone and nintedanib had acceptable safety and tolerability profiles, which was confirmed in other studies [245–247]. A Japanese study, however, revealed reduced values of the peak serum plasma concentration and area under the curve (AUC) of nintedanib when it was used simultaneously with pirfenidone [244]. However, further studies of the pharmacokinetics and safety of combination therapy with pirfenidone and nintedanib failed to reveal any pharmacokinetic interactions between these agents [245–247]. No randomised studies assessing the efficacy of combination therapy with pirfenidone and nintedanib compared with monotherapy with either of the agents have been performed to date. Vancheri *et al.* only observed a trend towards a lower FVC decline in a group receiving simultaneous treatment with nintedanib and pirfenidone, compared with a group treated with nintedanib alone [245].

Recommendation 11.

Currently, we DO NOT recommend simultaneous use of pirfenidone and nintedanib in IPF patients.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (simultaneous use of pirfenidone and nintedanib in IPF patients) — 0; conditionally for — 2; strongly against — 8; conditionally against — 7; abstained — 4

Commentary

There is scarce data on simultaneous treatment with pirfenidone and nintedanib in IPF patients. Different modes of action and targets of pirfenidone and nintedanib suggest the possibility of further deceleration of FVC decline with their simultaneous use in the treatment of IPF. By contrast, in the case of combination therapy, there is a threat of unexpected or previously not observed toxicity as well as an increased risk of adverse effects, which partially overlap in the case of pirfenidone and nintedanib, especially as regards gastrointestinal disorders and increased liver enzyme activity [81–83, 240]. The currently available studies of the safety and tolerability of combination treatment with these drugs covering a period of only 12 to 24 weeks have failed to reveal any new, unexpected adverse effects, and most patients completed the planned combination therapy [245, 246]. Given small study populations, a short duration of combination therapy assessment and lack of randomised studies of the efficacy of simultaneous treatment with nintedanib and pirfenidone as well as the high costs of simultaneous treatment with the two drugs, combination therapy only should be used within randomised clinical trials.

Question 12. Should patients diagnosed with IPF based on the clinical context and the "probable UIP" pattern in lung HRCT be treated with antifibrotic agents?

Introduction

Data on the efficacy and safety of antifibrotic treatment in IPF patients with the *probable UIP* pattern in lung HRCT are significantly limited.

This is because this term was introduced into clinical practice in 2018 [29, 31], after randomised phase 3 clinical trials of antifibrotics had been conducted. The terminology of radiographic patterns was based at that time on the international guidelines for IPF diagnosis of 2011 [10], which did not differentiate the *probable UIP* pattern. Nevertheless, patients with a pattern of reticular changes characterised by basal and peripheral distribution (formerly, "possible UIP") associated with peripheral traction bronchiectasis or bronchiolectasis suggestive of a fibrotic process but without the typical honeycombing in lung HRCT, which corresponds, in line with the current nomenclature, to the "probable UIP" pattern [29, 31], were enrolled into randomised phase 3 studies using nintedanib in IPF patients (approx. 30% of subjects) [83]. A subgroup analysis taking into account clinical characteristics and results of pulmonary function examinations demonstrated consistent effects of nintedanib in this patient group (without honeycombing in imaging) and the group of patients with "definite UIP" (presence of honeycombing) in lung HRCT [248]. There is currently no data assessing the effects of pirfenidone in IPF patients with the "probable UIP" pattern in lung HRCT. However, observational retrospective studies of IPF patients treated with pirfenidone indicate lack of differences in the effect on decelerated FVC decline between IPF patients with the "typical UIP" and "possible UIP" lung HRCT patterns [249] according to the nomenclature of radiographic patterns used in the previous international guidelines for IPF diagnosis of 2011 [10].

Recommendation 12.

We suggest that patients with IPF diagnosis established by a multidisciplinary team based on the clinical context and the probable UIP pattern in lung HRCT be started on antifibrotic agents.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (starting treatment with antifibrotic agents in patients with the probable UIP pattern) — 2; conditionally for — 15; strongly against — 0; conditionally against — 1; abstained — 3

Commentary

Retrospective analyses of randomised and observational studies demonstrated that reticular changes distributed peripherally and subpleurally associated with traction bronchiectasis or bronchiolectasis but without honeycombing in lung HRCT, identified as "possible UIP" [10] or "probable UIP" [29, 31], in patients with an appropriate clinical context are very likely to represent the histopathological pattern of UIP in biopsy material. When assessing the probability of the histopathological UIP pattern in these patients, it is helpful to take into account the clinical probability of IPF, which is higher in individuals above 60 years of age, current or former tobacco smokers and persons with no history indicative of other potential causes of lung fibrosis [29]. In the above context and in light of the evolving diagnostic recommendations on IPF, it seems justified to start antifibrotic treatment in patients with a diagnosis based solely on clinical assessment and the "probable UIP" pattern in lung HRCT. Out of the two drugs, nintedanib has better quality evidence for the efficacy of antifibrotic treatment in this patient population [248].

Question 13. Should IPF patients with mildly decreased or normal pulmonary function parameters be treated with antifibrotic agents?

Introduction

This problem has important implications for the efficacy and tolerability of the treatment. In most countries it is recommended to start treatment on diagnosis, irrespective of symptoms or the degree of lung dysfunction. This is associated with inevitable disease progression whose rate is unpredictable. However, the randomised clinical trials enrolled patients with specific demographic and functional profiles, which makes extending their results to the general population more challenging.

The CAPACITY and ASCEND studies involved patients whose FVC was at least 50% of predicted and not above 90%. In a post-hoc analysis of these studies, the subjects were assigned into subgroups depending on the degree of disease advancement: FVC < 80% of predicted (GAP II and III) or ≥ 80% (GAP I). An analysis of the placebo group revealed that disease progression was seen in patients with both higher and lower functional parameters. In the group receiving active treatment, patients of both subgroups experienced comparable benefits of using pirfenidone in terms of FVC decline rate and distance in the walking test [223, 250]. Japanese studies demonstrated that the greatest benefit of pirfenidone treatment was seen among patients

with better preserved lung function (FVC ≥ 70% of predicted). Patients with less advanced stage of IPF more frequently maintained stable lung function, with less common worsening during pirfenidone treatment than patients with lower baseline lung function parameters [251–253]. The INPULSIS studies did not use the exclusion criterion of the upper limit of FVC% of predicted. In these studies, an efficacy assessment was planned in pre-defined subgroups, for instance in individuals with FVC ≥ 70% and < 70%. Equal treatment outcomes were demonstrated in patients with both lower and higher FVC values. In addition, post-hoc analyses demonstrated that nintedanib was equally efficacious in patients with FVC > 90% and < 90% [241, 254]. The INPULSIS-ON study, in which patients continued taking nintedanib for up to 192 weeks, also failed to reveal any differences in the therapeutic effect depending on the degree of FVC decline.

Recommendation 13.

We suggest that antifibrotic treatment be proposed to IPF patients with mildly decreased or normal pulmonary function parameters.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (antifibrotic treatment of IPF patients with mildly decreased or normal respiratory functional parameters) — 2; conditionally for — 16; strongly against — 0; conditionally against — 0; abstained — 3

Commentary

In each case before treatment is started, the benefits of the therapy and risk of adverse effects should be discussed with the patient. Antifibrotic agents slow down IPF progression while decreasing the rate of FVC decline. Thus, it seems logical to start the treatment when the lung capacity is still well preserved. However, treatment can be problematic to patients who do not experience any disease symptoms. An especially concerning aspect is the risk of adverse effects which can lower the quality of life. It is important to inform the patient about the nature of the disease, with its unpredictable course and the possibility that the rate of vital capacity decline increases at any moment. The patient should also be advised that even persons with low disease activity lose more FVC a year than healthy individuals [255]. In some situations, especially in patients who have been diagnosed incidentally, without any clinical symptoms and with normal functional test results, a decision can be made jointly with the patient to use the "watch and wait approach". In such a case, however, lung function should be monitored regularly (every 3–6 months) and treatment should be started immediately after worsening is observed [87, 203, 256, 257]. Means of coping with adverse effects of the treatment should be discussed with the patient in particular detail. Given the possibility that a patient with normal results of lung function test may receive an antifibrotic for many years, it is necessary to inform them how they can reduce possible adverse effects.

Question 14. Should IPF patients with severe lung function impairment (FVC < 50% of predicted, $T_{L,CO}$ < 30% of predicted) be treated with antifibrotic agents?

Introduction

Randomised phase 3 clinical trials of pirfenidone (CAPACITY 004 and 006 and ASCEND) [81, 82] and nintedanib (INPULSIS 1 and 2) [83] did not enroll patients with advanced IPF and serious lung dysfunction (FVC < 50% of predicted, $T_{L,CO}$ < 30% of predicted). Data on the efficacy and safety of antifibrotic agents in IPF patients with severe lung function impairment (FVC < 50% of predicted, $T_{L,CO}$ < 30% of predicted) are indeed limited. Nevertheless, an increasing body of evidence from observational studies using antifibrotic agents in this patient population indicates they have similar efficacy and adverse reaction profiles as those observed in pre-marketing randomised clinical trials [253, 258–263]. This data supports antifibrotic treatment in IPF patients outside the range of pulmonary function parameters that was used in the inclusion criteria of randomised studies assessing the use of pirfenidone and nintedanib in IPF.

Recommendation 14.

We suggest that antifibrotic treatment following IPF diagnosis be proposed to all patients without contraindications for this treatment, irrespective of the degree of lung function impairment.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (antifibrotic treatment of IPF patients irrespective of the degree of

lung dysfunction) — 3; conditionally for — 13; strongly against — 0; conditionally against — 3; abstained — 2

Commentary

A sudden decline in lung function or AE-IPF can occur at any stage of the natural history of the disease. Data from randomised clinical trials and observational studies involving the population of IPF patients indicate that antifibrotic agents are efficient in slowing down progressive lung function decline, irrespective of the baseline degree of respiratory dysfunction [81–83, 241, 250, 253, 258–263]. The decision-making process regarding the initiation of pharmacotherapy should take into account the patient's treatment preferences. Patients should be informed about the anticipated disease course as well as the benefits and potential risks associated with starting antifibrotic treatment. Discussing the treatment limitations and achievable goals is especially important. It is key for the patient to understand that pharmacological treatment will not improve lung function but only slow down disease progression and that the patient will likely fail to experience much improvement in terms of disease symptoms and quality of life. The choice of an antifibrotic agent for IPF treatment should take into account the patient's individual preferences, comorbidities and concomitant treatment. Patients with serious comorbidities associated with a poor prognosis and short life expectancy will most likely not benefit from antifibrotic treatment.

Question 15. Is disease progression an indication for discontinuation of antifibrotic treatment?

Introduction

IPF is a chronic progressive disease and the currently used antifibrotic treatment offer no curative potential but only deceleration of disease progression [81–83, 240]. Based on clinical trials, it was assumed that an absolute FVC decline by ≥ 10% indicates insufficient treatment response. On this basis different local regulations and guidelines recommend discontinuation of pirfenidone or nintedanib in case of disease progression, i.e. an FVC decline by ≥ 10%, within 12 months of treatment [82]. The published pooled data from the CAPACITY and ASCEND trials provided evidence that continuation of pirfenidone treatment is beneficial to IPF patients who have experienced significant disease progression during treatment (defined as an FVC decline by ≥ 10% within 6 months of treatment), in the form of a reduced risk of further FVC decline or death [264]. Similar pooled data from the INPULSIS I and II studies, suggestive of treatment benefits despite reduced FVC, are available for nintedanib [265]. A recently published study assessed the frequency of multiple disease progression events within 12 months. The progression events were defined as a relative reduction in FVC by ≥ 10% of predicted, absolute reduction of distance in the 6MWT by ≥ 50 m, hospitalisations due to respiratory cause or death of any cause. It was demonstrated that pirfenidone significantly reduced the frequency of multiple progression events or death after any progression event within 12 months of treatment versus placebo [266]. The above study results suggest that continued antifibrotic treatment benefits IPF patients despite disease progression during the treatment.

Recommendation 15.

We suggest that disease progression NOT be an indication for discontinuation of antifibrotic treatment.

Quality of evidence: poor
Strength of recommendation: conditional
Votes: strongly for (recognising disease progression as an indication for discontinuing antifibrotic treatment) — 0; conditionally for — 2; strongly against — 5; conditionally against — 11; abstained — 3

Commentary

Currently, there is no unambiguous, commonly accepted definition of disease progression and, consequently, of antifibrotic treatment failure. The assessment of antifibrotic treatment efficacy in clinical trials was based on a long-term analysis of FVC, although it is known that this parameter is characterised by a certain intrapersonal variability. In addition to pulmonary function parameters (FVC, $T_{L,CO}$) a comprehensive assessment of the disease course should take into account other parameters, such as clinical symptoms (dyspnoea, cough, exercise capacity, etc.), possible complications (such as exacerbations, hospitalisations, pulmonary hypertension) or imaging examination results (HRCT). In a pooled analysis of the CAPACITY and ASCEND trials, Nathan *et al.* confirmed that FVC in long-term follow-up of IPF patients is characterised by a marked intrapersonal variability, which prevents a reliable assessment of therapeutic response using a series of FVC measurements

[264]. In addition, it should be stressed that even though a decline in FVC by ≥ 10% is indisputably significant, it does not prove lack of treatment efficacy. This is because it cannot be ruled out that a much larger FVC decline would have been observed if no treatment had been provided. The presented results of a pooled analyses of the above clinical trials proved that disease progression in IPF patients undergoing antifibrotic treatment should not be interpreted as treatment failure leading to discontinuation as long as tolerability is satisfactory [265]. No data is currently available on whether it is more beneficial to continue the same treatment or switch agents in case of disease progression. In case of further deterioration of respiratory function, it is recommended to refer the patient to a transplant centre unless contraindications for lung transplant exist [264, 266].

Question 16. In what situations should one consider switching from one antifibrotic agent to the other?

Introduction

It was demonstrated that both pirfenidone and nintedanib slow down IPF progression expressed as a reduced FVC decline over time. However, no head-to-head trials comparing both agents have been conducted to date [82, 83]. The choice between the two drugs is, therefore, based on the experience of the treating pulmonologist, contraindications and adverse effect profile of a given antifibrotic, concomitant use of other drugs and possible interactions as well as the patient's preferences. A possible justification of switching one drug for the other is the development of unacceptable adverse effects or lack of efficacy. This, however, must be adjudicated with great caution. The problem of defining IPF progression during antifibrotic treatment is discussed in Question 8. Treatment-related adverse events for pirfenidone and nintedanib partially overlap, especially as regards the gastrointestinal system (nausea, vomiting, diarrhoea) or increased liver enzyme activity as well as bodyweight loss. On the other hand, pirfenidone is additionally associated with skin adverse effects such as rash or photosensitivity reaction. Adverse effects associated with antifibrotic treatment are usually mild to moderate and adequate management (dose reduction, short treatment interruption or symptomatic management) makes it possible to continue the treatment in most patients. Clinical studies suggest that treatment-related adverse events were the cause of discontinuation in 15% of pirfenidone-treated [82] and 19% of nintedanib-treated cases [83]. The availability of two antifibrotic agents makes it possible to switch between the treatments in certain cases. Data on the switching of antifibrotic agents is limited and it pertains to switching from pirfenidone to nintedanib due to adverse effects or disease progression [267–269]. The above studies indicate that in selected patients who do not tolerate pirfenidone treatment, switching to nintedanib can be associated with good tolerability of the treatment in spite of the similar adverse effect profiles of both agents. It was additionally observed that individual responses to treatment with any of the drugs can differ. It was demonstrated that patients who were stable during the treatment with one of the antifibrotic agents experienced progression when using the other [268].

Recommendation 16.

We suggest switching from one antifibrotic agent to the other in case of significant lack of tolerance or adverse effects.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (changing an antifibrotic agent in case of intolerance or adverse effects) — 4; conditionally for — 15; strongly against — 0; conditionally against — 0; abstained — 2

Commentary

The first drug to have been approved in the treatment of IPF in Europe was pirfenidone. This happened in 2011 [270], after the publication of the CAPACITY study results [82]. That is why most patients in many centres providing IPF treatment were at first qualified for this treatment. The second agent to have been approved for IPF treatment in Europe was nintedanib, in 2015. This posed several important questions to pulmonologists, for instance, which of the agents should be used first and when switching from one agent to the other should be considered. Long-term open-label studies, pooled analyses of earlier randomised clinical studies and real-world data confirmed the beneficial safety and tolerability profiles of both pirfenidone [237, 238, 271, 272] and nintedanib [242, 267]. However, in a certain percentage of patients — in spite of dose adjustments, interruptions or symptomatic management — the treatment is discontinued because of persistent adverse effects. Despite the partial overlapping of the adverse effects of pirfenidone and nintedanib, different pharmacodynamic and

pharmacokinetic properties of the agents make it possible to switch the treatment safely in selected patients [242, 267]. No data on switching from nintedanib to pirfenidone has been published to date. Studies analysing nintedanib treatment in patients previously treated with pirfenidone additionally revealed there was an intrapersonal variability of responses to treatment, from stable to progressive disease, depending on the agent used [268]. In case of adverse effects preventing the use of one of the antifibrotic agents or disease progression, it seems worthwhile to consider switching from one antifibrotic to the other after assessing the anticipated risks and benefits and discussing it with the patient. In order to answer the question whether switching from one agent to the other in case of disease progression could be beneficial to IPF patients, prospective, randomised clinical trials are necessary.

Question 17. Should all IPF patients be treated with anti-acid agents?

Introduction

It is known that an increased frequency of gastroesophageal reflux disease (GERD) is observed in IPF patients. Studies have revealed that more than a half of patients with acid reflux experience symptoms of the disease. However, the severity of the gastroesophageal reflux (GER) is not correlated with severity of IPF. Moreover, in more than 60% of patients receiving standard anti-reflux treatment (AAT), episodes of low oesophageal pH are still observed [41]. Discussions about the causal relationship between GERD and IPF are ongoing [17]. The use of agents inhibiting hydrochloric acid secretion (proton pump inhibitor (PPIs), H2 blockers) in IPF patients has been an object of interest for years. PPIs are drugs of pleiotropic properties. *In vitro* studies demonstrated that they inhibit pro-inflammatory cytokines, adhesive molecules and metalloproteinases and induce cytoprotective enzymes, at the same time inhibiting fibroblast proliferation and decreasing collagen production stimulated by TGF-β [273]. Thus, the effect of PPIs in IPF patients is not necessarily linked with suppression of acidic GER but with additional anti-inflammatory and antifibrotic effects of these agents. The results of several retrospective studies indicate a longer survival in IPF patients taking AAT [274, 275] as well as a lower rate of FVC decline and reduction in acute exacerbations [276]. A meta-analysis of 13 observational studies assessing the effects of pharmacological treatment of reflux disease on the course of IPF demonstrated that using agents reducing gastric acid secretion caused a significant reduction in IPF-associated mortality as well as prolonged survival without lung transplant. However, no influence on all-cause mortality or pulmonary function parameters was observed. On the other hand, in patients with FVC < 70% of predicted a significant increase in the incidence of respiratory infections was observed. No randomised, placebo-controlled study was found that would assess the effects of anti-reflux treatment on the course of IPF. Therefore, the results of this meta-analysis should be interpreted with caution [277]. In addition, in some observational studies the presence of so-called immortal time bias was demonstrated — in order to undergo assessment, the subjects had to survive until the endpoint, which created a false impression of the drug's protective properties [278]. Despite numerous controversies and lack of randomised trials assessing their efficacy, the international guidelines of 2015 conditionally recommend regular use of AAT in IPF treatment, regardless of GERD symptoms [75].

Recommendation 17.

We suggest that anti-acid agents in IPF patients NOT be used in absence of other indications for such treatment.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (the use of anti-acid agents in IPF patients without indications for such treatment) — 0; conditionally for — 0; strongly against — 1; conditionally against — 17; abstained — 3

Commentary

Post-hoc analyses of randomised clinical studies of using pirfenidone and nintedanib in IPF treatment were free of immortal time bias and yielded opposite results on the protective role of AAT. Among IPF patients who received pirfenidone as part of three clinical phase 3 trials, nearly 44% took also agents inhibiting hydrochloric acid secretion. No differences were observed in any of endpoints assessing IPF progression between groups treated with PPIs and those not receiving this treatment. On the other hand, PPI-treated patients presented with more serious gastrointestinal adverse effects [228]. Similarly, an analysis of the placebo-treated groups in these same randomised trials failed to demonstrate any difference in the number of deaths, hospitalisations or FVC decline rate. An insignificantly higher rate of

infections, including respiratory infections, was observed in patients receiving PPIs [75]. Patients participating in the INPULSIS studies, irrespective of whether they were taking or not agents reducing hydrochloric acid secretion, were found to exhibit no changes in the natural history of the disease (placebo group) or the effect of these agents on nintedanib efficacy. Similarly to pirfenidone studies, an insignificantly higher rate of respiratory infections was observed in patients receiving PPIs [279]. The treatment of cough associated with IPF is a separate issue. Cough is known to be one of the most bothersome and most difficult-to-treat IPF symptoms. GERD can exacerbate cough. A single-centre, randomised, double-blind, placebo-controlled clinical trial was conducted to assess the efficacy of omeprazole in reducing cough episodes in IPF patients. A 39% decline in the rate of cough attacks was demonstrated in the omeprazole-treated group. No changes were observed in FVC, $T_{L,CO}$ or quality of life assessments during three months of follow-up. The study results can support the efficacy of omeprazole in managing cough in IPF patients and indicate a need of additional, multicentre trials with larger patient populations [280].

Question 18. Should N-acetylcysteine be used in IPF treatment?

Introduction

N-acetylcysteine (NAC) is a drug of antioxidant properties, a precursor of glutathione which is the basic endogenous antioxidant. *In vitro* and animal studies indicated that NAC inhibited the profibrotic effects of TGF-β on tissues and transformation of epithelial cells into mesenchymal cells [281, 282]. For this reason, it was believed that NAC use in IPF patients in whom the TGF-β action is an important disease mechanism would result in suppression of fibrosis and improvement in lung function parameters. The recommendations for NAC use in IPF patients were based on the results of the IFIGENIA study, which demonstrated that patients receiving NAC in combination with prednisone and azathioprine had a lower FVC decline during 12 months of treatment than placebo-treated patients. In addition, lower myelotoxicity of immunosuppressive treatment was seen in these patients, albeit with no differences in survival [283]. The results of the IFIGENIA study led to widespread use of triple instead of double therapy in IPF patients. In order to assess the efficacy of NAC monotherapy compared with triple therapy, the PANTHER-IPF study was designed. In this study, patients received NAC alone, placebo or NAC, prednisone and azathioprine. The PANTHER-IPF study demonstrated that triple treatment is associated with higher mortality and hospitalisation rate than NAC or placebo, and for this reason the study was discontinued [67]. However, the comparison of the placebo group with NAC monotherapy group was continued and no significant differences in the course of IPF were seen in the two patient groups [284]. Subgroup analysis assessing the influence of polymorphisms of single TOLLIP genes demonstrated that patients with the TT genotype of the *rs3750920* gene (TOLLIP) can benefit from NAC treatment, but NAC administration in patients with the CC genotype is associated with worsening of lung function. Therefore, the use of NAC in IPF patients should be preceded by a polymorphism analysis of the TOLLIP gene [285].

Recommendation 18.

We recommend that N-acetylcysteine NOT be used in the treatment of IPF patients, either as monotherapy or in combination with other agents.

Quality of evidence: poor
Strength of recommendation: strong
Votes: strongly for (the use of N-acetylcysteine in IPF patients) — 0; conditionally for — 0; strongly against — 11; conditionally against — 6; abstained — 4

Commentary

There are contradicting reports on combination therapy with NAC and pirfenidone. One Japanese study that enrolled patients with advanced disease who had experienced FVC decline ≥ 10% within 6 months preceding the study demonstrated that the add-on of inhaled NAC caused deceleration of FVC decline rate compared with a group taking pirfenidone alone. However, it was a case-control study and the study population was very small [286]. In another study, among patients with an early IPF form, the efficacy of inhaled NAC was observed in individuals with FVC < 95% of predicted and $T_{L,CO}$ < 55% of predicted [287]. On the other hand, the PANORAMA study, a multicentre, double-blind, placebo-controlled study involving 123 IPF patients, failed to reveal any positive effect of administering oral NAC at a dose of 3 × 600 mg in combination with pirfenidone. NAC failed to improve pirfenidone tolerability, and in the group receiving both agents, FVC decline was even higher than in the pirfenidone monotherapy

group [288]. The most recent recommendations for the treatment of IPF [75] sustained the earlier position on NAC treatment as contraindicated in most IPF patients. The use of NAC would be justified in patients with the TT genotype of the TOLLIP gene, although targeted therapy is not currently used.

Question 19. Should IPF patients receive immunosuppressive treatment?

Introduction

The initial concept of the disease process involved in IPF as having a largely inflammatory nature led to the use of immunosuppressive treatment. In the past, immunosuppressive treatment was considered an important element of IPF management and recommended in the first international diagnostic and therapeutic recommendations [9]. Despite the widespread past use of glucocorticosteroids (GCS) in IPF treatment, there are no randomised, placebo-controlled trials of adequate quality that would support their use in this indication [289]. In a similar vein, a systematic review of studies using other nonsteroidal immunosuppressive drugs, such as cyclophosphamide, azathioprine (AZA) or interferon-γ, failed to demonstrate their beneficial effects in the treatment of IPF patients [290]. Moreover, the once widely used triple treatment with prednisone, AZA and NAC proved to be associated with higher rates of hospitalisations and deaths compared with placebo [67]. Based on the current international IPF treatment guidelines, immunosuppressants received a strong recommendation against their use in the treatment of IPF patients [75].

Recommendation 19.

We recommend that NO type of immunosuppressive treatment be used in IPF patients.

Quality of evidence: poor
Strength of recommendation: strong
Votes: strongly for (the use of immunosuppressive treatment in IPF patients) — 0; conditionally for — 0; strongly against — 12; conditionally against — 6; abstained — 3

Commentary

Attempts at using immunosuppressant in the treatment of IPF patients have been made in the past usually in relation to the original theory which linked the pathobiology of IPF at least in part with inflammation. Few available studies, often of low quality, failed to demonstrate any benefit of such an approach. However, many adverse effects associated with this treatment were demonstrated and even, as in the case of triple treatment (GCS + AZA + NAC), an increased risk of death in actively treated patients [67]. Given lack of evidence confirming any benefits and observed toxicity, the use of immunosuppressive treatment in IPF should be considered harmful and inconsistent with evidence-based medicine [289, 290].

Question 20. Should agents dedicated to treating pulmonary hypertension be used in IPF patients?

Introduction

Pulmonary hypertension, defined as mean pulmonary artery pressure ≥ 25 mm Hg, is frequent in IPF patients, especially in an advanced stage of the disease or in case of concomitant emphysema [291, 292]. At diagnosis, approximately 8–15% patients have concomitant pulmonary hypertension [46, 293], and this percentage reaches 30–50% during qualification for transplant [292, 294, 295]. The presence of pulmonary hypertension in IPF patients is associated with increased mortality, more severe dyspnoea, decreased exercise tolerance, $T_{L,CO}$ impairment, more severe hypoxaemia and increased risk of an AE-IPF [294, 296]. Several randomised clinical trials assessed treating IPF patients with different drugs used in pulmonary hypertension but yielded negative results. As regards the treatment of IPF-associated pulmonary hypertension, lack of efficacy was demonstrated in the case of dual endothelin receptor antagonists (bosentan and macitentan) [76, 77, 297]. The selective antagonist ambrisentan, assessed in the ARTEMIS-IPF study and the terminated ARTEMIS-PH study, demonstrated lack of efficacy in the treatment of pulmonary hypertension and increased the frequency of hospitalisations due to respiratory causes [70]. A phase 2 study of riociguat, a soluble guanylate cyclase stimulator, in ILDs with symptomatic pulmonary hypertension was also preliminary terminated due to an increased risk of death and other serious adverse events in the riociguat-treated group *vs* placebo [298]. In a randomised controlled trial STEP-IPF of phosphodiesterase-5 inhibitor, sildenafil, used in patients with advanced IPF, defined as $T_{L,CO}$ < 35% of predicted, the primary endpoint, i.e. a significant increase of distance in the 6MWT, was not met [78]. On the other hand, in the sil-

denafil-treated group a significant improvement *vs* placebo was demonstrated in terms of secondary endpoints, i.e. dyspnoea severity, quality of life, blood oxygen saturation and $T_{L,CO}$. Based on this encouraging data, the INSTAGE study was conducted in patients with advanced IPF. The study analysed the efficacy and safety of nintedanib in combination with sildenafil compared with nintedanib and placebo [299]. However, no significant benefits of combination therapy with nintedanib and sildenafil were demonstrated compared with nintedanib monotherapy in this population of IPF patients. The only treatment currently recommended by the European Society of Cardiology/European Respiratory Society (ESC/ /ERS) for pulmonary hypertension in correlation with IPF involves long-term oxygen therapy, treatment of comorbidities and referring the patient to a transplant centre if no contraindications are present [300].

Recommendation 20.

We suggest that agents dedicated to treating pulmonary hypertension NOT be used in IPF patients.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (the use of agents dedicated to treating pulmonary hypertension in IPF patients) — 0; conditionally for — 1; strongly against — 3; conditionally against — 13; abstained — 4

Commentary

Coexistence of pulmonary hypertension in IPF patients is a well-defined prognosis-worsening factor in this serious disease. A retrospective analysis of IPF patients who underwent right heart catheterisation as part of pre-lung transplant assessments demonstrated higher annual mortality (28% *vs* 5, 5%) in the group of patients with pulmonary hypertension compared with those without pulmonary hypertension [294]. Despite many clinical randomised trials assessing the efficacy of different drug classes used in the treatment of pulmonary hypertension, no beneficial effects have been yet demonstrated in the case of IPF patients with concomitant pulmonary hypertension. The most encouraging results came from the STEP-IPF study (improvement only in terms of secondary endpoints), which enrolled 180 patients with advanced IPF [78]. In addition, data from the international COMPERA registry confirmed short-term functional improvement in certain patients treated with agents dilating pulmonary vessels, mostly phosphodiesterase-5 inhibitors [301]. Unfortunately, these results have not been yet confirmed in large randomised clinical trials. Therefore, agents dilating pulmonary vessels are not recommended for routine use in IPF patients associated with pulmonary hypertension outside of randomised clinical trials. There is an ongoing study of sildenafil added to pirfenidone treatment (clinicaltrials.gov NCT02951429) in patients with probable pulmonary hypertension assessed non-invasively [302].

NON-PHARMACOLOGICAL TREATMENT AND PALLIATIVE CARE

Question 21. Should pulmonary rehabilitation be used in IPF patients?

Introduction

Pulmonary rehabilitation is a complex intervention based on thorough assessment of the patient's condition, adjusted to their individual capabilities and involving training, education and shaping of appropriate health-promoting behaviours. It is aimed at improving the patients' physical and mental fitness and long-term compliance with the aforementioned behaviours [303]. The beneficial effect of rehabilitation in IPF patients has been documented in many prospective, non-randomised observational studies [304–310] and numerous randomised trials [311–318]. A 2014 meta-analysis of 5 randomised studies (86 patients with ILDs, including IPF, undergoing rehabilitation and 82 non-rehabilitated patients comprising the control group) confirmed the beneficial effects of rehabilitation on distance in the 6MWT, peak oxygen uptake, dyspnoea severity and quality of life, with lack of adverse effects [319]. The most recent meta-analyses of 5 randomised trials involving more than 130 IPF patients divided into a group of subjects receiving rehabilitation and a control group demonstrated an improvement in exercise tolerance, reduction of symptoms and quality of life improvement [320]. Another meta-analysis of 4 randomised trials (a total of 142 subjects) confirmed beneficial short-term effects of rehabilitation on exercise capacity and quality of life but failed to confirm any distant effects [321]. The most recent meta-analysis of 7 studies involving 190 IPF patients demonstrated improved exercise capacity measured as distance in the 6MWT and improved quality of life [322]. Pulmonary rehabilitation involves the following: physical exercises (aerobic, endu-

rance and flexibility exercises as well as arm and inspiratory muscle training), education (symptom management, oxygen therapy optimisation, self-care), optimisation of nutrition and psychosocial support [323]. A rehabilitation programme should be started in a specialist pulmonary rehabilitation centre, in the inpatient or outpatient setting, and led and supervised by adequately prepared medical staff [324]. Attempts should be made to continue the programme at home. Supervised home rehabilitation, with optional use of telemedicine, can be an alternative to the traditional method [325].

Recommendation 21.

We recommend the use of pulmonary rehabilitation in IPF patients.

Quality of evidence: moderate
Strength of recommendation: strong
Votes: strongly for (the use of pulmonary rehabilitation in IPF patients) — 15; conditionally for — 5; strongly against — 0; conditionally against — 0; abstained — 1

Commentary

The authors of the international guidelines for IPF diagnosis and treatment of 2011 recommend pulmonary rehabilitation in IPF patients (weak recommendation, very poor evidence quality), concluding that rehabilitation should be used in most IPF patients, but it may be appropriate to forgo it in a minority of them [10]. The update of treatment guidelines of 2015 does not pertain to pulmonary rehabilitation of IPF patients [75]. However, a majority of randomised trials were published after 2011 [311–314, 317]. Currently, the amount and quality of evidence should be considered sufficient to recommend pulmonary rehabilitation in IPF patients as an important component of treatment. The question of precise identification of patients who can benefit most from it still needs to be elucidated. Many authors stress the validity of initiating rehabilitation in an early period of the disease [307, 308], although greater early effects are achieved in patients with more advanced disease [313]. Another issue is one associated with individualisation and standardisation of the rehabilitation programme, taking into account the patient's capabilities and preferences and resulting, among others, from the degree of functional impairment, need for oxygen therapy and comorbidities. Another controversial question is that of the duration of the effects of rehabilitation, since many authors claim that the effects last up to 6 [307, 313, 321], 11 [326] or even 12 months [325] after completing the programme, while others do not confirm its lasting beneficial effects in a longer term [315, 321]. Lack of unequivocal data confirming distant effect indicates it is necessary to use rehabilitation in a continuous and systematic way.

Question 22. Should long-term oxygen therapy (LTOT) be used in patients with respiratory failure in the course of IPF?

Introduction

Sings of chronic hypoxaemic respiratory failure occur in IPF patients at a late stage of the disease. This is when one should consider indications for long-term home oxygen therapy (LTOT). However, there is no unambiguous evidence confirming the efficacy of LTOT in IPF patients. The studies conducted to date have only demonstrated a shorter survival in oxygen-treated patients due to respiratory failure in the course of ILD compared with COPD [327]. The cited studies were not randomised and contained no comparative groups, so the impact of LTOT on survival cannot be directly assessed. Recently published qualitative studies point to the fact that some IPF patients using LTOT reported improvement [328, 329]. Others complained about the bothersomeness of this type of treatment and the limitations in everyday life it causes [329].

Recommendation 22.

We recommend using long-term oxygen therapy (LTOT) in patients with chronic respiratory failure in the course of IPF.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (the use of long-term oxygen therapy in IPF patients with chronic respiratory failure) — 15; conditionally for — 5; strongly against — 0; conditionally against — 0; abstained — 1

Commentary

This recommendation is in line with the position presented in the international ATS/ERS/JRS/ALAT recommendations of 2011 (strong recommendation, very poor quality of evidence) [10]. There is limited data supporting the beneficial effects of LTOT in patients with respiratory failure in the course of IPF, so this recommen-

dation stems from medical knowledge of the pathophysiology of respiration and the established clinical management of respiratory failure. Above all, the authors took into account the results of studies confirming the efficacy of chronic oxygen therapy in patients with other chronic lung diseases, including COPD. The recommendation does not contradict recommendations in guidelines by working groups or pulmonology societies published after 2011 [87, 330, 331]. The authors of the ATS/ERS/JRS/ALAT guidelines (2011) failed to specify unambiguously the qualification criteria for LTOT, leaving this to the treating doctor's discretion [10]. The authors of Swiss [87], Japanese [330] and Australian [331] guidelines recommend LTOT in IPF patients diagnosed with resting hypoxaemia ($PaO_2 \leq 55$ mm Hg or $PaO_2 < 60$ mm Hg if one of the following signs is present: signs of pulmonary hypertension, signs of right ventricular hypertophy, polyglobulia). The patient should use oxygen for at least 15 hours a day and for the entire night.

Question 23. Should oxygen be used during exercise in IPF patients?

Introduction

The course of IPF involves limitation of exercise tolerance with concomitant shortness of breath, caused by insufficient amounts of oxygen delivered in relation to the demand. Reduced everyday physical activity and dyspnoea affect the patient's quality of life and prognosis [332]. Exertional desaturation and increased oxygen demand during exercise are negative prognostic factors for mortality and disease progression [333–335]. The use of oxygen therapy during exercise can reduce dyspnoea and improve physical capacity. However, there is an insufficient number of studies confirming the beneficial effects of oxygen therapy during exercise in IPF patients with exertional hypoxaemia. In a meta-analysis of three cross-over studies comparing the effects of oxygen and air from a portable oxygen source, two studies failed to confirm any benefits of oxygen therapy [336]. The third study [337] demonstrated improved oxygen saturation but with no effect on perceived dyspnoea. Another study demonstrated reduced dyspnoea, improved capacity and decreased desaturation degree in patients receiving oxygen during exercise, with high oxygen concentrations in inspiratory air ($FiO_2 > 0.50$) [338]. In another randomised, cross-over, two-week, prospective trial comparing the effects of two-week oxygen therapy using a portable oxygen source with a period without oxygen therapy in IPF patients with latent hypoxaemic respiratory failure, oxygen therapy was found to have a beneficial effect on the quality of life [339]. Oxygen therapy using a portable oxygen source does not reduce exercise-induced increase in pulmonary artery pressure [340].

Recommendation 23

We suggest using oxygen during exercise in IPF patients with dyspnoea and exertional desaturation.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (the use of oxygen during exercise in IPF patients with dyspnoea and exertional desaturation) — 5; conditionally for — 13; strongly against — 0; conditionally against — 0; abstained — 3

Commentary

According to the authors of the British Thoracic Society (BTS) guidelines, oxygen from a portable source should not be routinely used in patients who do not qualify for home oxygen therapy or those who already receive this treatment chronically [341]. It should, however, be recommended to LTOT patients who are still involved in outdoor activities as well as patients participating in pulmonary rehabilitation programmes if improved physical capacity has been demonstrated as a result of using a portable oxygen source [341]. The AmbOx trial results suggest that, compared with lack of oxygen therapy, the use of oxygen from portable sources during exercise decreases desaturation and dyspnoea during exercise and also improves the quality of life in patients with ILDs, without resting hypoxaemia [339]. When recommending the use of oxygen from portable sources, one should remember the costs and physical strain associated with carrying or pulling an oxygen-delivering device as well as the need for frequent refilling [342]. Therefore, it is necessary to perform further studies assessing the efficacy of oxygen therapy in patients with exertional hypoxaemia. It is recommended to perform an individual assessment of potential benefits based on objective examinations.

Question 24. Should preventive vaccinations be used in IPF patients?

Introduction

The elderly, especially patients with chronic lung diseases, contracting flu or pneumococcal pneumonia, are at a high risk of death. This

can be avoided through preventive vaccinations [343–345]. The Polish recommendations suggest vaccinating individuals above the age of 50 against pneumococci, stressing the fact that pneumococcal pneumonia in persons additionally affected by chronic lung disease is much more frequent, i.e. five times more frequent in IPF patients [346]. At the same time, we should remember that IPF by definition refers to people after the age of 50 and its incidence increases with age [4, 5, 347]. In line with the WHO guidelines, Poland's National Flu Centre (*Krajowy Ośrodek ds. Grypy*) recommends flu vaccinations in all individuals aged 6 months and more, especially in populations at the highest risk of flu or its serious complications. This group, similarly to pneumococcal pneumonia, includes the elderly and patients with chronic lung diseases [348]. Given the marked antigen variability of the influenza virus, every year a new vaccine is produced. Its aim is to protect the patient from flu and the serious consequences of its possible complications in the upcoming epidemiological season.

Recommendation 24.

We recommend use of pneumococcal and flu vaccinations in IPF patients.

Quality of evidence: very poor
Strength of recommendation: strong
Votes: strongly for (the use of protective vaccinations in IPF patients) — 13; conditionally for — 6; strongly against — 0; conditionally against — 0; abstained — 2

Commentary

Patients with IPF are at a higher risk of pneumococcal pneumonia and flu as well as serious complications of these diseases. It is important to note that IPF patients' breathing reserves are limited to varying degrees. In individuals with a markedly lowered FVC and/or significantly impaired carbon monoxide diffusion indicated by $T_{L,CO}$, a sudden further worsening of these parameters caused by bacterial or viral pneumonia can lead to acute respiratory failure necessitating invasive mechanical ventilation or even a life-threatening condition. Additionally, respiratory infection can be a factor causing an AE-IPF [349–351], according to the current definition of this condition [38]. It is associated with high mortality and can occur at any stage of the disease, even in asymptomatic patients who only have radiographic changes [210, 352]. Infection prevention should all the more comprise an important element of managing IPF patients. According to the current guidelines by the Centers for Disease Control and Prevention (CDC) [353] and Polish expert recommendations by the Polish Nationwide Flu Prevention Programme (*Ogólnopolski Program Zwalczania Grypy*) on flu prophylaxis [354], flu vaccination should be performed once a year, while a conjugated PVC13 vaccine against pneumococci requires a single administration. It is recommended to perform an additional pneumococcal vaccination with a polysaccharide PPSV23 vaccine after one year [353].

Question 25. Should patients with advanced IPF be referred to palliative care centres?

Introduction

The main objective of palliative care is to achieve the best possible quality of life in patients whose disease is not effectively treated with causal treatment [355, 356]. One of such diseases is IPF. As demonstrated by studies assessing the use of pirfenidone or nintedanib in IPF treatment, a specific therapy can slow down the course of the disease, but it reduces clinical symptoms only to a small extent [81, 83]. These symptoms (dyspnoea, cough, anxiety, depression, chronic fatigue) can at the same time affect the quality of life irrespective of the degree of disease advancement [357]. In addition to alleviating the somatic complaints as well as mental and spiritual suffering, comprehensive palliative care activities include also good communication with the patient and their family, help in solving social problems, affirmation of life with accepting death as a natural process, constant care until death and caution taken not to prolong the passing persistently. The international ATS/ERS/JRS/ALAT guidelines for the treatment of IPF patients explicitly recommend palliative care targeted at symptoms (palliation) as a mandatory component, complementary to specific (antifibrotic) treatment targeted at the underlying disease [10]. Such care should be offered to the patient at least from the moment the disease enters the advanced stage or the first life-threatening exacerbation occurs [331, 358, 359]. In advanced and terminal IPF stages patient care should be provided by trained multidisciplinary teams of home and inpatient care. It is believed that the best form of palliative care in this period is home care.

Recommendation 25.

We suggest that patients with advanced IPF be referred to palliative care centres.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (referring patients with advanced IPF to palliative care centres) — 9; conditionally for — 9; strongly against — 0; conditionally against — 0; abstained — 3

Commentary

Idiopathic pulmonary fibrosis patients, especially with advanced disease, can suffer from difficult-to-treat symptoms, such as dyspnoea, cough, fatigue or anxiety [360]. These symptoms significantly reduce the quality of life, irrespective of objective physiological parameters of the disease advancement. At the same time, patients experience a lot of spiritual suffering, being aware of the progression of the incurable disease and inevitability of death. Improvement of patients' quality of life at this stage can be best provided in a comprehensive way by specialist palliative care centres. Although no direct medical evidence is present (EBM, evidence-based medicine) supporting the benefits of palliative treatment in IPF, it is indirectly provided by extrapolation of results from studies of other advanced chronic lung diseases [361, 362]. However, compared for instance with lung cancer patients, IPF patients have limited access to palliative care [363]. It needs to be emphasised that care offered by palliative care centres should be individualised — adjusted to the patient's as well as caregivers' needs [10]. At present, palliative care options in the context of IPF patient care in Poland are severely limited. This is caused, above all, by an insufficient number of centres and lack of nursing personnel dedicated to caring for patients with ILDs.

Question 26. Should morphine be used in palliative treatment?

Introduction

Dyspnoea is a defensive mechanism leading to increased ventilation and improved respiratory gas exchange. It is also the most important symptom contributing to a poor quality of life in IPF patients [364]. Opioids have been demonstrated to decrease shortness of breath significantly in patients with chronic respiratory diseases, including IPF. They improve breathing comfort, exert anxiolytic action by decreasing the level of dyspnoea-associated anxiety and have a positive effect on sleep quality. The opioid of choice in the treatment of dyspnoea in patients with respiratory diseases is oral morphine, initially administered in an immediate-release form and, after the optimum daily dose has been established, also in a controlled-release form [365–370]. However, there is no unequivocal evidence for the efficacy of morphine inhaled from a nebuliser, despite hypothetical benefits of morphine acting on the peripheral receptors and lack of systemic adverse effects with this mode of administration [371].

Recommendation 26.

We suggest using oral morphine in patients with severe IPF in palliative treatment of persisting dyspnoea.

Quality of evidence: very poor
Strength of recommendation: conditional
Votes: strongly for (the use of morphine in patients with severe IPF) — 6; conditionally for — 11; strongly against — 0; conditionally against — 0; abstained — 4

Commentary

Morphine dosage should be decided on an individual basis, discussed with the patient and their family and strictly monitored. It is important to note that elderly, emaciated or benzodiazepine-treated patients or those with concomitant COPD are more susceptible to opioid action, and administration of morphine in patients with hypercapnia is associated with a risk of respiratory centre depression. The starting oral morphine dose of 2.5 mg, administered as frequently as every 4 hours, can be safely used in IPF patients and gradually increased every couple of days until optimum effects are achieved [372]. This approach to morphine dose titration until reaching the optimum daily dose, even one exceeding 30 mg, is not associated with sedative effects or respiratory depression [373]. There is, however, a possibility of a significant problem in the form of constipation during opioid treatment. Therefore, it is important to administer laxative or stool-loosening agents, such as senna or lactulose [374].

Question 27. Should invasive ventilation be used in IPF patients with acute respiratory failure?

Introduction

AE-IPF is defined as clinically relevant worsening of respiration characterised by the pre-

sence of new extensive changes in the alveoli in a patient with an existing or new IPF diagnosis. This deterioration cannot be explained by circulatory failure or overhydration and is characterised by unexplained dyspnoea (exacerbation or *de novo*), typically lasting for < 1 month [38]. There are no unequivocal recommendations for effective management both in the case of a known cause and an acute exacerbation in an IPF patients if the event is associated with life-threatening hypoxaemia. The choice of therapeutic methods is limited to invasive ventilation, non-invasive ventilation (NIV) support, extracorporeal membrane oxygenation (ECMO) or administration of oxygen through a high-flow nasal cannula (HFNC) [375]. Idiopatic pulmonary fibrosis patients admitted to intensive care units due to acute respiratory failure who require mechanical ventilation are burdened with a poor prognosis and high mortality [376]. In these patients no improvement has been demonstrated in terms of survival or distant prognosis. Therefore, it is generally recommended to avoid this type of treatment in IPF patients, except for a situation where it is possible to perform lung transplant in a short time (bridge therapy) [377].

Recommendation 27

We suggest that invasive ventilation NOT be used in IPF patients with acute respiratory failure.

Quality of evidence: poor
Strength of recommendation: conditional
Votes: strongly for (the use of invasive ventilation in IPF patients) — 0; conditionally for — 0; strongly against — 6; conditionally against — 12; abstained — 3

Commentary

An alternative to mechanical ventilation can be non-invasive ventilation (NIV). In a retrospective study by Vianello *et al.*, NIV use was associated in selected IPF patients with clinical benefits, such as longer survival and decreased rate of complications, including death [378]. Similarly, Gungor *et al.* [379] demonstrated that the use of NIV in IPF and other ILDs is associated with a better overall prognosis, although a higher mortality rate was observed in patients requiring continuous NIV use. Retrospective studies indicate higher mortality in patients who have undergone invasive ventilation compared with those treated with NIV [380, 381].

Question 28. Should IPF patients be referred to lung transplant centres and if so, when?

Introduction

The use of antifibrotic agents can slow down lung function decline. However, irrespective of whether such a treatment is used, the natural history of this disease inevitably leads to the development of respiratory failure, secondary pulmonary hypertension and death. Furthermore, this prognosis is worsened by coexistence of other chronic diseases, especially cardiovascular, and the presence of AE-IPF. If all suggested methods of both non-pharmacological and pharmacological treatment have been attempted, the only possible form of therapeutic management that could potentially improve the quality of life and prolong survival is lung transplant. The consensus report of the International Society for Heart and Lung Transplantation (ISHLT) specifies potential candidates for lung transplant as adult patients with a chronic lung disease in its end stage who additionally have a high risk of death within two years if no transplant is performed and, at the same time, are characterised by a high probability of survival after the procedure [382]. An important and beneficial global trend is the observed continuous increase in the number of lung transplant procedures [383]. IPF holds an important place among indications for lung transplant. On the other hand, considering the unfavourable prognosis associated with IPF (median survival of 2–3 years since diagnosis and 20–30% 5-year survival [10]) as well as lack of both causal treatments and therapies that would significantly modify survival, lung transplant will still hold an important place in the therapeutic strategy of this disease. It is also worth noting that since the Lung Allocation Score (LAS) was introduced in the US, pulmonary fibrosis has overtaken COPD as the main transplant category as regards the relative priority assigned for the distribution of lungs available for transplantation.

Recommendation 28A

We recommend referring to lung transplant centres all IPF patients without contraindications for the procedure.

Quality of evidence: poor
Strength of recommendation: strong
Votes: strongly for (referring all IPF patients without contraindications for lung transplant to transplant centres) — 14; conditionally for — 5;

strongly against — 0; conditionally against — 1; abstained — 1

Commentary

Given the fact that IPF is a progressive disease, irrespective of whether antifibrotic treatment is started, we can assume that referring all IPF patients to lung transplant centres is a valid approach unless they have contraindications for the procedure. The validity of performing lung transplants in patients with lung fibrosis is supported by literature data. However, the evidence is associated with significant limitations, mainly the retrospective design of studies or heterogeneity of groups caused by enrolment of patients with lung fibrosis forms other than IPF. In a single-centre study of 46 IPF patients, Thabut *et al.* reported a survival rate of 79.4% in the first, 63.5% in the second and 39% in the fifth year following lung transplant. A multivariate analysis revealed, after adjusting for potential confounding variables, that lung transplant reduced the risk of death by 75% (95% CI: 8–86%; $p = 0{,}03$). Median organ wait time in this study was 51 days [384]. Other trials report a five-year survival of as much as 50–56% [385, 386]. These include a study by Keating *et al.*, who demonstrated a more favourable long-term prognosis in IPF compared with other indications for lung transplant. Despite a clear tendency towards a higher number of bilateral transplants [383], the question of whether one or both lungs should be routinely transplanted in IPF remains open. The results of studies analysing the benefits and risks of both procedures are varied [387–398] and make it impossible to adopt an unambiguous position. Therefore, this decision needs to be taken on an individual basis for each patient. In addition, it should be noted that unilateral transplantation is associated with an undoubted benefit in terms of managing organs for transplantation and that bilateral transplant is associated with a longer wait time [391].

Recommendation 28B

We suggest referring IPF patients to lung transplant centres immediately after the disease is diagnosed.

Quality of evidence: very poor

Strength of recommendation: conditional

Votes: strongly for (referring IPF patients to transplant centres immediately after diagnosis) — 7; conditionally for — 12; strongly against — 0; conditionally against — 0; abstained — 2

Commentary

The times of referral and inclusion in the waitlist are clearly specified in the ISHLT consensus [382]. Patients should be referred to a transplant centre when at least one of the following criteria is met:

1. A histopathological or radiographic pattern warranting the diagnosis of UIP or fibrotic NSIP, irrespective of lung function.
2. Lung function impairment: FVC < 80% of predicted or $T_{L,CO}$ < 40% of predicted.
3. Any dyspnoea or functional limitation associated with lung disease.
4. Any requirement of oxygen, including situations when oxygen is needed only during exercise.
5. For ILD, inability to improve dyspnoea, oxygen demand and/or lung function after causal treatment.

On the other hand, including a patient in the waitlist is recommended when at least one of the following criteria is met:

1. An FVC decline ≥ 10% during a 6-month follow-up (a decline of 5% is also associated with a poorer prognosis and can be a basis to include in the list).
2. A decline in $T_{L,CO}$ > 15% within 6 months of follow-up.
3. Desaturation < 88% or distance < 250 m in the 6MWT or a decline in distance > 50 m in the 6MWT during 6 months of follow-up.
4. Pulmonary hypertension diagnosed based on heart catheterisation or 2D echocardiography.
5. Hospitalisation due to impairment of respiratory parameters, pneumothorax or disease exacerbation

It is clear from these recommendations that the mere diagnosis of the UIP pattern is an indication for referral to a lung transplant centre. In addition, the validity of early referrals of patients to such a centre is supported by literature data which indicate higher mortality in IPF patients waiting for transplantation [384, 391]. The position that patients should be referred to transplant centres is also in line with the current ATS/ERS/JRS/ALAT guidelines [29].

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