Year 2020 | Vol. 88 | No. 3 | May–June | ISSN 2451–4934

Advances in Respiratory Medicine

Formerly Pneumonologia i Alergologia Polska
Edited since 1926

EDITORIAL

ORIGINAL RESEARCHES

REVIEW ARTICLE

The Journal is indexed in the following databases: Index Medicus/Medline, EMBASE, EBSCO, Emerging Sources Citation Index (ESCI), Scopus, Index Copernicus 121,1 (2018), MNiSW 2019 (20 points)

www.journals.viamedica.pl

VIA MEDICA

Advances in Respiratory Medicine

www.journals.viamedica.pl

Formerly Pneumonologia i Alergologia Polska

www.ptchp.org

Opinions presented in the articles not necessarily represent the opinions of the Editors
Advances in Respiratory Medicine (ISSN 2451–4934) is published by VM Media sp. z o.o. VM Group sp.k., ul. Świętokrzyska 73, 80–180 Gdańsk phone: +48 58 320 94 94, fax +48 58 320 94 60, e-mail: redakcja@viamedica.pl
http://www.viamedica.pl
project manager: weronika.kordyka@viamedica.pl
Editorial Address: Biuro ZG PTChP, ul. Wronia 45, lok. 132, Warszawa, Poland
Subscription Rates: Paper subscription, 6 issues incl. package and postage individual 60E
Paper subscription, 6 issues incl. package and postage institutional 90E.
Payment should be made to: Fortis Bank Polska SA, Gdańsk, Poland, Acc.: PL 15 1600 1303 0004 1007 1035 9001; SWIFT: PPABPLPK.
Single issues, subscriptions orders and requests for sample copies should be send
to e-mail: prenumerata@viamedica.pl
Electronic orders option available at: https://journals.viamedica.pl/advances_in_respiratory_medicine/about/subscriptions
Advertising: For details on media opportunities within this journal please contact the advertising sales department, ul. Świętokrzyska 73, 80–180 Gdańsk, Poland, phone: +48 58 320 94 94; e-mail: dsk@viamedica.pl
The Editors accept no responsibility for the advertisement contents.

Editorial policy and information for authors available on https://journals.viamedica.pl/public/journals/30/0B_ARM_2017_1_zasady1.pdf.
Polish Ministry of Science and Higher Education score: 20 pts.

19-0179.012.001 VIA MEDICA

Advances in Respiratory Medicine

www.journals.viamedica.pl

Formerly Pneumonologia i Alergologia Polska

www.ptchp.org

Contents

GUIDELINES AND RECOMMENDATIONS

CASE REPORTS

CLINICAL VIGNETTES

LETTERS

Harpreet Singh[1], **Tarun Popli**[2]

[1]Sutter Gould Medical Foundation, Stockton, United States
[2]New York Medical College, New York, United States

Stopping the SARS-CoV-2 surge in the USA-CDC recommendations and ground realities

Introduction

As of May 10, 2020, the United States of America (USA) has 1,367,079 cases of SARS-CoV-2 and 80,773 deaths associated with the disease. New York alone has more than 333,000 cases and nearly 21,271 deaths. We are having about 20,000 new cases every day and the deaths are exceeding 1000 a day. There is overwhelming evidence that the most effective way of controlling the virus from spreading is restricting movement to prevent human to human exposure. As a result, economies were put on a lockdown worldwide. In the USA, lockdown began in California on March 19th, 2020, with stay home orders, allowing only for essential jobs, errands, and some exercise outside. Other states followed soon.

Opening the economy seems necessary. Lockdown was at least partially successful, but as expected, the economy slowed and jobs were lost. The latest job report per the US labor department showed 26 million Americans have been laid off and filed for unemployment benefits. The US unemployment now stands at 14.7% meaning 1 out of every 6 is jobless. This issue is the toll of the SARS-CoV-2 on the largest economy of the world. Most states now are looking toward the opening. Most of the "shelter in place" orders expire in May and some states like Georgia have already opened its businesses.

Dangers involved with the reopening

Re-opening will pose challenges. The biggest risk we face is a surge in the immediate cases of new infections. The second wave of infection in the fall has also been predicted. Prediction models have increased the United States deaths to 130,000 by early August this year given the reopening and relaxation of social distancing guidelines. The surge can overburden the healthcare system. If we were to see a second wave similar to the first, our present health care system will stretch again and mortality will increase directly due to SARS COV-2 and related conditions such as heart attacks and stroke. In order to reduce mortality and health care utilization, it is important to identify and secure the most vulnerable and protectable. The older and the frail are at particular risk of contracting the disease and losing their lives.

Lessons learned until now about the most impacted group

As per the Center for Disease Control and Prevention's (CDC) latest data set, among the dead from SARS-COV-2 in the USA, 80% were 65 years or older and that has not changed since March 18th, 2020. As per CDC, on May 8th, 2020, the hospitalization rate was highest in people 65 years or older in age at 162.2 per 100,000 as compared to that rate in people 50–64 years of age was 79.0 per 100,000. The cumulative hospitalization rate was 50.3 per 100,000 [1]. It is logical to conclude that the group facing maximum mortality will also need more intensive care support. The CDC also studied the number of people above 65 years of age requiring intensive care shown and found it to be 53% in that age group [2]. Patients older

Address for correspondence: Harpreet Singh, Sutter Gould Medical Foundation, Stockton, United States; e-mail: harpreet91@gmail.com
DOI: 10.5603/ARM.a2020.0099
Received: 14.05.2020

ISSN 2451–4934

than 65 years released from the hospital were also more likely to be readmitted or released to a nursing home or rehabilitation facility, as opposed to home.

Living arrangements of people above 65 years of age

Based on these facts, the demographics including living arrangements of people above 65 years of age were studied. The number of people living in the USA above 65 years of age is 49.2 million as per the last available census report for 2016. As per, 2018 profile of senior living by Administration for Community living and Administration of Aging in the USA, the majority of men and women over 65 years of age live in their own homes. About 1.2 million people lived in nursing homes in 2017 who were above 65 years of age and constituted 1% of their population. The percentage increases with age to 3% for people, between 75–84. However, about 9% people lived in nursing homes that were above 85 years of age [3]. About 1.3 million people have been estimated to be living and working in nursing homes in the USA. Other long-term facilities include assisted living and intermediate care facilities that have about 800,000 and 75,000 patients respectively. About 3 million people work on these facilities as health care personnel (HCP) and support staff [4]. CDC has defined HCPs as health care providers like doctors, nurse practitioners, PAs, nurses, their aids, and trainees, emergency medical technicians, pharmacists, therapists, phlebotomists, technicians, and staff employed under the Environmental Services Department. There are 6 million people in this group as compared to the population of the USA, which is 328 million.

Despite lower percentages of people living in nursing homes, and the fact that they represented only 11% of total cases of SARS-CoV-2 cases, maximum death rate has been seen in residents of these facilities. A staggering 27,700 people died in long-term facilities in the USA as per database by New York Times [5]. These deaths accounted for one third of the deaths related to SARS-CoV-2, making it the most intensively hurt group of all. There are about 7,700 such facilities having 150,000 cases of the virus so far. It has been clear that patients in long-term facilities are particularly at risk for acquiring and dying from the corona virus. Advanced age, underlying health conditions make these patients vulnerable. Because of the enclosed environment and common utilities, it is easier for the virus to spread there. There is constant exposure as well from transitions to other health care services like dialysis units, wound care centers, physician appointments and hospitalizations. HCP's getting in and out of these facilities and move from one room to the other contributing to the exposure. Given the burden of the disease, the healthcare workforce has been stretched thin and some of these HCPs visit multiple facilities. This issue leads to HCP being both the host (could be asymptomatic) and the vector for SARS-CoV-2.

Benefits of controlling the virus in these facilities could be up to one-third reduction in mortality, reduced hospitalizations in the group, reduced re-hospitalization, saving resources, and beds in intensive care units for the younger population who will be more exposed now after the lockdown is relaxed. This strategy can be used to avoid overwhelming the health care system while providing for the patients below 65 years of age. The advantage is that restricting mobility is possible in these places as compared to the rest of the population. As the US is trying to open its economy, various organizations are helping to prevent the pandemic from worsening. The Center for Medicare and Medicaid services in the USA (CMS) is working towards helping long-term facilities reduce the impact of SARS-CoV-2. There is guidance available on topics like infection control and visitation policies and infection control in these facilities. CMS has issued directive on April 19th, 2019 that requires cases of SARS-CoV-2, to be reported directly to the organization, detected in Nursing Homes. Other major steps being taken include many states coming forward in allocating testing resources for these facilities. Experts agree that testing for SARS-CoV-2 is the key to moving forward and returning to business as usual. Measures like temperature check are not sufficient because of asymptomatic carriers. A study published in New England Journal of Medicine conducted in a Nursing Home in Seattle, USA, found that 50 % of the residents tested positive for SARS-CoV-2 and did not have any symptoms [6]. Similarly, asymptomatic workers can easily walk in and start a new spread. There is a need to spot these carriers who are unaware of their own infection.

The ground reality is that unfortunately, even now, most of these facilities do not have enough tests to stop the outbreak. So far, the major organizations like CDC and CMS have not mandated testing of all the residents and staff. The leading experts like Mark Parkinson, CEO of the American Health Care Association, said that there are not enough tests available and only a small percen-

tage of staff and residents are being checked [7]. Two-third of these facilities do not have access to enough tests as per Chris Laxton who is the director for the Society of post acute and long term care Medicine. (AMDA). [8] These facilities are not getting the same priority as hospitals.

Suggestions

We suggest special targeting of residents of long-term care facilities, and the HCPs involved in these facilities to stop the spread of SARS--CoV-2. Extreme measures including the highest testing numbers should be allocated to these facilities and rigorous infection control measures should be undertaken so that the SARS-CoV-2 virus do not enter and infect the patients in these facilities and if it does, the infection remains limited to facility. HCPs are usually younger than the residents of long-term facilities and are more likely to serve as a vector to SARS-COV-2. Increased testing can lead to an early exclusion from work to reduce the spread of SARS-CoV-2.Testing includes both RT-PCR (reverse transcriptase PCR) and the newer antibody testing. The long-term facilities should be prioritized as opposed to the younger population or urgent care facilities. About 150,000 tests are being done every day in the USA and there is need for increased allocation of resources toward towards the long-term care facilities at state and federal level.

Secondly, testing should follow prompt and specific infection control measures. Asymptomatic SARS-CoV-2 carriage leads to increased transmission. Separating positive patients to specific wards to stop the spread can follow early identification with increased testing.

Thirdly, a point prevalence survey is necessary for NH residents and HCP visiting the facility to successfully complete a test-based prevention strategy. National Guard teams are being deployed for the purpose but the need is to train the staff and provide necessary tests and personal protective equipment (PPE) so that all facilities can do their own testing. It is necessary that all residents of NH and other long-term facilities need to be tested frequently to curb the spread of SARS-CoV-2. Currently, available data suggests that where there are confirmed SARS COV-2 cases, there is an equal or greater number of asymptomatic SARS-CoV-2 carriers. Once PPS is carried out in these high incidence long-term facilities along with the HCP visiting them, necessary appropriate cohorting of these patients can be performed. A separate unit or facility can be created to keep these residents to curb the spread. Also, it is important to identify the asymptomatic SARS-CoV-2 carriers, and separating them would also be needed to complete the task. Meanwhile, if facility-wide PPS cannot be achieved, then at least separate units of symptomatic patients should undergo testing on a prioritized basis in these long-term facilities. There can be situations where resources may not allow facility-wide PPS and unit-wide PPS. At that point, prioritized testing of all symptomatic residents, residents admitted from high-risk hospitals, residents who leave the facilities frequently such as for the hemodialysis, wound care or rehabilitation reasons and residents coming in contact of symptomatic patients should be done.

With these strategies, the high-risk group of people should be secured so that the Corona viral surge can be stopped while we are re opening the economy.

Conflict of interes

None declared.

References:

1. A weekly update on Corona Virus by Center for Disease Control and Prevention. COVIDView, May 8th update on SARS-CoV-2. Available at: www.cdc.gov/coronavirus/2019-ncov/cases-updates/index.html. [Last accessed at: May 25th, 2020].
2. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 343–346. DOI: http://dx.doi.org/10.15585/mmwr.mm6912e2.
3. 2018 profile of senior living by Administration for community living and Administration of Aging, U.S. Census Bureau, the National Center for Health Statistics, and the Bureau of Labor Statistics. Available at: https://acl.gov/sites/default/files/Aging%20and%20Disability%20in%20America/2018OlderAmericansProfile.pdf. [Last accessed at: May 25th, 2020].
4. Chidambram P. State Reporting of Cases and Deaths Due to COVID-19 in Long-Term Care Facilities April 23, 2020. Available at: https://www.kff.org/medicaid/issue-brief/state-reporting-of-cases-and-deaths-due-to-covid-19-in-long-term-care-facilities/. [Last accessed at May 25th, 2020].
5. Yourish K, Lai R, Ivory D, et al. One-Third of All U.S. Coronavirus Deaths Are Nursing Home Residents or Workers. The New York Times, May 11th, 2020. Available at: www.nytimes.com/interactive/2020/05/09/us/coronavirus-cases-nursing-homes-us.html. [Last accessed at May 25th, 2020].
6. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med. DOI: 10.1056/NEJMoa2008457.
7. Stockman F, Richtel M, Ivory D, et al. coronavirus claims at least 6900 nursing home deaths in US. The New York Times, April 17th, 2020. Available at: https://www.nytimes.com/2020/04/17/us/coronavirus-nursing-homes.html. [Last accessed at: May 25th, 2020].
8. Associated press.11,000 Deaths: Ravaged Nursing Homes Plead for More Testing April 24, 2020. Available at: https://courier-newsroom.com/2020/04/23/10000-deaths-nursing-homes-more-testing. [Last accessed at: May 25th, 2020].

Mamatha Munaf[1], Chitra Rajeswari T[2], Rajaram Manju[3], Hemavathi Balachander[2]

[1]Department of Cardiac Anesthesia, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum, Thiruvananthapuram, India
[2]Department of Anaesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
[3]Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

A study on the effect of intraoperative continuous positive airway pressure (CPAP) on the postoperative pulmonary function in overweight patients undergoing lower limb, lower abdominal or vaginal surgeries under spinal anesthesia

Abstract

Introduction: Spinal anaesthesia, supine position and higher BMI are risk factors for pulmonary atelectasis. NIV, PEEP and CPAP are employed in ICU's to treat atelectasis postoperatively. However, we wanted to investigate whether CPAP was protective against atelectasis when used intraoperatively, in high risk patients.

Material and methods: This study was a randomized controlled trial. Overweight patients, who were to undergo surgeries under spinal anesthesia were included in the study. After informed consent, 126 patients underwent preoperative pulmonary function tests (PFT: FEV_1, FVC, PEFR). Following the onset of spinal anaesthesia patients were randomised into group E (n = 63, received CPAP) and control group, group C (n =63, received nil intervention). Postoperative PFT was done at 20 minutes, 1 hour, 2 hours and 3 hours after surgery. Patients were followed up till discharge for pulmonary complications.

Results: We observed significant reduction in pulmonary function (FEV_1, FVC and PEFR) postoperatively compared to baseline. CPAP group had better pulmonary function when compared to control group, the difference being significant 20 minutes after the surgery($p < 0.05$). No postoperative pulmonary complication was reported among the 126 patients studied.

Conclusion: Intraoperative use of CPAP in overweight patients undergoing surgeries under spinal anaesthesia could be beneficial in improving pulmonary function in the immediate post-operative period.

Key words: intraoperative CPAP, spinal anesthesia, overweight, pulmonary function

Adv Respir Med. 2020; 88: 176–183

Introduction

Postoperative pulmonary complication (PPC) is a recognised event. Incidence of postoperative atelectasis is 20–69% and that of postoperative pneumonia is 9 to 40% [1]. The duration of hospital admission, morbidity and mortality increase significantly in patients with respiratory dysfunction. Age ≥ 60 years, body mass index (BMI) ≥ 27, history of cancer, impaired cognitive function in the preoperative setting, upper abdominal, or both upper/lower abdominal incision site and positive smoking history within the past 8 weeks are the identified predictors [2] of development of postoperative pulmonary dysfunction.

Overweight and obese individuals have higher intraabdominal pressure which can lead to basal atelectasis [3, 4]. Increased chest wall stiffness causes higher respiratory elastance in patients with obesity [5]. Atelectasis which worsens during general anaesthesia and do not disappear after surgery is documented in obese patients.

Supine position during surgery causes cephalad movement [6] of the diaphragm and reduction in cross-sectional area of the thorax. Relative pooling of blood in the thorax during

Address for correspondence: Chitra Rajeswari T, Department of Anaesthiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Pudcherry, India; e-mail: dr.chitrarajeswari@gmail.com
DOI: 10.5603/ARM.2020.0105
Received: 29.09.2019

ISSN 2451–4934

supine position reduces the pulmonary volume.

For a wide range of lower limb, abdominal, vaginal and inguinal surgeries, general as well as spinal anaesthesia are equally feasible. Atelectasis during both general and spinal anaesthesia are well documented [7].

The application of positive end-expiratory pressure (PEEP) is effective against atelectasis in general anaesthesia [8]. In spontaneously breathing awake patients, PEEP can be provided using EzPAP® [9, 10]. Overweight patients in supine position under spinal anaesthesia are definitely a high-risk group of development of postoperative atelectasis.

The aim of our study was to assess whether administering EzPAP® intraoperatively to overweight patients improved their pulmonary function postoperatively, compared to controls, after surgeries under spinal anaesthesia.

Materials and methods

This study was an open-label randomised control trial undertaken in the Department of Anaesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) between January 2015 and May 2016. A total of 126 American Society of Anaesthesiology (ASA) Class 1 and 2 patients in the age group of 18 to 60 years with BMI between 25 to 30 undergoing elective lower limb, inguinal or vaginal procedures under spinal anaesthesia were included in the study after approval from the institute ethics committee, Clinical Trial Registry of India (CTRI), registration and written informed consent from participants. Patients who were claustrophobic, pregnant, having cardiorespiratory diseases causing poor effort tolerance were excluded from the study. Inability to comprehend the application of EzPAP® was also an exclusion criterion.

During preoperative assessment, the procedure was explained and the use of a PFT machine was demonstrated to all participants. All the patients received standard premedication as per institute protocol which included famotidine 20 mg and diazepam 5 mg at night followed by 20 mg famotidine, 5 mg diazepam and 10 mg metoclopramide in the morning unless otherwise specified.

In the operation theatre, in supine position, standard ASA monitors were attached. They included ECG, pulse oximetry and Non-Invasive Blood Pressure monitoring. Baseline pulmonary function test (PFT) was done using a handheld spirometer (190513 MIR Spirobank G). A nose clip was used during the spirometry, which was performed by the anaesthesiologist assigned to the case. Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and PEFR were noted down. Each time spirometry was repeated three times in supine position and the best of the three results was taken as per the European Respiratory Society guidelines [11].

Spinal anaesthesia was administered with hyperbaric bupivacaine and block height was documented. After the onset of spinal anaesthesia, the anaesthesia resident assigned to the operating table opened a sealed opaque envelope. The envelope contained a random number which was computer-generated by block randomisation. The block sizes were 4, 6 and 8, and the original generated list contained 130 numbers. The list was created and sealed with the help of an independent anaesthesiologist, unrelated to the study.

PEEP was provided during the study by the anaesthesiologist assigned to the case using a device called EzPAP® (PORTEX® EzPAP® Positive Airway Pressure System, manufactured by Smiths Medical). It is an FDA approved device, for treatment and prevention of atelectasis and mobilisation of endobronchial secretions. The device consists of a mouthpiece, an air inlet, pressure port with a cap, gas inlet port with tubing and a manometer. Once EzPAP® is connected to the oxygen flow meter from the wall port, the patient has to breathe in through the mouth piece. Oxygen flow is then adjusted to generate a PEEP of 10 cm H_2O (9), which is measured by the manometer. Airflow to the convex parts of the PEEP valve causes it to attach and adhere due to coanda effect, generating PEEP. A nose clip is not a part of the device and was not used during the study. EzPAP® was administered throughout the duration of the surgery. Fixed CPAP of 10 cm H_2O was used for better comparability, as per protocol.

Intraoperatively, the group E (n = 63) received EzPAP® and the control group, group C (n = 63) received oxygen by face mask at a flow rate of 6 L/min.

Throughout the surgery, at 5 minutes intervals, noninvasive blood pressure, ECG and SpO_2 were documented.

Postoperatively, PFT was repeated in supine position using the same spirometer, as before, at 20 minutes, 1 hour, 2 hours and 3 hours after the end of surgery. This was done after assessing the visual analogue scale (VAS) score for pain. PFT was measured only when VAS score was less than 2 to remove the confounding effect of pain on PFT. Rescue analgesics (paracetamol and

ketorolac) were used to ensure adequate analgesia whenever VAS score was > 2. Postoperative nausea and vomiting were documented. Patients were followed up clinically till discharge for postoperative pulmonary complications.

Postoperative pulmonary complication was defined as the development of pneumonia any time before discharge. Diagnosis was based on the presence of new onset of cough with expectoration, fever (temperature > 38.3°C), leucocytosis (total leucocyte count > 20,000/μL) or leucopenia (total leucocyte count < 4000/μL) and radiological infiltrates.

Sample size calculation and statistical analysis were done by using SPSS version 13.0 software. Sample size calculation was based on a similar study [7] which documented reduction in FEV_1, FVC and PEFR following spinal anaesthesia. Distribution of data was tested using one-sample Kolmogorov Smirnov test. Categorical data were expressed as frequency and percentages and were compared by using chi-square test or Fischer's exact test. The data on age, anthropometric parameters, level of pain and pulmonary function parameters were expressed as mean with standard deviation or median with range and were compared with the help of independent student t test/Mann-Whitney U test/one-way analysis of variance or Kruskall-Wallis test based on the distribution of data and the number of groups. Spinal block height was expressed as median with interquartile range and analysed using the Mann-Whitney U test. The statistical significance of the longitudinal changes in FEV1, FVC and PEFR in each group was calculated by one-way repeated measures of ANOVA. The longitudinal changes over time between the groups were analysed using two-way repeated measures of ANOVA. Post hoc analysis of ANOVA results was performed using the Tukey Test in SPSS software. Statistical analysis was carried out at 5% level of significance and 80% power, and p value < 0.05 was considered as significant.

Results

A total of 150 patients were assessed for eligibility. 4 individuals did not fit into inclusion criteria, 10 persons opted not to participate in the study and 10 patients had failed spinal anaesthesia. Finally, 126 subjects were included in the study. 63 patients were randomly allotted to the test group and control group. Consort Diagram is represented as Figure 1. Demographic characteristics are represented in Table 1.

The duration of surgery was found to be significantly different (P < 0.01) between the

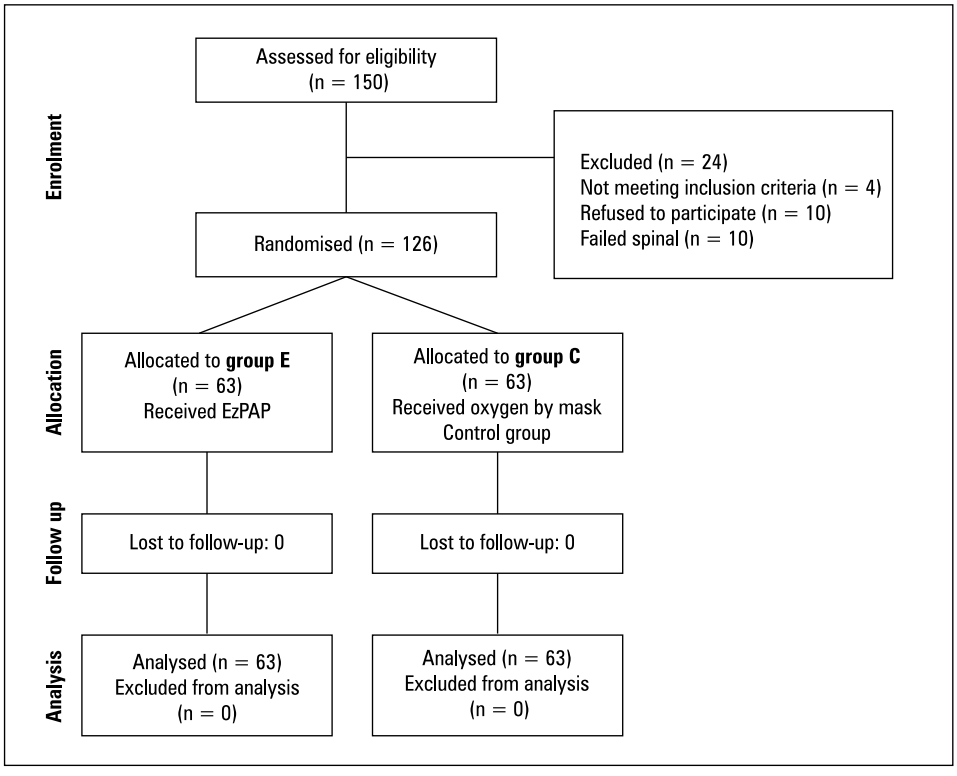


Figure 1. Consort diagram

Table 1. Distribution of age, sex, body mass index (BMI) and duration of surgery between the two groups

Parameter	E group	C group	P value
Age (Years — mean ± SD)	39.7 ± 9.01	38.06 ± 9.1	0.29
Sex (male:female %)	39.7 ± 60.3	42.9 ± 57.1	0.717
Duration of surgery (hours — mean ± SD)	1.81 ± 0.76	1.46 ± 0.69	0.007
BMI (Kg/m^2 — mean ± SD)	26.63 ± 1.11	26.34 ± 1.03	0.124

Table 2. Comparison of FEV_1, FVC, PEFR between the groups at different time points

	FEV_1*			FVC*			PEFR*		
Time point	**Group E**	**Group C**	**P value**	**Group E**	**Group C**	**P value**	**Group E**	**Group C**	**P value**
Baseline	3.3 ± 0.41	3.3 ± 0.4	0.8	3.97 ± 0.48	4.05 ± 0.52	0.39	500 ± 75.9	505 ± 85.1	0.71
20 minutes	3 ± 0.4	2.82 ± 0.4	0.01*	3.68 ± 0.46	3.5 ± 0.51	0.046*	468 ± 70	440 ± 78.2	0.035*
1 hour	3.1 ± 0.38	2.97 ± 0.39	0.18	3.75 ± 0.48	3.67 ± 0.5	0.38	475 ± 71.2	458 ± 77	0.2
2 hours	3.1 ± 0.38	3.11 ± 0.4	0.8	3.82 ± 0.48	3.82 ± 0.5	0.98	485 ± 71.98	476 ± 80.4	0.51
3 hours	3.2 ± 0.38	3.21 ± 0.4	0.98	3.9 ± 0.5	3.9 ± 0.5	0.94	492 ± 72.55	488 ± 82.3	0.76

*All results in mean ± SD (L). FEV_1 — forced expiratory volume in the first second; FVC — forced vital capacity; PEFR — peak expiratory flow rate

two groups with the EzPAP® group (group E) undergoing surgeries for a longer duration. End operative block height among the group E was comparable to the group C (P = 0.633). Mean end operative block height was T8 (T8–T10) in both the groups.

22.2% of patients in each group required analgesia before doing PFT postoperatively. Either paracetamol (19/28–67.85%) or ketorolac (9/28–32.15%) was used as analgesic. None of the patients had postoperative nausea or vomiting.

FEV_1, FVC and PEFR were found to be significantly better among the group E compared to the group C, 20 minutes after surgery ($p < 0.05$). Baseline PFT parameters and those at 1 hour, 2 hours and 3 hours after surgery were comparable between the groups (Table 2, Figures 2–4).

None of the patients in either group had SpO_2 values <95% at any point of time. SpO_2 trend in either group during the first hour of surgery is represented in Figure 5. The distribution of the type of surgery is illustrated in Figure 6.

There is a significant fall in FEV_1, FVC and PEFR after spinal anaesthesia and surgery, measured at the end of 20 minutes, 1 hour, 2 hours and 3 hours postoperatively when compared to baseline in the E group as well as C group (Table 3, 4). None of the patients developed postoperative pulmonary complications till discharge.

Discussion

Overweight patients have higher chances of atelectasis and postoperative complications compared to normal weight patients [12]. Spinal anaesthesia and supine position are also independent risk factors for reduction in pulmonary function. Positive end expiratory pressure improves pulmonary function by lung expansion in patients undergoing surgeries under general anaesthesia. Given the current data by World Health Organization (WHO), nearly 40% of the adult population in the world is overweight. We wanted to address the effects of spinal anaesthesia and potential results of PEEP on the pulmonary function of overweight patients [13] undergoing surgeries.

We recruited 126 overweight patients (BMI 25–30 kg/m^2) who underwent lower limb, vaginal or inguinal surgeries under spinal anaesthesia. Meira *et al.* [14] and Sternberg *et al.* [7] have documented atelectasis in overweight patients undergoing surgeries under spinal anaesthesia. But the application of EzPAP® in overweight patients to prevent atelectasis is not well studied.

Both groups of patients were comparable in terms of distribution of age (group E *vs* group C: 39.7 ± 9.01 years' *vs* 38.06 ± 9.01 years; $p > 0.05$), sex (M:F group E *vs* group C: 39.7 ± 60.3 *vs* 42.9 ±

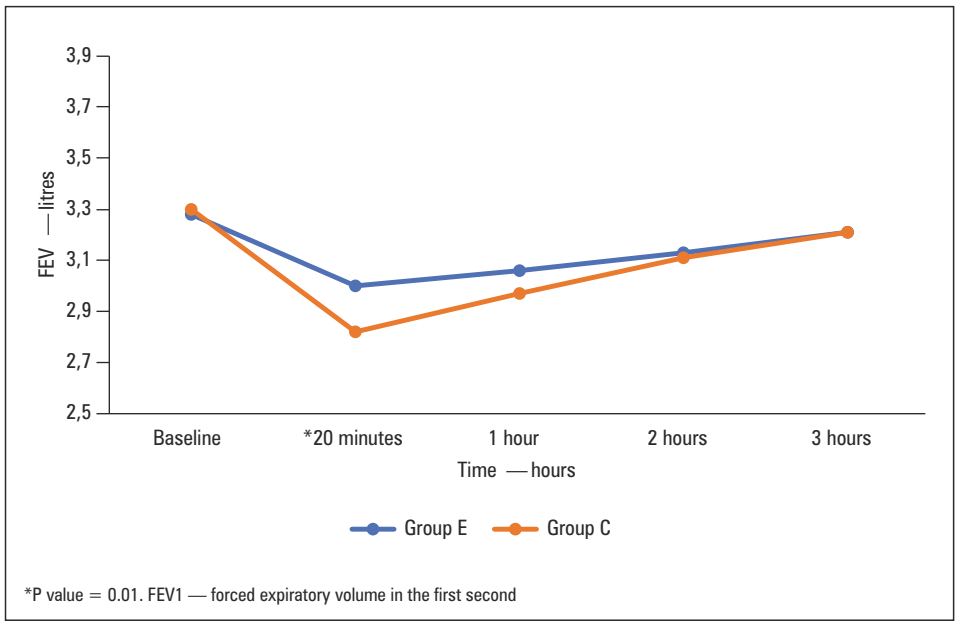


Figure 2. Comparison of FEV_1 (L) between group E and group C at different time points

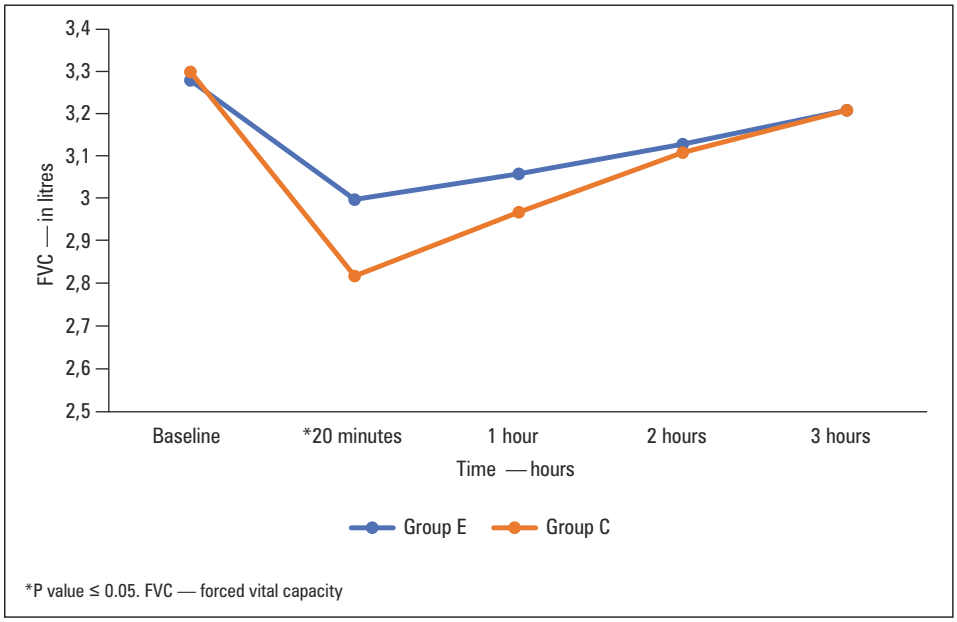


Figure 3. Comparison of FVC between group E and group C at different time points

57.1; $p > 0.05$) and BMI (group E *vs* group C 26.63 ± 1.11 *vs* 26.34 ± 1.03; $p > 0.05$). BMI in both groups were only marginally higher than that of normal as our study focused strictly on overweight patients.

The test group had a significantly longer duration of surgery (1.81 ± 0.76 hours) compared to the control group (1.46 ± 0.69 hours; $p < .05$). A possible explanation is that setting up EzPAP® and ensuring the patient compliance and comfort during the procedure might have caused the delay. However, end operative block height in the test group as well as the control group was T8 (T8–T10) with a p value of 0.63, which indicates that irrespective of the duration of surgery, end operative block heights were comparable.

All patients were pain-free throughout the surgery and did not require intraoperative analgesics. Patients belonging to both groups were haemodynamically stable throughout the surgery.

All PFT measurements including baseline measurement were done in supine position to en-

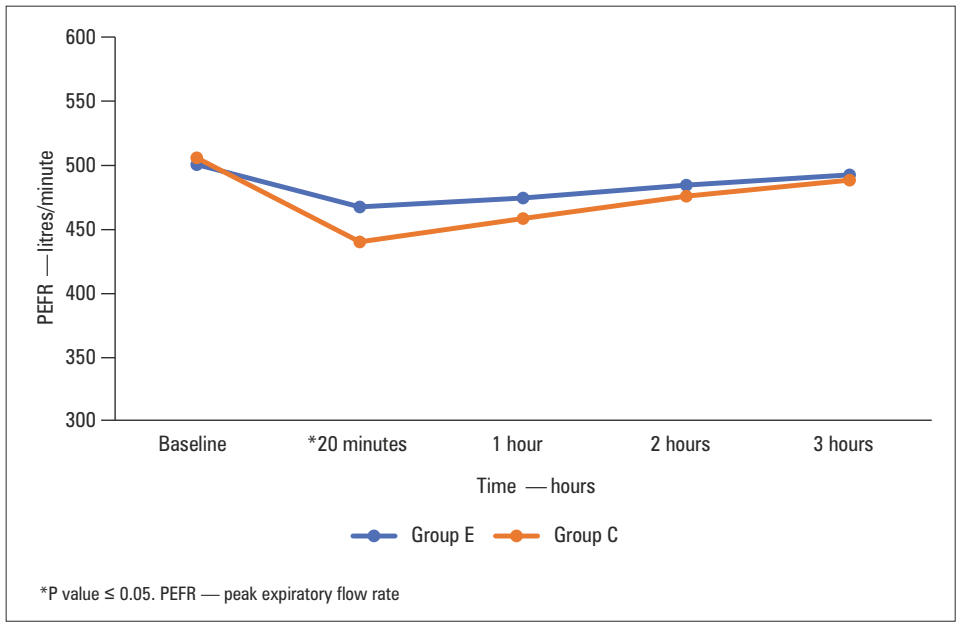


Figure 4. Comparison of PEFR between group E and group C at different time points

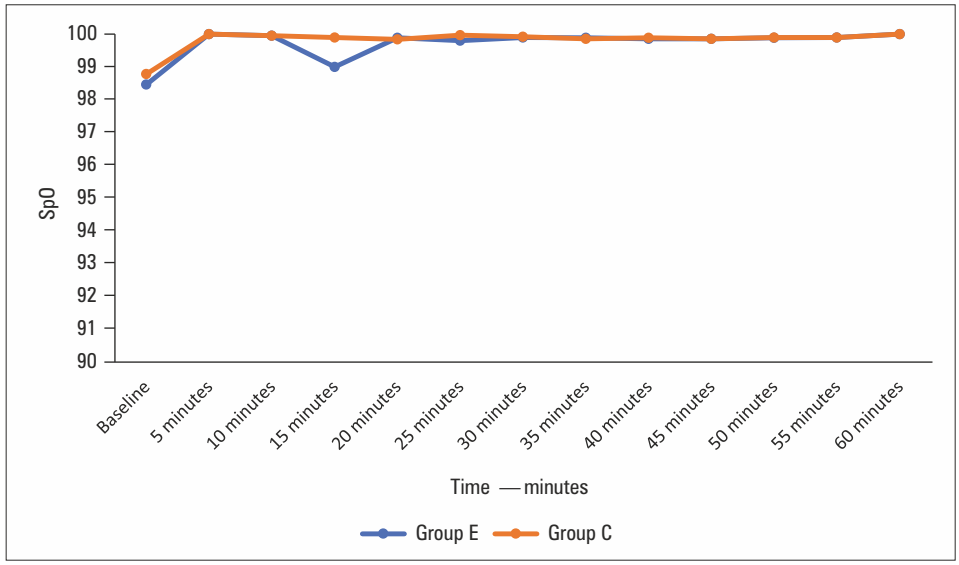


Figure 5. Variation of SpO_2 with time in group E and group C during surgery

sure uniformity. Both groups had significant fall in PFT, i.e. FEV_1, FVC and PEFR when compared to baseline at 20 minutes, 1 hour, 2 hours and 3 hours after the surgery. This is in accordance with previous studies which have documented reduction in pulmonary function after spinal anaesthesia [7, 11, 14].

FEV1 , FVC and PEFR declined in both groups over time, though the difference was significant only at 20 minutes. However, PFT values declined less in the group E, which could be attributed to better lung expansion in in this group. Another study in cardiology ICU setting [15] has demonstrated similar findings in a group of postoperative cardiac surgery patients receiving CPAP, though they were receiving CPAP for a significantly longer duration.

A limitation we felt during the study was the lack of PaO2 measurements for comparison. However, this aspect was considered and decided against during the planning stage as we felt it was unethical to take arterial prick samples from awake ASA1 and 2 patients when it did not directly benefit them in terms of management. Furthermore, FRC couldn't be assessed as it was unsafe to mobilise immediate postoperative patient to PFT lab for getting the FRC done. The patients

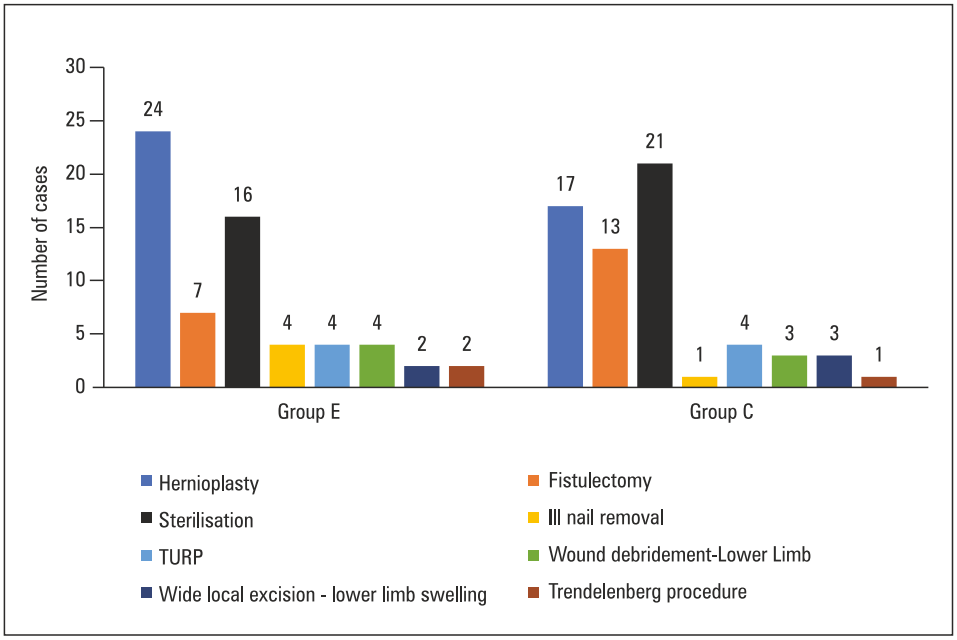


Figure 6. The distribution of the type of surgery

Table 3. Comparison of FEV_1, FVC, PEFR at different time points when compared to baseline in group E

Baseline	Time points	FEV_1 — mean with SD (L)	P value
FEV_1* 3.28 ± 0.412	20 minutes	3 ± 0.4	< 0.001*
	1 hour	3.06 ± 0.38	< 0.001*
	2 hours	3.13 ± 0.38	< 0.001*
	3 hours	3.21 ± 0.38	0.01*
FVC* 3.97 ± 0.48	20 minutes	3.68 ± 0.46	< 0.001*
	1 hour	3.75 ± 0.48	< 0.001*
	2 hours	3.82 ± 0.48	< 0.001*
	3 hours	3.9 ± 0.5	0.021*
PEFR* 500.16 ± 75.85	20 minutes	467.92 ± 70	< 0.001*
	1 hour	474.94 ± 71.2	< 0.001*
	2 hours	484.52 ± 71.98	< 0.001*
	3 hours	492.16 ± 72.55	0.01*

*All results in mean ± SD (L). FEV_1 — forced expiratory volume in the first second; FVC — forced vital capacity; PEFR — peak expiratory flow rate

were not evaluated by lung ultrasound for atelectasis due to lack of availability of a dedicated ultrasound machine for the study. Similarly, they were not assessed for obstructive sleep apnoea by polysomnography due to practical difficulties of high caseload in the sleep lab and unavailability of the same for 126 patients. As we included only overweight patients belonging to ASA 1 and 2 in the study, the results might not be generalisable to morbidly obese or elderly patients with multiple comorbidities. Postoperative pulmonary complications might not have developed in our study population probably because our study was limited to overweight patients without significant comorbidities.

Conclusions

Intraoperative use of EzPAP® in overweight patients undergoing surgeries under spinal anaesthesia may improve pulmonary function in the immediate postoperative period. However, further studies are needed to evaluate the impact it has on arterial PaO2 as well as FRC. Furthermore,

Table 4. Comparison of FEV_1, FVC and PEFR at different time points when compared to baseline in group C

Baseline (L)	Time points	FVC — mean with SD (L)	P value
FEV_1* 3.3 ± 0.44	20 minutes	2.82 ± 0.4	< 0.001*
	1 hour	2.97 ± 0.39	< 0.001*
	2 hours	3.11 ± 0.4	< 0.001*
	3 hours	3.21 ± 0.4	0.01*
FVC* 4.05 ± 0.52	20 minutes	3.5 ± 0.51	< 0.001*
	1 hour	3.67 ± 0.5	< 0.001*
	2 hours	3.82 ± 0.5	< 0.001*
	3 hours	3.9 ± 0.5	< 0.001*
PEFR* 505.4 ± 85.14	20 minutes	439.67 ± 78.17	< 0.001*
	1 hour	457.86 ± 77	< 0.001*
	2 hours	475.48 ± 80.4	< 0.001*
	3 hours	487.97 ± 82.27	< 0.001*

*All results in mean ± SD (L). FEV_1 — forced expiratory volume in the first second; FVC — forced vital capacity; PEFR — peak expiratory flow rate

combined intraoperative and postoperative use of EzPAP® in the same subset of patients might sustain the improvement in lung function and needs to be evaluated.

Author's contribution

HB, CR and MM designed the study. Technical input related to spirometry and PFT was given by MR. MM collected the data, analysed and wrote the paper, which was reviewed by HB.

Conflict of interest

None declared.

References:

1. Hall J, Tarala R, Hall J, et al. A multivariate analysis of the risk of pulmonary complications after laparotomy. Chest. 1991; 99(4): 923–927, doi: 10.1378/chest.99.4.923.
2. Brooks-Brunn J. Predictors of postoperative pulmonary complications following abdominal surgery. Chest. 1997; 111(3): 564–571, doi: 10.1378/chest.111.3.564.
3. Dattani R, Swerner C, Stradling J, et al. Exploratory study into the effect of abdominal mass loading on airways resistance and ventilatory failure. BMJ Open Respiratory Research. 2016; 3(1): e000138, doi: 10.1136/bmjresp-2016-000138.
4. Damia G, Mascheroni D, Croci M, et al. Perioperative changes in functional residual capacity in morbidly obese patients. Br J Anaesth. 1988; 60(5): 574–578, doi: 10.1093/bja/60.5.574.
5. Pelosi P, Croci M, Ravagnan I, et al. The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. Anesth Analg. 1998; 87(3): 654–660, doi: 10.1213/00000539-199809000-00031.
6. Pulletz S, Elke G, Zick G, et al. Effects of restricted thoracic movement on the regional distribution of ventilation. Acta Anaesthesiol Scand. 2010; 54(6): 751–760, doi: 10.1111/j.1399-6576.2010.02233.x.
7. Ungern-Sternberg BSv, Regli A, Reber A, et al. Comparison of perioperative spirometric data following spinal or general anaesthesia in normal-weight and overweight gynaecological patients. Acta Anaesthesiol Scand. 2005; 49(7): 940–948, doi: 10.1111/j.1399-6576.2005.00754.x.
8. Talab H, Zabani I, Abdelrahman H, et al. Intraoperative ventilatory strategies for prevention of pulmonary atelectasis in obese patients undergoing laparoscopic bariatric surgery. Anesth Analg . 2009; 109(5): 1511–1516, doi: 10.1213/ane.0b013e3181ba7945.
9. Rieg AD, Stoppe C, Rossaint R, et al. EzPAP® therapy of postoperative hypoxemia in the recovery room: experiences with the new compact system of end-expiratory positive airway pressure. Anaesthesist. 2012; 61(10): 867–874.
10. Talley H. EZ-PAP in the postoperative period: a pilot study. J Anesth Clin Res . 2012; 03(08), doi: 10.4172/2155-6148.1000236.
11. Levy ML, Quanjer PH, Booker R, et al. General practice airways group. Diagnostic spirometry in primary care: proposed standards for general practice compliant with american thoracic society and european respiratory society recommendations. Primary Care Respiratory Journal. 2009; 18(3): 130–147.
12. Thomas E, Goldman L, Mangione C, et al. Body mass index as a correlate of postoperative complications and resource utilization. Am J Med. 1997; 102(3): 277–283, doi: 10.1016/s0002-9343(96)00451-2.
13. World Health Organization. Obesity and overweight. Available from: www.who.int/mediacentre/factsheets/fs311/en/. [Last accessed at May 25th, 2020].
14. Meira M, Carvalho C, Galizia MS, et al. Atelectasis observed by computerized tomography after Caesarean section. Br J Anaesth. 2010; 104(6): 746–750, doi: 10.1093/bja/aeq090.
15. Regli A, Ungern-Sternberg BS, Reber A, et al. Impact of spinal anaesthesia on peri-operative lung volumes in obese and morbidly obese female patients. Anaesthesia. 2006; 61(3): 215–221, doi: 10.1111/j.1365-2044.2005.04441.x.
16. Borghi-Silva A, Mendes R, Costa F, et al. The influences of positive end expiratory pressure (PEEP) associated with physiotherapy intervention in phase I cardiac rehabilitation. Clinics. 2005; 60(6), doi: 10.1590/s1807-59322005000600007.

Chinnu Sasikumar, Ketaki Utpat, Unnati Desai, Jyotsna Joshi

Department of Pulmonary Medicine, Topiwala National Medical College & BYL Nair Hospital, Mumbai, Maharashtra, India

The role of GeneXpert in the diagnosis of *Mycobacterium tuberculosis*

Abstract

Introduction: GeneXpert (GX) is a novel, integrated, cartridge-based, nucleic acid amplification test with an established role for rapid diagnosis of *Mycobacterium tuberculosis* and detection of rifampicin resistance.

Aim: To evaluate the role of GX in pulmonary and extrapulmonary tuberculosis (TB) cases.

Material and methods: A prospective study was conducted in the pulmonary medicine department of a tertiary care hospital after the Ethics Comittee permission. Data of 257 presumptive TB patients was retrieved for GX, acid fast bacilli smear and culture (AFB smear and culture) and drug susceptibility test (DST). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of GX in diagnosis and determination of rifampicin resistance in pulmonary and extrapulmonary TB cases were calculated and compared with culture and DST results.

Results: Our study included 132 pulmonary and 125 extrapulmonary cases. On the basis of clinicoradiological and microbiological correlation, diagnosis of TB was confirmed in 104 pulmonary and 103 extrapulmonary cases. Out of a total of 104 pulmonary TB cases, 73 were rifampicin-sensitive and 31 were rifampicin-resistant cases. 103 extrapulmonary TB patients included 66 rifampicin-sensitive and 37 rifampicin-resistant cases. The sensitivity, specificity, PPV, NPV of GX in diagnosis and detection of rifampicin resistance in pulmonary TB was 95%, 93%, 98%, 84% and 96%, 100%, 100%, 96%, respectively. The sensitivity, specificity, PPV, NPV of GX in diagnosis and detection of rifampicin resistance in extrapulmonary TB cases was 79%, 86%, 96%, 47% and 97%, 95%, 97%, 95%, respectively.

Conclusions: GX results are superior to smear microscopy and comparable to culture with shorter turnaround time.We recommend using it in routine TB diagnosis as this will expedite the management of patients with presumptive TB.

Key words: GeneXpert, presumptive TB cases, AFB culture

Adv Respir Med. 2020; 88: 184–188

Introduction

Tuberculosis remains a major health problem accounting for millions of new cases and deaths every year worldwide. Therefore, rapid detection of *Mycobacterium tuberculosis* (MTB) and rifampicin resistance in presumptive TB cases is essential for the early diagnosis and treatment, thereby reducing the risk of transmission of the disease, mortality rates and emergence of drug-resistant TB. AFB culture is considered as the gold standard test for final determination of TB but the turnaround time is 2–8 weeks, and it requires trained personnel and expensive lab equipment [1]. Smear microscopy for acid fast bacilli (AFB) is one of the rapid and inexpensive tests available, but it has poor sensitivity and poor predictive value in the diagnosis of both pulmonary and extrapulmonary tuberculosis [2, 3]. Thus, rapid identification, which is essential for early treatment, improves patient outcomes, and more effective public health intervention relies on nucleic acid amplification techniques.

The GeneXpert MTB/RIF (rifampicin) assay is a novel, integrated, cartridge-based, nucleic acid amplification test (CBNAAT) for rapid diagnosis of MTB and quick detection of rifampicin resistance in both pulmonary and extrapulmonary

Address for correspondence: Jyotsna Joshi, Department of Pulmonary Medicine, Topiwala National Medical College & BYL Nair Hospital, Mumbai, Maharashtra, India; e-mail: drjoshijm@gmail.com

DOI: 10.5603/ARM.2020.0102
Received: 18.10.2019

ISSN 2451–4934

samples [4–6]. GeneXpert (GX) test has been developed and launched by a foundation for innovative new diagnostics (FIND) and Cepheid Corporation in 2004. However, the development of the GeneXpert test was completed in 2008. The World Health Organisation (WHO) endorsed the GeneXpert for the use in TB endemic countries in December 2010 declaring it a major milestone for global diagnosis of tuberculosis [7].

The test isolates *Mycobacterium* genome from captured bacteria and amplifies DNA (deoxynucleic acid) using polymerised chain reaction. GeneXpert test identifies relevant 81bp (base pair) fragment of MTB rpoB gene using flourescent probes called molecular beacons. GeneXpert assay detects MTB by polymerise chain reaction (PCR) amplification of rpo gene and determination of rifampicin resistance by subsequent probing of this region for mutations that are associated with rifampicin resistance [8, 9]. Turnaround time of the test is 90 mins. GeneXpert requires approximately 130 bacilli per ml of sputum for positive result, whereas Ultra test needs 16 bacilli per ml of sputum for the test to be positive. It is specific for MTB complex; i.e., it can differentiate MTB from other mycobacteria. For each specimen, the test is carried out in a closed system (cartridge), so there is a reduced risk of cross-contamination and human error.

Several studies have showed successful use of GeneXpert test on pulmonary and extrapulmonary samples with high sensitivity and specificity [10, 11]. However, fewer false positive and false negative results of GeneXpert have also been reported recently, hence we decided to study and analyse its diagnostic accuracy in pulmonary and extrapulmonary TB.

Material and methods

We conducted a prospective study over a period of 2 years (1/9/2015–1/9/2017) in the pulmonary medicine department of a tertiary care hospital after the Ethics Comittee permission. Data of 257 consecutive presumptive TB patients (pulmonary and extrapulmonary) was retrieved for GeneXpert, AFB culture and drug susceptibility test (DST). Demographic data, clinical history, examination findings and radiological tests of these patients were also noted. Extrapulmonary cases included in our study were lymph node TB cases, TB pleural effusion cases, TB spine cases, other bone TB cases and TB meningitis cases. Presumptive TB pleural effusion cases were subjected to closed needle pleural biopsy and pleural biopsy samples were analysed for GeneXpert and AFB smear and culture tests. All cases involved in the study had clinical and radiological signs consistent with TB. Diagnosis of TB was made with the help of clinicoradiological correlation and microbiological tests positivity. Patients having no or incomplete data were excluded from the study. Sensitivity, specificity, negative predictive value and positive predictive value of GeneXpert in diagnosis and determination of rifampicin resistance in pulmonary and extrapulmonary TB cases were calculated by comparing it with culture and DST results. AFB culture method utilised for the study was MGIT liquid culture test, and the DST used was liquid culture DST.

Statistics

The sensitivity, specificity, positive predictive value and negative predictive value of GeneXpert were calculated according to the following formula.

Sensitivity: (true positive / true positive + false negative) × 100 implies the test is positive when actually disease is present. Specificity: (true negative / true negative + false positive) × 100 implies the test is negative when actually disease is absent.

Positive predictive value (PPV): (true positive/ /true positive + false positive) × 100 calculates the probability that disease is present when the test is positive.

Negative predictive value:(true negative/ /true negative + false negative) × 100 calculates the probability that disease is absent when the test is negative.

By applying the above mentioned formulas to the contingency tables, the sensitivity, specificity, PPV and NPV of GeneXpert in the diagnosis and detection of rifampicin resistance in pulmonary and extrapulmonary TB cases were calculated.

Results

Our study enrolled 257 presumptive TB cases which included 132 pulmonary and 125 extrapulmonary presumptive TB cases. On the basis of clinicoradiological and microbiological correlation, diagnosis of TB was confirmed in 104 pulmonary and 103 extrapulmonary cases. Of the 103 extrapulmonary TB cases; 48 were lymph node TB cases, 31 were TB pleural effusion cases, 11 were TB spine cases, 9 were other bone TB cases and 4 were TB meningitis cases. Out of a total of 104 pulmonary TB cases, 73 were rifam-

picin-sensitive and 31 were rifampicin-resistant cases. 103 extrapulmonary TB cases included 66 rifampicin-sensitive and 37 rifampicin-resistant cases.

The sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis of pulmonary TB and detection of rifampicin resistance in pulmonary TB was 95%, 93%, 98%, 84% and 96%, 100%, 100%, 96%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis of extrapulmonary TB and detection of rifampicin resistance in extrapulmonary TB cases was 79%, 86%, 96%, 47% and 97%, 95%, 97%, 95%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis and detection of rifampicin resistance in lymph node TB cases was 77%, 80%, 95%, 42% and 100%, 89%, 94%, 100%, respectively. Sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis and detection of rifampicin resistance in TB pleural effusion cases was 71%, 100%, 100%, 53% and 86%, 100%, 100%, 91%, respectively. Sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis and detection of rifampicin resistance in TB spine cases was 100%, 100%, 100%, 100%, respectively. When compared to previous studies, sensitivity of GeneXpert in pleural effusion cases was higher in our study as pleural biopsy samples obtained through closed needle pleural biopsy were also subjected to analysis. Low sensitivity of GeneXpert in pleural fluid samples could be due to very low numbers of bacilli as in the majority of cases, the accumulation of pleural fluid results from hypersensitivity reaction to tuberculous antigen rather than direct invasion of the organism into the pleura. Sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis and detection of rifampicin resistance in other bone TB cases was 100%, 100%, 90%, 100% and 100%, 100%, 100%, 100%, respectively. Sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis and detection of rifampicin resistance in CNS TB cases was 75%, 100%, 100%, 100% and 100%, 100%, 100%, 100%, respectively.

GeneXpert test was diagnostic in 13 AFB culture-negative extrapulmonary TB cases and 5 culture-negative pulmonary TB cases. However, the test was false negative in 5 pulmonary and 21 extrapulmonary cases. GeneXpert test was false positive in all 5 cases, out of which 2 were pulmonary and 3 were extrapulmonary cases. The sensitivity of AFB smear was lower than GeneXpert sensitivity in both pulmonary and extrapulmonary TB.

The 68 DR TB cases on further DST were diagnosed as 50 (24%) MDR TB, 17 (8%) PreX-DR(FQ), and 1 (0.4%) XDR TB cases. There were 6 lymph node, 8 pulmonary, 2 spine and 1 CNS PRE XDR(FQ) TB cases.

Discussion

TB is a curable disease if detected early and treated effectively, thus it is highly important to have efficient and cost-effective diagnostic tests. Early diagnosis and appropriate treatment of TB can help in improving cure rates, reducing transmission rates, morbidity and mortality. ZN smear microscopy carries high risk of false negative results due to low sensitivity and it doesn't help to discriminate between drug susceptible and drug-resistant strains of MTB [2, 3]. These are owing to poor sample quality coupled with a need for technical expertise. Meanwhile, culture being the gold standard test for detecting MTB, requires several weeks to yield results, and largely depends on well-equipped laboratory facilities and skilled technicians [1]. Nucleic-acid-amplification tests provide more timely and accurate diagnosis of TB, thereby contributing to early initiation of TB treatment. GeneXpert test is an integrated fully automated nucleic-acid-amplification test that detects MTB and rifampicin resistance within 90 mins. GeneXpert is a promising test with high sensitivity, specificity and rapid turnaround time [4–6]. The test is highly efficacious in pulmonary TB cases when compared to extrapulmonary cases. In addition, GeneXpert test is likely to improve the diagnostic accuracy of TB at places where AFB culture or DST facilities are not available.

In our study, the performance of GeneXpert test was analysed with pulmonary and extrapulmonary samples. Overall sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis and detection of rifampicin resistance in pulmonary TB cases was 95%, 93%, 98%, 84% and 96%, 100%, 100%, 96%, respectively. In extrapulmonary TB cases, sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis and detection of rifampicin resistance cases was 79%, 86%, 96%, 47% and 97%, 95%, 97%, 95%, respectively. These results are consistent with Cochrane metaanalaysis. Previous studies

of the GeneXpert test have reported sensitivities of 47 to 90% in smear-negative, culture-positive pulmonary tuberculosis cases and 98 to 100% in cases of smear-positive, culture-positive pulmonary tuberculosis, with the specificity of GeneXpert being 99% to 100% [2, 12].

In the study conducted by Boehme *et al,*. the sensitivity was 99.8% for smear and culture-positive cases and 90.2% for smear-negative, culture-positive cases [13]. The sensitivity and specificity of the GeneXpert test in smear- and culture-positive pulmonary specimens was 98% and 100%, respectively, which was consistent with data of previous studies. For smear-negative pulmonary specimens, the sensitivity of the test was 88%, which is higher than that of Armand *et al*., and specificity was 100% comparable with previous studies [14]. For extrapulmonary smear-positive samples, sensitivity and specificity of GeneXpert was 100%, whereas for extrapulmonary smear-negative samples, sensitivity and specificity was 67% and 100%, respectively. The sensitivity and specificity for detecting rifampicin resistance in pulmonary and extrapulmonary samples was 96% , 100% and 97%, 95%, respectively, with respect to culture as reference standard.

Diagnosing extrapulmonary TB infection is quite challenging when compared to pulmonary TB due to significant low numbers of the organisms that can be recovered in the extrapulmonary samples. In our study, we found that the GeneXpert test was more sensitive in detecting spine and bone TB cases than pleural effusion and lymph node TB cases. The detection rate of MTB among smear-negative non-respiratory specimens by the GeneXpert test varies between studies with sensitivity rate of 20-66%. As per studies by Armand *et al*., Causse *et al*., Tortoli *et al*. and Boehme *et al*., GeneXpert sensitivity in lymph node samples using AFB culture as reference standard, ranged from 50% to 100% [13–16]. Sensitivity and specificity of GeneXpert in lymph node TB cases was 83.1% and 93.6%, respectively, according to Denkinger metaanalysis [17]. Our study results of GeneXpert sensitivity in lymph node TB cases were 77%, which was comparable with previous studies.

Metaanalysis findings of Denkinger *et al*. revealed sensitivity and specificity of this test among pleural fluid to be 46% and 99%, respectively [17]. Another metaanalysis findings of E. Penz *et al*. suggested sensitivity amongst pleural fluid was 37% and specificity of 98% [18]. However, in our study, sensitivity and specificity of GeneXpert in pleural effusion cases were 71% and 100%, respectively. According to Denkinger meta-analysis, sensitivity and specificity of GeneXpert in CNS TB was 81% and 98%, respectively [17]. As per study done by Penz *et al*., sensitivity and specificity of GeneXpert in CNS TB was 69% and 97%, respectively [18]. In our study, sensitivity and specificity of GeneXpert in CNS TB was 75% and 100 %, respectively, and was consistent with previous studies.

Sensitivity and specificity of GeneXpert in bone TB as per study conducted by Held M. was 95% and 96%, respectively [19]. Our results in bone TB were consistent with previously reported data.

In routine practice, the GeneXpert test is faster when compared to culture [4-6]. The GeneXpert test was positive for 163 of 194 culture-positive and 19 of 64 culture-negative samples from tuberculosis cases. In our study, the sensitivity of the GeneXpert test was found to be higher as that of culture in pulmonary cases, whereas lower than AFB culture in extrapulmonary samples. There were 5 and 21 false negative cases of GeneXpert for pulmonary and extrapulmonary cases, respectively. For AFB culture test, there were 5 and 13 false negative results in pulmonary and extrapulmonary samples, respectively. GeneXpert test was positive for all except for one smear-positive specimen, but the smear was positive only for 88 of 181 the GeneXpert test M.TB detected specimens. The sensitivity of microscopy was 58% (62/101) for culture-positive pulmonary specimens and 24% (26/93) for culture-positive extrapulmonary specimens. Therefore, the sensitivity of the GeneXpert test which was as rapid as smear was much higher than that of smear.

Smear-negative TB cases pose a challenge for the TB control programmes as they are associated with delayed or failure of diagnosis, unnecessary initiation of empirical tuberculous therapy and high risk of transmission. Therefore, the use of GeneXpert test, especially in countries with high TB prevalance like India, will help in rapid diagnosis and better treatment outcomes of smear-negative TB cases.

In our study, GeneXpert test was false positive in two pulmonary cases and 3 extrapulmonary cases. False positivity of GeneXpert test results has been reported previously and occurs because of the presence of dead MTB in the test samples, particularly among previously treated patients. There are highly likely chances for such patients to receive avoidable anti-TB therapy. Hence, careful history taking with emphasis on previous treatment with anti-TB drugs is essential

to prevent unnecessary treatment of such false positive cases.

Our study included 31 pulmonary and 37 extrapulmonary DR TB cases. The percentage of DR-TB (24%) cases in our study was higher when compared to the results of previous researches [20-22] due to referral bias, and it does not indicate true prevalence of DRTB in the population.

GeneXpert is useful for rapid detection of TB and identification of rifampicin resistance, especially in a high prevelance country like India. The results are superior to smear microscopy and comparable to culture with shorter turnaround time. We recommend using it in routine TB diagnosis as this will help in early diagnosis and the management of patients with presumptive TB. The test results must always be confirmed by culture and further DST in clinically discordant and DRTB cases.

Conflict of interest

None declared.

References:

1. Luetkemeyer A, Firnhaber C, Kendall M, et al. Evaluation of xpert MTB/RIF versus AFB smear and culture to identify pulmonary tuberculosis in patients with suspected tuberculosis from low and higher prevalence settings. Clinical Infectious Diseases. 2016; 62(9): 1081–1088, doi: 10.1093/cid/ciw035.
2. Walusimbi S, Bwanga F, Costa ADe, et al. Meta-analysis to compare the accuracy of GeneXpert, MODS and the WHO 2007 algorithm for diagnosis of smear-negative pulmonary tuberculosis. BMC Infectious Diseases. 2013; 13(1), doi: 10.1186/1471-2334-13-507.
3. Opota O, Senn L, Prod'hom G, et al. Added value of molecular assay Xpert MTB/RIF compared to sputum smear microscopy to assess the risk of tuberculosis transmission in a low-prevalence country. Clinical Microbiology and Infection. 2016; 22(7): 613–619, doi: 10.1016/j.cmi.2016.04.010.
4. Lawn S, Nicol M. Xpert®MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiology. 2011; 6(9): 1067–1082, doi: 10.2217/fmb.11.84.
5. Chang K, Lu W, Wang J, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: A meta-analysis. Journal of Infection. 2012; 64(6): 580–588, doi: 10.1016/j.jinf.2012.02.012.
6. Marlowe EM, Novak-Weekley SM, Cumpio J, et al. Evaluation of the cepheid xpert MTB/RIF assay for direct detection of mycobacterium tuberculosis complex in respiratory specimens. Journal of Clinical Microbiology. 2011; 49(4): 1621–1623, doi: 10.1128/jcm.02214-10.
7. WHO, Rapid implementation of Xpert MTB/RIF Diagnostic test, WHO, 2011. Available at http://Whqubdoc.who.int?Publication/2011/9789241501569. [Last accessed on Nov 15th, 2017].
8. Hillemann D, Rusch-Gerdes S, Boehme C, et al. Rapid molecular detection of extrapulmonary tuberculosis by the automated genexpert MTB/RIF system. Journal of Clinical Microbiology. 2011; 49(4): 1202–1205, doi: 10.1128/jcm.02268-10.
9. Blakemore R, Story E, Helb D, et al. Evaluation of the analytical performance of the xpert MTB/RIF assay. Journal of Clinical Microbiology. 2010; 48(7): 2495–2501, doi: 10.1128/jcm.00128-10.
10. Maynard-Smith L, Larke N, Peters J, et al. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. BMC Infectious Diseases. 2014; 14(1), doi: 10.1186/s12879-014-0709-7.
11. Sharma S, Kohli M, Yadav R, et al. Evaluating the diagnostic accuracy of Xpert MTB/RIF assay in pulmonary tuberculosis. PLOS ONE. 2015; 10(10): e0141011, doi: 10.1371/journal.pone.0141011.
12. Ramirez HLB, García-Clemente MM, Álvarez-Álvarez C, et al. Impact of the Xpert® MTB/RIF molecular test on the late diagnosis of pulmonary tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2014; 18(4): 435–437, doi: 10.5588/ijtld.13.0747.
13. Boehme C, Nicol M, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. The Lancet. 2011; 377(9776): 1495–1505, doi: 10.1016/s0140-6736(11)60438-8.
14. Armand S, Vanhuls P, Delcroix G, et al. Comparison of the Xpert MTB/RIF Test with an IS6110-TaqMan Real-Time PCR Assay for Direct Detection of Mycobacterium tuberculosis in Respiratory and Nonrespiratory Specimens. Journal of Clinical Microbiology. 2011; 49(5): 1772–1776, doi: 10.1128/jcm.02157-10.
15. Causse M, Ruiz P, Gutierrez-Aroca JB, et al. Comparison of two molecular methods for rapid diagnosis of extrapulmonary tuberculosis. Journal of Clinical Microbiology. 2011; 49(8): 3065–3067, doi: 10.1128/jcm.00491-11.
16. Tortoli E, Russo C, Piersimoni C, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. European Respiratory Journal. 2012; 40(2): 442–447, doi: 10.1183/09031936.00176311.
17. Denkinger CM, Schumacher SG, Boehme CC, et al. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. European Respiratory Journal. 2014; 44(2): 435–446, doi: 10.1183/09031936.00007814.
18. Penz E, Boffa J, Roberts DJ, et al. Diagnostic accuracy of the Xpert® MTB/RIF assay for extra-pulmonary tuberculosis: a meta-analysis. The International Journal of Tuberculosis and Lung Disease. 2015; 19(3): 278–284, doi: 10.5588/ijtld.14.0262.
19. Held M, Laubscher M, Zar HJ, et al. GeneXpert polymerase chain reaction for spinal tuberculosis. The Bone & Joint Journal. 2014; 96-B(10): 1366–1369, doi: 10.1302/0301-620x.96b10.34048.
20. Jain A, Dixit P, Prasad R. Pre-XDR & XDR in MDR and ofloxacin and kanamycin resistance in non-MDR mycobacterium tuberculosis isolates. Tuberculosis. 2012; 92(5): 404–406, doi: 10.1016/j.tube.2012.05.010.
21. Kozińska M, Brzostek A, Krawiecka D, et al. MDR, pre-XDR and XDR drug-resistant tuberculosis in Poland in 2000–2009. Pneumonol Alergol Pol. 2011; 79: 278–87.
22. Jain A, Mondal R, Prasad R, et al. Prevalence of multidrug resistant Mycobacterium tuberculosis in Lucknow, Uttar Pradesh. Indian J Med Res. 2008; 128: 300–306.

Magdalena Knetki-Wróblewska[1], Dariusz M. Kowalski[1], Grzegorz Czyżewicz[2], Maciej Bryl[3], Anna Wrona[4], Rafał Dziadziuszko[4], Robert Kieszko[5], Janusz Milanowski[5], Daria Świniuch[6], Rodryg Ramlau[6], Ewa Chmielowska[7, 8], Maciej Krzakowski[1]

[1]Department of Lung Cancer and Chest Tumors, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Department of Oncology, The John Paul II Specialist Hospital, Kraków, Poland
[3]Oncology Department, E.J. Zeyland Wielkopolska Center of Pulmonology and Thoracic Surgery, Poznan, Poland
[4]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland
[5]Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Lublin, Poland
[6]Department of Oncology, Poznan University of Medical Scienses, Poznan, Poland
[7]Department of Oncology, Oncology Centre, Bydgoszcz, Poland
[8]Clinical Oncology Department, Oncology Hospital Tomaszow Mazowiecki, Poland

Effectiveness of osimertinib in patients with lung adenocarcinoma in clinical practice — the Expanded Drug Access Program in Poland

Abstract

Introduction: Osimertinib is a third-generation, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that has demonstrated efficacy in the treatment of *EGFR*-mutant non-small-cell lung cancer (NSCLC) in prospective clinical trials.
Material and methods: This retrospective analysis evaluated the outcomes of 32 pretreated patients with *EGFR* T790M mutation who received osimertinib in clinical practice at seven centers in Poland within the Expanded Drug Access Program. Osimertinib was used in the second line in 59% of patients and in later lines in 41%.
Results: Objective response was attained in 16 patients (50%), and 12 subjects (38%) had stable disease. Median progression -free survival was 11.3 months in the overall population, 12.6 months in patients with *EGFR* exon 19 mutation and 7.5 months in patients with *EGFR* exon 21 mutation ($p = 0.045$). Median overall survival (OS) was 18.3 months. Overall, 58.4% and 45.6% of patients remained in follow-up after 12 and 24 months, respectively. Median OS appeared longer for patients without cerebral metastases than for those with cerebral metastases (27.4 *vs* 9.4 months, respectively; $p = 0.078$), and for patients with the Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1 than those with ECOG PS 2 (27.4 *vs* 11.8 months, respectively; $p = 0.189$), although neither result reached statistical significance. Median OS of patients with partial response, stable disease and progressive disease was 27.4, 12.7 and 4.5 months, respectively ($p < 0.001$). Age, comorbidities, line of treatment with osimertinib, and type of activating *EGFR* mutation did not impact on OS. Adverse events of any grade or grade 3/4 were reported in 38% and 9% of patients, respectively. One person discontinued due to interstitial pneumonia.
Conclusion: These results confirm the value of osimertinib in patients with previously treated *EGFR* T790M-mutant NSCLC. Clinical benefit was evident in patients with cerebral metastases and moderate performance status.

Key words: non-small-cell lung cancer, epidermal growth factor receptor tyrosine kinase inhibitor, T790M mutation, osimertinib, clinical practice

Adv Respir Med. 2020; 88: 189–196

Introduction

Advanced non-small-cell lung cancer (NSCLC) remains a disease of poor prognosis. The effectiveness of chemotherapy is limited: overall response rates (ORRs) do not exceed 25–30%, and median overall survival (OS) is 10–12 months [1]. Patients whose tumors harbor activating mutations in the epidermal growth factor receptor (*EGFR*) gene — most of whom have adenocarcinoma — comprise a clinically important subgroup. The prevalence of *EGFR* mutation varies accor-

Address for correspondence: Magdalena Knetki-Wróblewska, Department of Lung Cancer and Chest Tumors, Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland; e-mail: magdalena.knetki@coi.waw.pl
DOI: 10.5603/ARM.2020.0130
Received: 14.11.2019

ISSN 2451–4934

ding to ethnicity and is estimated at 30–45% in Asian patients and 10–20% in Caucasian patients [1]. The prognosis of this molecularly selected subgroup of patients has significantly improved with the introduction of EGFR tyrosine kinase inhibitor (TKI) drugs. In first-line treatment, erlotinib, gefitinib or afatinib provide an ORR of approximately 60% and a median progression-free survival (PFS) of around 10–12 months [2–4], while dacomitinib and osimertinib yield a median PFS of approximately 18 months [5, 6].

Until recently, the treatment of choice for disease progression during EGFR TKI therapy was chemotherapy with platinum-based drugs. However, identification of the molecular mechanisms responsible for resistance to anti-EGFR treatment has allowed the development of novel drugs targeting resistant tumors. Currently, osimertinib is the only agent approved for use in this setting.

Osimertinib is a third-generation, irreversible EGFR TKI. It has demonstrated significant benefit vs platinum-based chemotherapy after failure of first- or second-generation EGFR TKIs in patients whose tumors harbor the T790M resistance mutation, of whom 60% showed primary TKI sensitivity [7, 8]. Furthermore, osimertinib is also characterized by high activity in the first-line treatment of subjects with activating *EGFR* mutation-positive tumors [6].

This paper reports the outcomes of osimertinib treatment in patients with advanced NSCLC with confirmed *EGFR* T790M mutation after disease progression during EGFR TKI therapy. Treatment was carried out as a part of the Expanded Drug Access Program prior to reimbursement of the osimertinib in Poland.

Material and methods

Eligibility criteria

The study included 32 patients who qualified for treatment with osimertinib as a part of the Expanded Drug Access Program at seven cancer centers in Poland between July 2016 and March 2018. Eligible patients had a diagnosis of advanced NSCLC at stage IV or stage IIIB (with no radical treatment options), confirmed *EGFR* T790M mutation, measurable lesions, age > 18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2, normal laboratory indicators of renal, hepatic and hematopoietic function, and absence of clinically active secondary central nervous system (CNS) lesions. Patients with a history of interstitial lung disease, radiation pneumonitis requiring glucocorticosteroid use, electrocardiogram abnormalities or risk factors for QT prolongation were not eligible for treatment.

Osimertinib was administered at a daily dose of 80 mg until progressive disease (PD) was confirmed, unacceptable toxicity occurred, or a patient's consent was withdrawn. Response assessment was based on computed tomography (CT) performed approximately every 8 weeks.

Before starting the treatment, patients signed an informed consent form for osimertinib therapy.

Study objectives and outcomes

The aim of the study was to assess the efficacy and safety of osimertinib in patients diagnosed with advanced NSCLC and T790M mutation after failure of previous systemic treatment. Treatment outcomes were retrospectively evaluated using available medical documentation. Radiological images were not reassessed for the purposes of this study.

Response was assessed according to Response Evaluation Criteria in Solid Tumors v. 1.1. In addition, PFS was evaluated as the duration from osimertinib initiation until documented radiological/clinical disease progression or death. OS was defined as the duration from the initiation of osimertinib until death. The study also assessed the prognostic value of selected clinical and molecular factors: age; gender; ECOG PS; smoking status; previous cancer treatment; presence of cerebral metastases; type of *EGFR* activating mutation; and response to previous treatment. The safety of the drug was analyzed by evaluation of adverse reactions, which were classified according to the Common Terminology Criteria for Adverse Events v. 4.0.

Statistical methods

PFS and OS were analyzed using Kaplan-Meier estimators. Results are presented as median survival and 12- and 24-month survival rates. The log-rank test was used to compare PFS and OS between subgroups defined basing on the analyzed clinical and molecular variables. A significance level (*alpha*) of 0.05 was applied in all calculations. Analyses were conducted using the R statistical program v. 3.5.1 (2018; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient population

A total of 32 patients were included in the study. At the time of the analysis, 15 subjects

remained in follow-up, of whom 7 persons continued to receive osimertinib. The median duration of follow-up since the initiation of the treatment was 40.9 months.

Table 1 summarizes key patient characteristics at the start of osimertinib therapy. Overall, 15 patients (47%) had never smoked, while 12 subjects (38%) were past smokers and 2 individuals (6%) were current smokers. A total of 17 patients (53%) had documented comorbidities, the most common of which was hypertension (11 patients; 34%). All patients subjects had a diagnosis of lung adenocarcinoma. Twenty patients (63%) had stage IV disease at diagnosis, while the remaining patients (n = 12; 38%) were diagnosed at stages I–IIIB and had previously received treatment with radical intent prior to diagnosis of advanced disease. Between initial diagnosis and eligibility for the osimertinib treatment, 8 patients (25%) had secondary changes within the CNS for which they had received palliative brain irradiation.

Table 1. Patient characteristics at the initiation of osimertinib

	Patients (n = 32)
Median age (range), years	64 (37–82)
Gender, n (%)	
Male	13 (41)
Female	19 (59)
ECOG PS, n (%)	
0	3 (9)
1	19 (59)
2	10 (31)
Type of *EGFR* activating mutation, n (%)	
Del 19	22 (69)
L858R	8 (25)
Other	1 (3)
Smoking history, n (%)	
Never	15 (47)
Past smoker	12 (38)
Current smoker	2 (6)
Missing	3 (9)
Location of metastatic lesions, n (%)	
Lungs	17 (53)
CNS	8 (25)
Liver	6 (19)
Bone	8 (25)
Adrenal glands	2 (6)
Number of prior treatment lines, n (%)	
1	19 (59)
2	5 (16)
3	5 (16)
4	2 (6)

CNS — central nervous system; Del 19 — exon 19 deletion; ECOG PS — Eastern Cooperative Oncology Group performance status; EGFR — epidermal growth factor receptor

Previous treatment

All study subjects had received systemic treatment prior to the initiation of osimertinib. Most patients (59%) had received one line of prior systemic treatment with a first- or second-generation EGFR TKI (erlotinib, 53%; afatinib, 33%; gefitinib, 10%; dacomitinib, 3%). The most common types of activating mutation in the *EGFR* gene were exon 19 deletions (71%). Among 30 patients with documented response assessments during prior EGFR TKI therapy, 25 individuals (83%) had achieved response to treatment. After EGFR TKI treatment, 13 patients (40%) received chemotherapy, which mostly consisted of platinum-containing regimens. Liquid biopsy was used to confirm the presence of the T790M mutation in most cases (27 patients; 84%).

Effectiveness

Response. Response to the treatment was evaluated in all 32 study subjects (Table 2). Objective response was documented in 16 patients (50%), while 12 patients (38%) attained stable disease (SD). A total of 28 patients (88%) therefore obtained clinical benefit. In 4 patients (13%), progressive disease (PD) was reported as the best response to treatment. Among the 8 patients with CNS lesions, 1 individual (13%) achieved complete regression of lesions, 4 patients had partial response (PR; 50%) and 3 patients had SD (38%) within the CNS.

There was no effect of selected clinical/molecular factors (age, smoking status, ECOG PS, and type of activating *EGFR* mutation) on the ORR to osimertinib treatment.

Of the 25 patients who discontinued osimertinib, PD data were available in 23 cases. The most frequent sites of PD were the lungs (50%)

Table 2. Response to treatment with osimertinib

	Patients, n (%)
Overall response (n = 32)	
PR	16 (50)
SD	12 (38)
PD	4 (13)
Response of CNS lesions (n = 8)	
CR	1 (13)
PR	4 (50)
SD	3 (38)

CR — complete response; PD — progressive disease; PR — partial response; SD — stable disease

and liver (15%). Progression within the CNS was observed in 2 patients (including 1 individual with symptomatic brain metastases who had previously received radiotherapy to the brain). After PD, 6 patients (24%) received another line of systemic treatment, while 13 subjects (44%) received only best supportive care or palliative irradiation. Data on post-progression therapy were unavailable for the remaining 6 patients.

Progression-free survival. At the time of the analysis, 15 patients (47%) were still alive and 7 patients (22%) were still receiving osimertinib. Median PFS was 11.3 months. The proportions of patients who remained alive and without signs of PD were 49.2% at 12 months and 17.0% at 24 months.

Age, comorbidities, osimertinib treatment line, and type of prior EGFR TKI therapy had no impact on PFS. However, a correlation between PFS and the type of activating *EGFR* mutation was shown: median PFS was 12.6 months in patients with exon 19 deletions, compared with 7.5 months in those with exon 21 point mutations ($p = 0.045$; Figure 1). The prognostic value of the type of activating mutation was also shown in terms of PFS rates at 12 months (exon 19 deletions, 54%; exon 21 point mutations, 17%) and 24 months (exon 19 deletions, 14%; exon 21 point mutations, 0%).

In addition, response to prior first- and second-generation EGFR TKI treatment also demonstrated prognostic value (Figure 2). In patients with objective response to prior treatment, median PFS during osimertinib treatment was 12.6 months. Two patients with PD as the best response to previous EGFR TKI therapy did not benefit from osimertinib: PD was documented in the first CT examination performed 2 months after the start of therapy ($p < 0.001$).

Overall survival. Median OS was 18.3 months. The percentage of patients who remained in follow-up after 12 and 24 months of therapy was 58.4% and 45.6%, respectively. Age, comorbidities, osimertinib treatment line, and type of activating *EGFR* mutation had no effect on OS. However, response to osimertinib demonstrated prognostic value: median OS was 27.4 months in the subjects with PR, 12.7 months in patients with SD, and 4.5 months in patients with PD as the best response to treatment ($p < 0.001$; Figure 3).

Response to the prior first- and second-generation EGFR TKI treatment also had a significant prognostic impact on OS following the osimertinib treatment. Median OS was 18.3 months in patients with objective response to prior treatment ($n = 25$), whereas the 2 individuals with PD during previous anti-EGFR treatment had OS times of 2.5 and 4.0 months ($p < 0.001$; Figure 4).

The impact of ECOG PS at the time of qualification for osimertinib on survival rates was also analyzed. Patients with very good and good performance score (ECOG PS 0–1) had longer median OS (27.4 months) than those with moderate performance score (ECOG PS 2; 11.8 months). However, the observed difference was not stati-

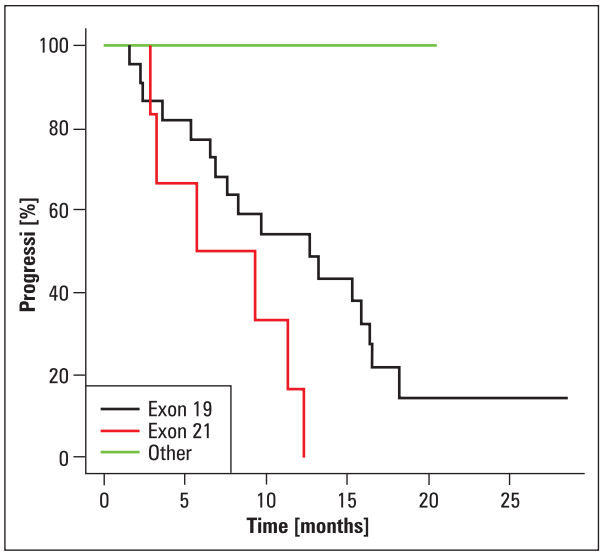


Figure 1. PFS curves according to type of activating *EGFR* mutation. Del 19 — exon 19 deletion; EGFR — epidermal growth factor receptor; Point 21 — exon 21 point mutation; PFS — progression-free survival

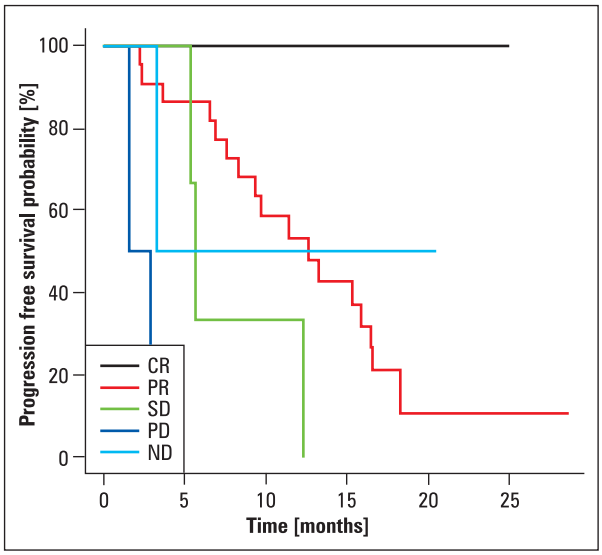


Figure 2. PFS curves according to response to prior TKI therapy. CR — complete response; PD — progressive disease; PFS — progression-free survival; PR — partial response; SD — stable disease; ND — no data

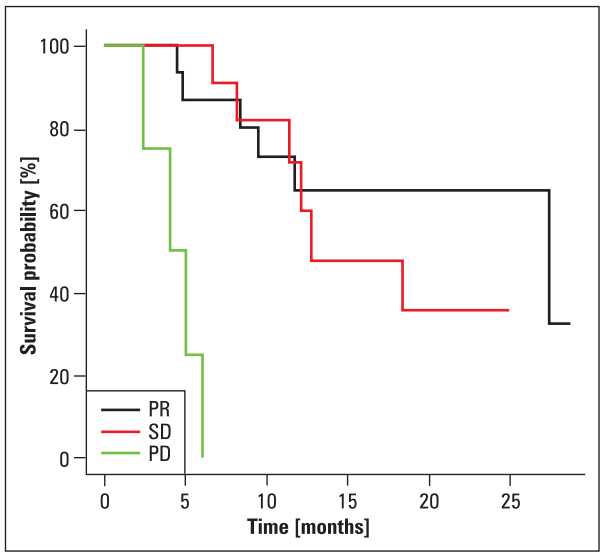


Figure 3. OS curves according to response to osimertinib. OS — overall survival; PD — progressive disease; PR — partial response; SD — stable disease

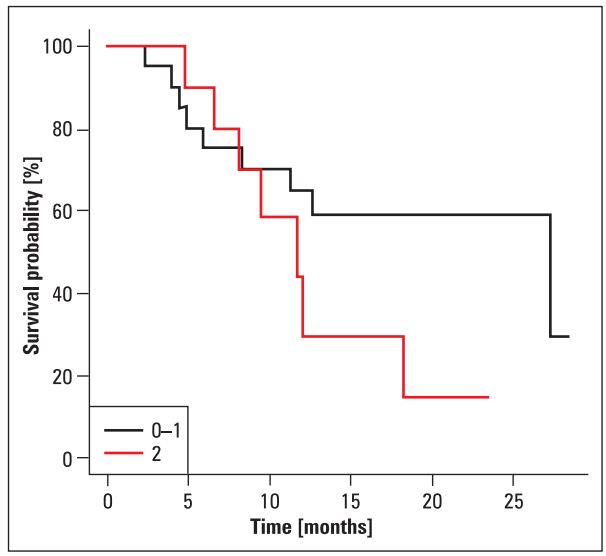


Figure 5. OS curves according to ECOG PS. ECOG PS — Eastern Cooperative Oncology Group performance status; OS — overall survival

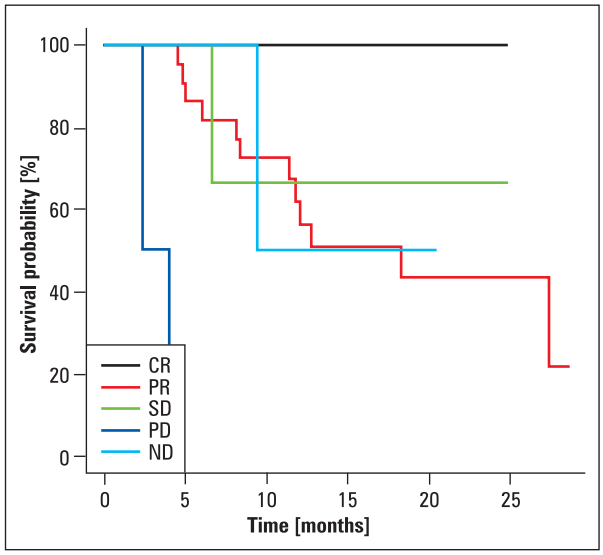


Figure 4. OS curves according to response to previous first- or second-generation EGFR TKIs. CR — complete response; EGFR — epidermal growth factor receptor; OS — overall survival; PD — progressive disease; PR — partial response; SD — stable disease; TKI — tyrosine kinase inhibitor

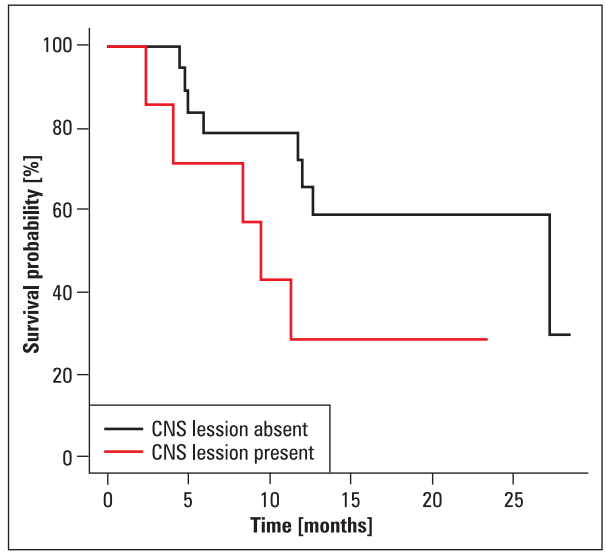


Figure 6. Overall survival (OS) curves according to the presence of secondary lesions in the CNS

stically significant (p = 0.159; Figure 5).

The presence of cerebral metastases also impacted on the course of the disease. Patients without secondary brain lesions lived longer than those with documented brain lesions, with median OS of 27.4 and 9.4 months, respectively (p = 0.078; Figure 6).

Due to the small size of the patient population, no multifactorial analysis was performed. Univariate analyses assessing the prognostic value of selected clinical and molecular factors in terms of OS are summarized in Table 3. Survival parameters for the overall group are presented in Table 4.

Safety

Adverse events were reported at any grade for 12 patients (38%) and at grade 3/4 for 3 patients (9%; Table 5). In total, 6 study subjects (18%) had skin lesions and 3 patients (9%) had diarrhea. Other adverse events each occurred in

Table 3. The prognostic value of selected parameters in terms of OS

	Median OS, months	P-value
ECOG PS: 0–1 *vs* 2	27.4 *vs* 11.8	0.189
Age: < 60 years *vs* ≥ 60 years	27.4 *vs* 12.7	0.686
CNS metastases: present *vs* absent	27.4 *vs* 9.4	0.078
Bone metastases: present *vs* absent	27.4 *vs* 11.9	0.089
Liver metastases: present *vs* absent	12.1 *vs* 9.4	0.160
Response to osimertinib: CR/PR *vs* PD	27.4 *vs* 4.5	< 0.001
Response to prior first- or second-generation EGFR TKIs: CR/PR *vs* PD	18.3 *vs* 3.2	< 0.001
Type of *EGFR* mutation: Del 19 *vs* L858R	18.3 *vs* 12.1	0.379
Line of osimertinib treatment: second *vs* third or later	27.4 *vs* 9.9	0.088

CR — complete response; ECOG PS — Eastern Cooperative Oncology Group performance status; EGFR — epidermal growth factor receptor; OS — overall survival; PD — progressive disease; PR — partial response; TKI — tyrosine kinase inhibitor

Table 4. PFS and OS in the analyzed group of patients

	Median, months	12-month rate, %	24-month rate, %
PFS	11.3	49.2	17.0
OS	18.3	58.4	45.6

OS — overall survival; PFS — progression-free survival

Table 5. Adverse reactions to osimertinib (n = 32)

	Patients, n (%)	
	Any grade	Grade 3/4
All adverse events	12 (38)	3 (9)
Skin lesions	6 (19)	–
Diarrhea	3 (9)	2 (6)
Interstitial pneumonia	1(3)	1 (3)
Elevated activity of liver enzymes	1 (3)	–

1 individual [interstitial pneumonia, elevated activity of liver enzymes, and "other" (no further data available)]. Clinically significant side effects included interstitial pneumonia (1 patient) and diarrhea (2 patients). In 4 subjects (13%), adverse events led to treatment interruption. The patient with interstitial pneumonia associated with osimertinib permanently discontinued treatment. There were no treatment-related deaths.

Discussion

This report describes treatment outcomes with osimertinib in 32 patients diagnosed with advanced lung adenocarcinoma and documented activating T790M *EGFR* mutation after failure of first- or second-generation EGFR TKI therapy. Treatment was carried out in routine clinical practice in the general patient population and not as part of a clinical trial. At the time of the analysis, 15 patients (47%) were still alive and 7 patients (22%) were still receiving osimertinib.

Clinical benefit was observed in 88% of the study subjects and PR in 50% of patients. The ORR is slightly lower than in the AURA2 study and other reports [6–8], which could be explained by less precise assessment of CT results in clinical practice compared with clinical trials — ORR was evaluated basing on medical documentation and less strict qualification to EAP comparing to

the clinical trials. The very high proportion of patients with clinical benefit is consistent with other reports and confirms the efficacy of osimertinib in patients with T790M-positive NSCLC. No correlation was found between treatment response and the clinical factors analyzed. In case of the patients with documented PD as the best response to osimertinib, the presence of other concomitant mechanisms of resistance to TKI EGFR treatment, apart from the T790M mutation, should be considered [9].

In the analyzed group, a relationship was demonstrated between the type of activating mutation in the *EGFR* gene found initially and the duration of response to osimertinib. More favorable outcomes were observed in patients with exon 19 deletions than in those with exon 21 point mutations (median PFS, 12.6 *vs* 7.5 months, respectively). Recently published, updated results from patients treated with osimertinib in two phase II studies also showed the type of activating *EGFR* mutation to be a prognostic factor [10]. In that analysis, patients with exon 19 deletions derived a greater benefit than individuals with exon 21 mutation in terms of ORR (70% *vs* 57%), median PFS (11.1 *vs* 9.5 months) and median OS (29.1 *vs* 21.4 months) [10]. The current study also provided some evidence that the type of activating mutation impacted on OS, although the difference was not statistically significant. In another analysis based on a larger group of osimertinib-treated patients in clinical practice, median OS was significantly longer in subjects with exon 19 deletions than in patients with exon 21 mutations (23.1 *vs* 15.3 months; $p = 0.03$) [11].

We observed a relationship between response to osimertinib and OS in the present study. Similar conclusions have been presented from an analysis of 27 patients treated in clinical practice [12]. The median OS of patients who achieved objective response to treatment was 24.2 months *vs* 13.5 months in the group of patients with SD or PD.

In the current study, 10 patients (31%) had ECOG PS 2 at the time of qualification for osimertinib treatment. The collecting of data on the efficacy and safety of the drug in this group of patients is particularly important, because only individuals with ECOG PS 0 or 1 are usually qualified for therapy in the clinical trials. Poor performance status seems to be a negative prognostic factor in patients receiving EGFR TKIs. In our dataset, median OS appeared longer in patients with ECOG PS 0–1 than in those with ECOG PS 2 (27.4 *vs* 11.8 months, respectively), although the difference was not statistically significant. Data from the GIOTAG observational study, which evaluated sequential treatment with afatinib and osimertinib in 204 patients, also indicate that worse performance status is associated with poorer outcomes [13]. Median duration of the sequential treatment strategy was 31.3 months in patients with ECOG 0–1 and 22.2 months in patients with ECOG ≥ 2 ($p < 0.001$) [13]. Recently, results of osimertinib treatment in a group of 30 patients with moderate performance status (ECOG 2–3) have been published, in which 53% of patients attained objective responses to treatment and median PFS was 8.2 months [14]. The majority of the subjects (63%) had an improvement in their general condition and the rates of adverse reactions and treatment-related deaths were in line with expectations based on other reports in the literature. In a separate analysis of the efficacy and safety of osimertinib in a group of 12 patients (out of 51 in total) with a moderate performance status (ECOG 2–3), the prognostic value of patient fitness was not specifically evaluated, but the authors emphasized that almost all subjects with ECOG 2–3 had clinical benefit from treatment [15].

Cerebral metastases are a significant clinical problem in *EGFR* mutation-positive NSCLC that are estimated to affect approximately 20% of patients at diagnosis and almost 60% at some point during the course of their disease [16]. The treatment of choice is whole-brain radiotherapy (WBRT) or, if possible, local treatment using stereotactic radiotherapy or surgery. Due to its high CNS penetration, osimertinib could be a relevant treatment option in this setting [17]. Supporting clinical data are provided by the FLAURA study of first-line osimertinib in a subgroup analysis of patients with CNS lesions at baseline. In that subgroup, osimertinib was associated with an ORR in the CNS of 66% (compared with 43% with gefitinib) [18]. Osimertinib also significantly reduced the risk of progression of CNS lesions (median CNS PFS not reached with osimertinib *vs* 13.8 months with gefitinib; hazard ratio, 0.48). In that study, brain imaging was not mandatory for all patients and was performed only in those with clinical suspicion of secondary CNS lesions. Only 25% of patients with confirmed CNS lesions had previous radiotherapy to the CNS; the remaining subjects were qualified for the osimertinib treatment.

In the Expanded Access Drug Program, patients with CNS lesions are required to receive

local treatment and demonstrate complete control of symptoms to be eligible for osimertinib and other EGFR TKIs. In the current study, CNS were identified at some point after diagnosis in 8 patients, all of whom had prior local treatment (WBRT) and derived clinical benefit from subsequent osimertinib therapy. However, it should be emphasized that CNS imaging was not mandatory and the data presented may not be complete.

Summary

The present study confirms the efficacy and safety of osimertinib in patients with NSCLC after EGFR TKI failure. Clinical benefit was obtained by patients with the T790M mutation in both the second and subsequent lines of treatment, as well as in the subjects with secondary CNS lesions and moderate performance status. The type of activating mutation present at initial diagnosis showed prognostic value for PFS, while response to osimertinib treatment and response to prior TKI therapy both had an effect on OS.

Conflict of interest

MKW: lectures: Astra-Zeneca, Roche, Boehringer-Ingelheim, Pfizer, MSD, BMS.

DMK: advisory board and consultancy: Roche, Boehringer-Ingelheim, AstraZeneca, MSD, BMS, TAKEDA, Pfizer, MERCK.

MB: advisory board and lectures : Roche, Boehringer-Ingelheim, AstraZeneca, MSD, BMS, Pfizer.

AW: travel grants and lectures: BMS, Roche, Pfizer, Takeda.

RD: advisory board and honoraria: AstraZeneca, Roche, Boehringer-Ingelheim, Pfizer, Novartis, MSD, Seattle Genetics, Foundation Medicine.

RR: advisory board: Boehringer-Ingelheim, Roche, Takeda, MSD, Pfizer, Novartis, BMS, Abbvie.

References:

1. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2018; 29: iv192–iv237, doi: 10.1093/annonc/mdy275.
2. Sequist L, Yang JH, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Journal of Clinical Oncology. 2013; 31(27): 3327–3334, doi: 10.1200/jco.2012.44.2806.
3. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012; 13: 239–246.
4. Mok T, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. New England Journal of Medicine. 2009; 361(10): 947–957, doi: 10.1056/nejmoa0810699.
5. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2017; 18(11): 1454–1466, doi: 10.1016/s1470-2045(17)30608-3.
6. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. New England Journal of Medicine. 2018; 378(2): 113–125, doi: 10.1056/nejmoa1713137.
7. Mok T, Wu YL, Ahn MJ, et al. Osimertinib or platinum–pemetrexed in EGFR t790m–positive lung cancer. New England Journal of Medicine. 2017; 376(7): 629–640, doi: 10.1056/nejmoa1612674.
8. Goss G, Tsai CM, Shepherd F, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. The Lancet Oncology. 2016; 17(12): 1643–1652, doi: 10.1016/s1470-2045(16)30508-3.
9. Chen M, Xu Y, Zhao J, et al. Concurrent driver gene mutations as negative predictive factors in epidermal growth factor receptor-positive non-small cell lung cancer. EBioMedicine. 2019; 42: 304–310, doi: 10.1016/j.ebiom.2019.03.023.
10. Ahn M, Tsai C, Shepherd F, et al. Osimertinib in patients with T790M mutation-positive, advanced non–small cell lung cancer: Long-term follow-up from a pooled analysis of 2 phase 2 studies. Cancer. 2018; 125(6): 892–901, doi: 10.1002/cncr.31891.
11. Auliac J, Pérol M, Planchard D, et al. Real-life efficacy of osimertinib in pretreated patients with advanced non-small cell lung cancer harboring EGFR T790M mutation. Lung Cancer. 2019; 127: 96–102, doi: 10.1016/j.lungcan.2018.11.037.
12. Yoshimura A, Yamada T, Okura N, et al. Clinical characteristics of osimertinib responder in non-small cell lung cancer patients with EGFR-T790M mutation. Cancers. 2019; 11(3): 365, doi: 10.3390/cancers11030365.
13. Hochmair M, Morabito A, Hao D, et al. Sequential treatment with afatinib and osimertinib in patients with EGFR mutation -positive non-small-cell lung cancer: an observational study. Future Oncology. 2018; 14(27): 2861–2874, doi: 10.2217/fon-2018-0711.
14. Nakashima K, Kimura M, Akamatsu H, et al. Osimertinib for patients with EGFR T790M mutation-positive non–small-cell lung cancer and a poor performance status. Japanese Journal of Clinical Oncology. 2019; 49(7): 671–675, doi: 10.1093/jjco/hyz041.
15. Stratmann J, Michels S, Hornetz S, et al. Efficacy and safety analysis of the German expanded access program of osimertinib in patients with advanced, T790M-positive non-small cell lung cancer. Journal of Cancer Research and Clinical Oncology. 2018; 144(12): 2457–2463, doi: 10.1007/s00432-018-2754-x.
16. Wrona A, Dziadziuszko R, Jassem J. Management of brain metastases in non-small cell lung cancer in the era of tyrosine kinase inhibitors. Cancer Treatment Reviews. 2018; 71: 59–67, doi: 10.1016/j.ctrv.2018.10.011.
17. Ballard P, Yates J, Yang Z, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clinical Cancer Research. 2016; 22(20): 5130–5140, doi: 10.1158/1078-0432.ccr-16-0399.
18. Reungwetwattana T, Nakagawa K, Cho B, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non–small-cell lung cancer. Journal of Clinical Oncology. 2018; 36(33): 3290–3297, doi: 10.1200/jco.2018.78.3118.
19. Goss G, Tsai CM, Shepherd FA, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. Annals of Oncology. 2018; 29(3): 687–693, doi: 10.1093/annonc/mdx820.

Daniele Lombardo[1], Giovanni Ciampi[1], Lucia Spicuzza[2]

[1]U.O.C. M.C.A.U. Osservazione Breve Intensiva, Blocco Operatorio d'Urgenza, Azienda Garibaldi, Catania, Italy
[2]Dipartimento di Medicina Clinica e Sperimentale, Università di Catania, Italy

Severe and fatal measles-associated pneumonia during an outbreak in Italy: data from the heart of the epidemic

Abstract

Introduction: Measles is a contagious disease that re-emerged among young adults as a consequence of suboptimal vaccination coverage. Since in the pre-vaccination era measles affected mainly children, little is known about measles-associated respiratory complications in adults. The aim of this study was to describe clinical and radiological findings in adults affected by measles who developed respiratory complications during a recent measles outbreak.

Material and methods: In this retrospective chart review-based study we analyzed data from patients admitted for measles from January to June 2018 to a large tertiary care hospital, in one of the main cities in the south of Italy. This city has been the country's heart of the epidemic with a high morbidity and mortality rate.

Results: Among 177 patients (mean age 26 ± 9 years), only 2 were vaccinated. Thirty patients (16.9%) had signs of pneumonia on chest radiography. Computed tomography scan showed the following abnormalities: centrilobular nodules (63%), ground-glass attenuation (63%), air-space consolidation (36%), pleural effusion (16%) and pneumothorax (10%). Five patients developed severe lung injury and hypoxemia requiring admission to Intensive Care Unit. Two young unvaccinated women with no past medical history died from acute respiratory failure. The death was sudden and unpredictable.

Conclusions: Measles-associated pneumonia in unvaccinated young adults can cause severe respiratory impairment and death. Our findings support the need for a mandatory vaccination policy.

Key words: measles, viral pneumonia, acute hypoxemia

Adv Respir Med. 2020; 88: 197–203

Introduction

Measles is a highly contagious systemic disease resulting from infection with measles virus. This virus is a member of the genus *Morbillivirus* (*Paramyxoviridae* family), most often transmitted between humans by respiratory droplets over a short distance [1]. The virus causes a systemic illness beginning with fever, cough, coryza, Koplik's spots and conjunctivitis followed by a typical generalized rash. Complications of measles can affect most organ systems. These include pneumonia, encephalitis, chronic neurological conditions, ear infection with permanent hearing loss and blindness [2]. Since the implementation of vaccination strategies, measles morbidity and mortality have decreased worldwide [3]. In 2010, the World Health Assembly declared that measles can and should be eradicated, mainly through vaccination strategies [4]. Subsequently, the vaccination coverage increased, however, in 2015, the global coverage with the first dose of vaccine reached a plateau at 85%, remaining below the target fixed for eradication (90–95%). Since 2016 measles outbreaks have been reported in the European area with a consequent re-emerging of life-threatening complications [5, 6]. In 2017, Italy has been included in the list of European countries with ongoing endemic transmission [7]. Studies have shown that the resurgence of measles in Western countries is due to a suboptimal vaccine coverage

Address for correspondence: Lucia Spicuzza, Dipartimento di Medicina Clinica e Sperimentale, Università di Catania, Italy;
e-mail: luciaspicuzza@tiscali.it
DOI: 10.5603/ARM.2020.0118
Received: 20.12.2020

ISSN 2451–4934

[8, 9]. This is true particularly in Italy, where the goal of vaccine coverage for measles eradication fixed by the World Health Organization (WHO) in 2010 and 2015 has not been met [7, 10]. In addition, the emergence of anti-vaccination movements, particularly active in this country, has further decreased the coverage [5, 7]. As measles vaccine uptake has been low, particularly in those born in the 1990s and 2000s, this has led to large vaccination gaps among young adults, who have become more vulnerable to the infection [11, 12]. From January to November 2018, 2,427 cases of measles and 8 deaths have been reported in Italy [13]. The highest incidence (50% of all reported cases) was recorded in Sicily, an island of five million inhabitants in the southern part of the country [13]. It is well acquired that pneumonia accounts for most measles-associated morbidity and mortality [2]. However, as in the pre-vaccination era, measles was more common among school-aged children, there are few data on measles-associated respiratory complications in adults. The recent measles outbreak among young adults has provided a unique opportunity to examine the presentation of measles and its respiratory complications in the adult population. The aim of this study was therefore to describe the clinical presentation, the radiological findings and the course of the disease in a group of adults affected by measles who developed respiratory complications (pneumonia and respiratory failure) during a recent measles outbreak.

Material and methods

Study design

Soon after the 2018 measles outbreak, we performed a retrospective study based on chart review. The study consisted in collecting data from the medical records of patients hospitalized for measles in a large city hospital known as "Ospedale Garibaldi". This hospital is located in the city of Catania (300,000 inhabitants), one of the two main cities in Sicily that has been the site of a large measles epidemic where two, out of eighth deaths reported in the country, occurred. This hospital is renowned for providing tertiary care for infectious diseases. Therefore, general practitioners from the city and from the hinterland, refer more severe measles cases to its adults' Emergency Department (ED) in order to access, successively, the Infectious Disease Department.

We therefore reviewed all medical electronic records of patients admitted for measles to this ED from January to June 2018 (no cases were recorded from July to November 2018). All patients were local residents and the infection could be linked to local transmission.

Data collection and measles case definition

We reviewed electronic records of each patient focusing on demographic data, anamnesis (underlying comorbidities), clinical data (symptoms, signs and presentation of the disease), laboratory and radiological findings. For all patients included in the study, the diagnosis of measles was based on the European Commission case definition [14]. According to this definition, all patients were considered "confirmed cases" when presenting laboratory evidence of infection with measles virus, i.e. detection of viral RNA in a biological sample and/or a positive IgM result in serum.

A "respiratory complication" was defined as the presence of pneumonia on chest X-ray (presence of consolidation and/or diffuse opacities) with or without respiratory failure. As a distinction between secondary bacterial superinfection and primary measles pneumonia could not be made, the term of "measles-associated" pneumonia has been used for this study. All patients who had radiological findings compatible with pneumonia had a computed tomography (CT) scan. For all patients arterial oxygen saturation (SaO_2%) was available and for those with $SaO_2 < 90$%, blood gas analysis was also accessible. Respiratory failure was defined as a partial pressure of oxygen (PaO_2) < 60 mm Hg at rest; severe respiratory failure was defined as the percentage of inspired oxygen (FiO_2)/PaO_2 ratio < 200. Critically ill patients were defined as those who required admission to the Intensive Care Unit. Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin criteria [15]. The Local Ethic Committee approved the study and informed consent was obtained by the patients or caregivers.

Data analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were shown as numbers (%). To compare the differences between the groups for continuous variables, t-test was used. To contrast the differences between the groups for categorical variables, a chi-square test was used. Results were considered statistically significant at P value < 0.05. Statistical analyses were performed using SPSS software (IBM, NY).

Table 1. Demographic and clinical data of patients with or without pneumonia

	Pneumonia	Without pneumonia	P value
N. of patients	30	147	
Age (yrs)	26 ± 1	26 ± 7	ns
Sex (male)	53%	49%	ns
Previous medical history (n.)			
Asthma	2	2	ns
Other	2	0	ns
Complications			
Hepatitis	72%	60%	ns
Diarrhea	3%	8%	ns
Thrombocytopenia	50%	63%	< 0.05
Leukopenia	24%	34%	< 0.05

Results

Clinical presentation in all study patients

From January to June 2018, a total of 177 patients were referred to the ED for measles (49% males, mean age 26 ± 9 years, range 16–45). Ten patients were rapidly dismissed for mild disease. Out of 177, only two individuals had been previously vaccinated (both with two doses, both dismissed for mild diseases). None reported measles during childhood. Given the young age of the patients, the past medical history was generally unremarkable with some exceptions. Four patients reported mild asthma (2 in the group with pneumonia and 2 in the group without pneumonia), one had Down Syndrome and one had a previous gastric bypass (both in the group with pneumonia) (Table 1). Common clinical manifestations included fever, generally > 38°C (89%), maculopapular rash (93%), cough (43%), Koplik's spots (32%) and conjunctivitis (43%). Common complications included thrombocytopenia, acute hepatitis, leukopenia and diarrhea (Table 1). Two patients presented acute pancreatitis and in one person, seizures occurred.

Patients with respiratory complications

Pneumonia was diagnosed in 30 patients (16.9% of those referred to the ED) (mean age 26 ± 1 years, 53% males). No statistical difference was found in the mean age or in the percentage of males between the group with pneumonia and the group without pneumonia (Table 1). All patients had the risk factor of not having been vaccinated. None had an apparent cause of pre-existing immunodepression. Nine patients with pneumonia (30%) developed respiratory failure. Among these, 5 developed severe respiratory failure and critical illness requiring ICU admission, whereas 4 patients had a mild hypoxemia requiring only low flow oxygen administration and were managed in non ICU wards. Excluding the respiratory tract involvement, measles clinical presentation in patients with pneumonia was similar to those without pneumonia. However, in the subjects with pneumonia, leukopenia and thrombocytopenia were significantly less common than in patients without pneumonia (24% *vs* 34% for leukopenia, $P < 0.05$ and 50% *vs* 63 % for thrombocytopenia, $P < 0.05$) (Table 1).

A chest CT scan was performed in all patients who had abnormal X-ray. Bilateral lesions were observed in 89% of the study subjects. The most common radiological findings were as follows: centrilobular nodules (63%), ground-glass attenuation (63%), air-space consolidation (36%), pleural effusion (16%) and pneumothorax (10%) (Table 2). Mild cases had mainly scattered

Table 2. Radiological findings on CT scan in patients with measles-associated pneumonia

	Frequency
Centrilobular nodules	+++
Ground-glass attenuation	+++
Air-space consolidation	++
Pleural effusion	+
Pneumothorax	+

Frequency is reported as ≤ 25% ≥ 75%

Table 3. Demographic and clinical data of the patients admitted to ICU

Pt no.	Age	Sex	Chronic conditions	Hepatitis	CRP	Leukopenia	Thrombocytopenia	CT scan	Survival
1	22	F	Allergic asthma	No	31	No	No	Consolidation Ground glass opacities	Yes
2	28	M	No	Yes	355	No	Yes	Consolidation Ground glass opacities Massive sx pneumothorax	Yes
3	32	M	Gastric by-pass	Yes	73	Yes	Yes	Extensively diffused centrolobular nodules	Yes
4	26	F	No	Yes	38	No	No	Consolidation Minimal ground glass opacities	No
5	38	F	No	No	354	No	No	Consolidation Ground glass opacities Nodules	No

CRP — C-reactive protein; ECMO — extracorporeal membrane oxygenation

centrilobular nodules and ground attenuation, whereas the CT scans of patients with severe respiratory failure varied greatly (see below). Patients presented mainly with dry cough so that sputum could not be collected for microbiological examination. As it was difficult to establish the presence of bacterial superinfection, all patients received a wide spectrum antibiotic treatment with a β-lactam, a macrolide or a fluoroquinolone. Support treatment particularly hydration and electrolytes adjustment, was also given. Oxygen supplementation was used in patients with $PaO_2 < 60$ mm Hg, *via* nasal cannula or mask (if not admitted to ICU).

Patients with severe hypoxemia and lung injury

Five patients (2.9% of those admitted) developed severe hypoxemia, refractory to oxygen administration ($PaO_2/FiO_2 < 150$) and, being critically ill, were admitted to ICU. Two of these individuals died from acute respiratory failure (1.1%).

None of these patients was vaccinated and none smoked. One of them suffered from mild asthma and another one had previous gastric bypass. The remaining three patients had no significant medical history. All reported 2- to 7-day fever and maculopapular rash before arriving at the ED. Microbiological assessment, in order to exclude bacterial superinfection, included broncoaspirate and blood culture (aerobic and anaerobic bacteria). All these cultures were negative in three patients (n. 1, 2, 3). Rhinovirus was detected in the nasal swab of patient n. 3. No microbiological data were available for the two women who died suddenly. The clinical course and the radiological findings varied greatly among these five patients (Table 3).

The patient n. 1 (a girl with mild asthma, no inhaled steroids use reported) had severe hypoxemia and bilateral extensive areas of ground glass with little consolidation on CT scan, however, she rapidly recovered and within 10 days CT scan was normal. The patient n. 3 also had rapid recovery although CT scan showed a massively diffused centrilobular nodules.

The patient n. 2 had a complicated, long clinical course that is worth mentioning. This 32-year-old man (gastric bypass one year earlier, but normal body mass index) after 4 days of symptoms (fever and vomiting) was transported to the ED in severe respiratory distress ($PaO_2/FiO_2 < 150$) and transferred immediately to the ICU where he was treated with extracorporeal membrane oxygenation (ECMO). The CT scan at admission showed diffuse ground glass areas and consolidation, and successively, he developed left massive pneumothorax, pneumomediastinum and subcutaneous emphysema (Figure 1). A chest tube was positioned and removed after 5 days. The patient was recovering very slowly and areas of consolidation were still present after 20 days. At 2 months of follow-up, the chest X-ray was normal.

The patient n. 4 was a 26- year-old woman with no past medical history. After 7 days of fever (amoxicillin was prescribed at home) she was admitted to the ED perfectly conscious with SaO_2 90% at room air and diffuse bronchospasm. Laboratory data showed an increase in AST (234/UL) and a mild increase in CRP (38 mg/L), normal leucocytes and platelets. The chest X-ray showed a right basal opacity. The patient, whose

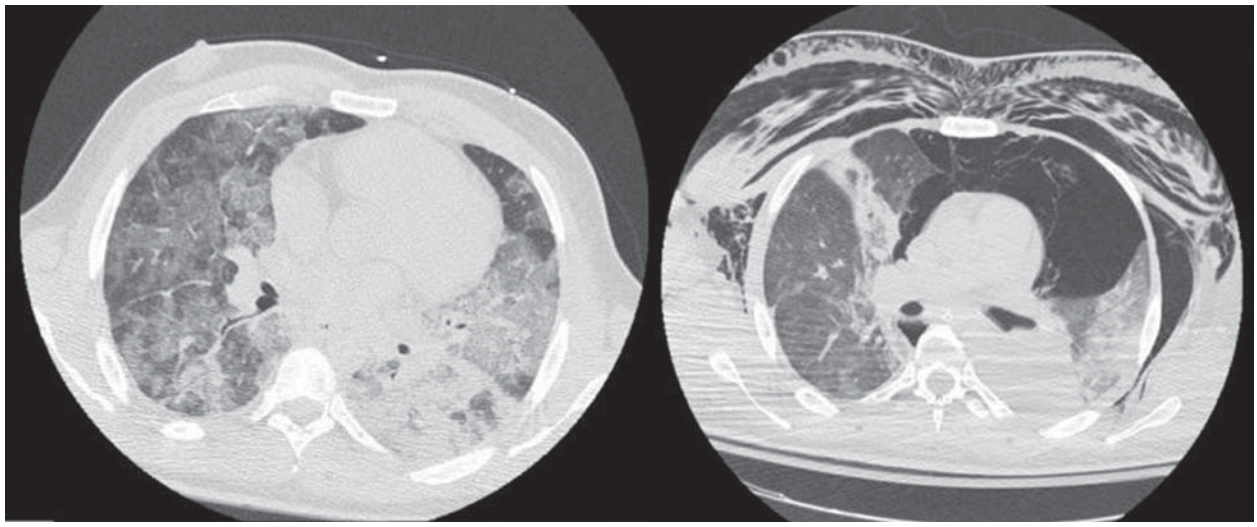


Figure 1. CT scan of patient n. 2 at admission (left) and after 3 days (right)

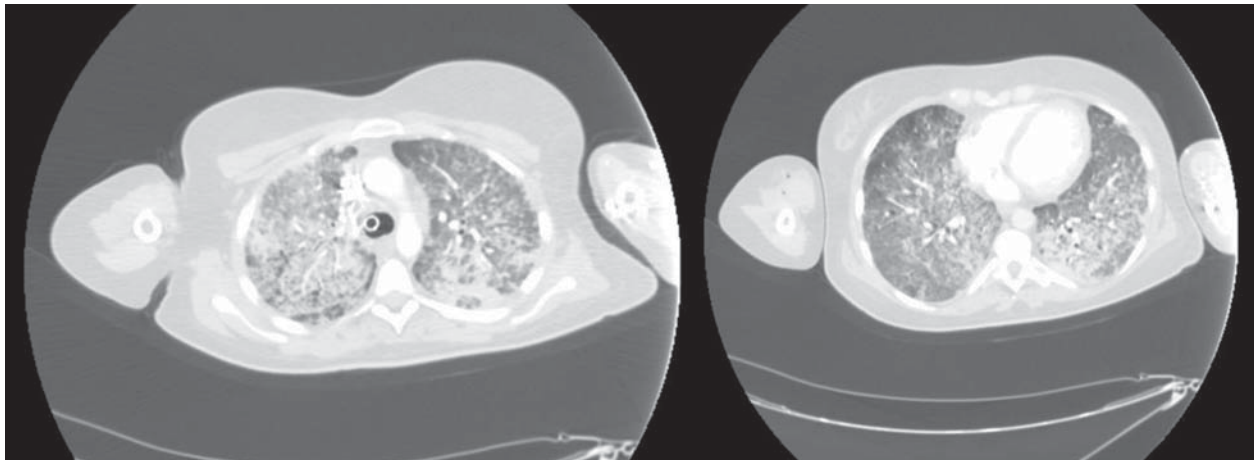


Figure 2. CT scan of patient n. 5 at admission before intubation. She died soon after

condition did not appear so severe in the first evaluation, received support treatment with hydration and a wide spectrum β-lactam. Within 48 hours, the respiratory conditions suddenly deteriorated, respiratory distress increased and PaO_2/FiO_2 was below 100. The patient died soon after admission to ICU and intubation. It is peculiar that the CT scan showed two areas of consolidation in the right lung while the left lung was substantially spared with only a minimal amount of ground glass in the left lower lobe. The extension of the lung damage on CT scan did not reflect the severity of hypoxemia.

The patient n. 5 was a 38-year-old woman with no past medical history. After two days of fever and rash she was admitted with SaO_2 83% at room air, PaO_2/FiO_2 150, leukocytes 10700/mcL, CRP 354 mg/L, AST 136 UI/L. Differently from the previous patient, her CT scan showed a massive involvement of both lungs with diffuse consolidation, ground glass and nodules (Figure 2). The woman was intubated but soon after she died from ARDS.

Discussion

In this study, we describe the clinical and radiological presentation of measles-associated pneumonia during a recent measles outbreak in a group of patients admitted to the emergency room of a large tertiary care city hospital. Few previous researches have evaluated measles-associated respiratory complications in adults [16, 17]. The low availability of data is due to the fact that in pre-vaccine time measles occurred, at least in Western countries, mainly in school-aged children. Therefore, data on respiratory

complications in selected adult groups are rare, although it is generally accepted that the burden of complications in adults is heavier than in children [2]. Pneumonia is one of the most common life-threatening complications [18]. The main finding of our study is that, during this latest outbreak, measles-associated pneumonia has been common, severe and fatal among unvaccinated otherwise healthy young adults. Making a comparison with other studies on the incidence of measles-associated pneumonia during the latest outbreaks is difficult, due to differences among methodologies. In the city of Messina (not far from Catania) in 2017, in a group of 59 patients with measles, only 4% developed pneumonia [19]. We found a definitely higher incidence; however, we assessed patients who were referred to the ED for a severe clinical presentation. It is noteworthy that, in the same time frame evaluated in our study (January to July 2018), the incidence of measles-associated pneumonia in Italy has been around 10%, with 7% of the patients presenting respiratory failure [13]. This percentage includes children (probably lowering the incidence), but it is relevant that the highest frequency of complications and mortality has been reported in adults > 20 years [7, 13]. In addition, six out of eight deaths in Italy were adults. An observation that can be inferred from our data is that, although the lack of vaccination was a major risk factor for all patients, the respiratory morbidity and mortality from measles was unpredictable. In a previous report on patients admitted to ICU for measles, a number of patients had immunodepression (organ transplantation of HIV infection) and important respiratory morbidity [17]. In our patients, there was no known cause of immunodepression. It is true that two out of 5 patients admitted to ICU had a comorbidity (mild asthma and gastric bypass), but the two patients who died, apparently, had no previous or chronic disease. Perhaps, a difference in infecting genotypes can be evoked, however, we were not able to differentiate the genotypes and so far, no correlation between the genotype and the severity of the disease has been suggested [2]. In addition, we were not able to discern a putative bacterial superinfection, as there was no time for collecting bronchial aspirate. Perhaps, in one of the two patients (n. 5), a bacterial infection could be suspected as CRP was high. However, this is only a speculation as no post-mortem was available.

One of the aims of this study was to define radiological features of measles-associated pneumonia. It is well acquired that the main feature of viral pneumonia is a radiological interstitial pattern [20, 21, 22]. A typical measles pneumonia is characterized by peribronchial nodular infiltration and reticulonodular infiltration with thickened interlobular septa [20]. Hilar lymphadenopathy and pleural effusion have also been described [21]. Sometimes fibrosis has been observed on follow-up images 20]. In a previous report describing critically ill adults, the CT scan showed an exclusive pattern of interstitial pneumonitis in 61 % of the patients, whereas only in a minority of cases, alveolar consolidation was found [17]. We observed that 4 out of 5 patients had consolidation and this can be due to the severity of the disease. Usually, as the viral disease progresses, consolidation areas can overlap ground-glass. In addition, bacterial coinfection cannot be excluded as the cause of consolidation, particularly if associated with increased inflammation markers [23]. One remark is that in critically ill patients, we did not find a clear correlation between radiological findings and the severity of hypoxemia. Kakoullis *et al*. recently reported in 11 cases of pneumonia that occurred in Greece, an inverse correlation between PaO_2/FiO_2 and the presence of reticular pattern [16]. We found that patients with mild respiratory impairment had predominately a ground glass pattern and the presence of reticular patterns was uncommon. Also, the two patients who died had different radiological features. One had a massive extension of centrilobular nodules and consolidation in both lungs, whereas the other one only had well defined consolidations in one lung, yet she was severely hypoxemic.

We conclude that during the latest measles epidemic the respiratory impairment has been frequent, severe, fatal and unpredictable. The paradigm that complications from viral infections occur only in fragile or immunodeficient patients should now be revisited. The non-vaccinated status is a major risk factor for measles-associated complications even in healthy young subjects. These data strongly support the concept that implementation of vaccination policies should be mandatory.

Conflict of interest

None declared.

References:

1. Remington P. Airborne transmission of measles in a physician's office. JAMA. 1985; 253(11): 1574, doi: 10.1001/jama.1985.03350350068022.
2. Moss W. Measles. The Lancet. 2017; 390(10111): 2490–2502, doi: 10.1016/s0140-6736(17)31463-0.

3. Coughlin M, Beck A, Bankamp B, et al. Perspective on global measles epidemiology and control and the role of novel vaccination strategies. Viruses. 2017; 9(1): 11, doi: 10.3390/v9010011.
4. World Health Organization. Sixty-Third World Health Assembly. 25 March 2010 Global eradication of measles. Report by the Secretariat.
5. European Centre for Disease Prevention and Control (ECDC). Epidemiological update: Measles - monitoring European outbreaks, 7 July 2017. Stockholm: ECDC; Available from: https://ecdc.europa.eu/en/news-events/epidemiological–update–measles–monitoring–europeanoutbreaks–7–july-2017.
6. Angelo K, Gastañaduy P, Walker A, et al. Spread of measles in Europe and implications for US travelers. Pediatrics. 2019; 144(1): e20190414, doi: 10.1542/peds.2019-0414.
7. Filia A, Bella A, Manso MD, et al. Ongoing outbreak with well over 4,000 measles cases in Italy from January to end August 2017 — what is making elimination so difficult? Eurosurveillance. 2017; 22(37), doi: 10.2807/1560-7917.es.2017.22.37.30614.
8. Mulholland E, Griffiths U, Biellik R. Measles in the 21st Century. New England Journal of Medicine. 2012; 366(19): 1755–1757, doi: 10.1056/nejmp1202396.
9. Lopez H, Laguna S, Marin R. Spotlight on measles 2010: an ongoing outbreak of measles in an unvaccinated population in granada, spain, october to november 2010: an ongoing outbreak of measles in an unvaccinated population in Granada, Spain, October to November 2010. Euro Surveill. 2010; 15: 15.
10. World Health Organization Regional Office for Europe (WHO/Europe) (2016). Fifth Meeting of the European Regional Verification Commission for Measles and Rubella Elimination (RVC) 24-26 October 2016, Copenhagen, Denmark. Copenhagen: WHO/ Europe; Available from: http://www. euro.who.int/__data/assets/pdf_file/0005/330917/5th-RVCmeeting-report.pdf?ua=1. [Last accessed at: May 25th, 2020].
11. Muscat M. Who Gets Measles in Europe? Journal of Infectious Diseases. 2011; 204(Supplement 1): S353–S365, doi: 10.1093/infdis/jir067.
12. Muscat M, Bang H, Wohlfahrt J, et al. Measles in Europe: an epidemiological assessment. The Lancet. 2009; 373(9661): 383–389, doi: 10.1016/s0140-6736(08)61849-8.
13. Instituto Superiore di Sanità (2018) EpiCentro portal. Morbillo e Rosolia News. Report n. 47. December 2018 Italian. Available at: http://www.epicentro.iss.it/problemi/morbillo/bollettino.asp. [Last accessed at: May 25th, 2020].
14. European Commission (2012) Commission Implementing Decision of 8 August 2012 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Luxembourg: Publications Office of the European Union. L262 Sep 27, 2012. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ%3AL%3A2012%3A262%3ATOC. [Last accessed: May 25th, 2020].
15. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012; 307(23), doi: 10.1001/jama.2012.5669.
16. Kakoullis L, Sampsonas F, Giannopoulou E, et al. Measles**X?**associated pneumonia and hepatitis during the measles outbreak of 2018. International Journal of Clinical Practice. 2019; 74(2), doi: 10.1111/ijcp.13430.
17. Rafat C, Klouche K, Ricard JD, et al. Severe measles infection. The spectrum of disease in 36 critically ill adult patients. Medicine. 2013; 92(5): 257–272, doi: 10.1097/md.0b013e3182a713c2.
18. Hutchins S, Amler R, Maes E, et al. Evaluation of the measles clinical case definition. The Journal of Infectious Diseases. 2004; 189(Supplement_1): S153–S159, doi: 10.1086/379652.
19. Palamara MA, Visalli G, Picerno I, et al. Measles outbreak from February to August 2017 in Messina, Italy J Prev Med Hyg. 2018; 59(1): E8–E13.
20. Koo H, Lim S, Choe J, et al. Radiographic and CT features of viral pneumonia. RadioGraphics. 2018; 38(3): 719–739, doi: 10.1148/rg.2018170048.
21. Kim E, Lee K, Primack S, et al. Viral pneumonias in adults: radiologic and pathologic findings. RadioGraphics. 2002; 22(suppl_1): S137–S149, doi: 10.1148/radiographics.22.suppl_1.g02oc15s137.
22. Schoini P, Karampitsakos T, Avdikou M, et al. Measles pneumonitis. Adv Respir Med. 2019; 87(1): 63–67, doi: 10.5603/ARM.a2019.0010, indexed in Pubmed: 30830960.
23. Pavia AT. Viral infections of the lower respiratory tract: old viruses, new viruses, and the role of diagnosis. Clinical Infectious Diseases. 2011; 52(Supplement 4): S284–S289, doi: 10.1093/cid/cir043.

Joanna Lange[1], Jerzy Kozielski[2], Kinga Bartolik[3], Paweł Kabicz[3], Tomasz Targowski[4]

[1]Department of Pediatric Pulmonology and Allergy, Medical University of Warsaw, Poland
[2]Department of Lung Diseases and Tuberculosis, Medical University of Silesia, Katowice, Poland
[3]Department of Analysis and Strategy, Ministry of Health, Warsaw, Poland
[4]Department of Geriatrics, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland

Analysis of the incidence of acute respiratory diseases in the paediatric population in Poland in the light of the "Health Needs Map"

Abstract

Introduction: Statistical data on the structure of acute respiratory diseases incidence in the paediatric population are still scarce. The demand for such data results mainly from the need to constantly implement new systemic and economic solutions.
The aim of the study was to attempt to use reported data for an assessment of the incidence of acute respiratory diseases in various age groups.

Material and methods: An analysis of selected acute respiratory diseases was conducted in relation to diagnoses reported from 1 January to 31 December 2014 to the National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) in accordance with the codes of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision. The study was conducted under the Knowledge Education Development operational programme co-funded by the European Social Fund.

Results: A total of 101,000 children were hospitalised due to acute respiratory diseases, which amounted to 1,554 hospitalisations per 100.000. The most common causes of hospitalisation were pneumonia and bronchitis/bronchiolitis. Boys were hospitalised more often in each age group. The shortest average length of stay (ALOS) was 5.21 days and concerned hospitalisation due to bronchitis. The longest length of stay for children was due to tuberculosis (14.3 days). The highest age average of a child was recorded in pleural diseases (10.51 years) and the lowest in bronchitis (2.93 years). Rehospitalisation was necessary in children in whom tuberculosis or pleural diseases were diagnosed (1.43 *vs* 1.34). A total of 67 inpatient deaths were recorded, of which 19 were due to pneumonia or its complications.

Conclusions: Epidemiological data reported to the National Health Fund (NFZ) seem quite reliable and do not differ significantly from those reported in other European countries. The analysed data may be useful in estimating health needs in paediatrics.

Key words: children, hospitalisation, lung infection

Adv Respir Med. 2020; 88: 204–214

Introduction

Acute respiratory diseases in the paediatric population are one of the most common causes of paediatrician or general practitioner visits, both in outpatient and hospital care. The demand for epidemiological data on this group of diseases in children results from the need to implement well-thought-out systemic solutions which cover above all the assessment of health needs of this age group. Epidemiological knowledge is necessary for planning an appropriate level of contracting, both in hospital and outpatient care, and for assessing the institutional and staff needs in order to secure them. Outpatient and hospital databases are among valuable repositories of clinical information that may provide an important insight into the health needs of the population [1]. They may also be used to develop locally relevant indicators of child's health and well-being [2]. The aim of

Address for correspondence: Joanna Lange, Department of Pediatric Pulmonology and Allergy, Medical University of Warsaw, Warsaw, Poland; e-mail: iskry47@gmail.com
DOI: 10.5603/ARM.2020.0106
Received: 07.01.2020

ISSN 2451–4934

Table 1. Basic statistics (by sex and age group) for children hospitalised due to pneumonia, bronchitis and tuberculosis

	No. of hospitalisations	Cumulative % of hospitalisations in subgroups	No. of patients	Cumulative % of patients in subgroups	No. of hospitalisations per patient	No. of person-days	ALOS
Pneumonias	**73255**	**100**	**68543**	**100**	**1.07**	**534334**	**7.29**
0–1	**30208**	**41.24**	**28006**	**40.86**	**1.08**	**240340**	**7.96**
Female	12650	41.88	11825	42.22	1.07	99928	7.90
Male	17558	58.12	16181	57.78	1.09	140412	8.00
2–5	**29919**	**40.84**	**28064**	**40.94**	**1.07**	**200355**	**6.70**
Female	13482	45.06	12689	45.21	1.06	91200	6.76
Male	16437	54.94	15375	54.79	1.07	109155	6.64
6–17	**13128**	**17.92**	**12473**	**18.20**	**1.05**	**93639**	**7.13**
Female	6179	47.07	5866	47.03%	1.05	44616	7.22
Male	6949	52.93	6607	100.00%	1.05	49023	7.05
Bronchitis	**32366**	**100**	**30585**	**100**	**1.06**	**168661**	**5.21**
0–1	**15221**	**47.03**	**14212**	**46.47**	**1.07**	**88142**	**5.79**
Female	5907	38.81%	5550	39.05	1.06	33994	5.75
Male	9314	61.19	8662	61.95	1.08	54148	5.81
2–5	**12136**	**37.50**	**11512**	**37.64**	**1.05**	**56718**	**4.67**
Female	4899	40.37%	4670	40.57%	1.05	23328	4.76
Male	7237	59.43	6842	59.43	1.06	33390	4.61
6–17	**5009**	**15.47**	**4861**	**15.89**	**1.03**	**23801**	**7.96**
Female	2252	44.96%	2184	44.93%	1.03	10968	4.87
Male	2757	55.04	2677	55.07	1.03	12833	4.65
Tuberculosis	**668**	**100**	**467**	**100**	**1.43**	**12534**	**14.30**
0–1	**73**	**10.93**	**44**	**9.42**	**1.66**	**802**	**8.77**
Female	28	38.36	18	40.91	1.56	363	11.11
Male	45	61.64	26	59.09	1.73	439	7.31
2–5	**157**	**23.50**	**109**	**23.34**	**1.44**	**2159**	**11.76**
Female	67	42.68	49	44.95	1.37	1149	13.64
Male	90	57.32	60	55.05	1.50	1010	10.37
6–17	**438**	**65.57**	**314**	**67.42**	**1.39**	**9573**	**16.19**
Female	226	51.60	149	47.45	1.52	4731	16.17
Male	212	48.40	165	52.55	1.28	4842	16.20

the paper was to analyse the data reported to the National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) in order to assess the incidence of selected acute respiratory diseases in children.

Material and methods

Data analysis was conducted under the "Maps of Health Needs — Database of Systemic and Implementation Analyses" project which was co-funded by the European Social Fund under the Knowledge Education Development operational programme. On 31 December 2016, the project results were published on the website of the Ministry of Health, including data on acute respiratory diseases in children. The Polish project was carried out by the Department of Analyses and Strategy of the Ministry of Health. Its main

Table 2. Analysis of deaths and death rate in children

Disease group	No. of patients	Share of inpatient deaths	Death rate 30 days after discharge	Death rate 90 days after discharge	Total
Pneumonias	68538	19	24	74	117
Bronchitis	30582	0	5	11	16
Acute respiratory failure	929	46	14	22	82
Tuberculosis	467	0	0	0	0
Pleural diseases	370	2	0	1	3
Other	140	0	0	0	0

goal was to improve the quality of management in the current health care system based on the data reported to the NFZ. Continuation of the commenced analytical actions will make it possible to take a position on decisions taken by persons responsible for health care management in Poland on the national, regional and local levels, carried out by individual service providers.

Analyses of acute respiratory diseases were conducted in relation to the diagnoses reported between 1 January 2014 and 31 December 2014 to the National Health Fund (NFZ) as per the codes of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10): pneumonias A37, B44, J10–J18, J69, bronchitis/bronchiolitis J20–J22, pleural diseases J85, J86, J90–J94, tuberculosis A15–A19, A31, B90, pulmonary oedema J81, acute respiratory failure J80, J96.0, other J68, J95, R05, T81.8.

The registered incidence rate was defined as the number of new patients with a given diagnosis reported as part of the health care system financed from the public funds per 100,000 inhabitants in a year. The analyses considered the age group of children. A child reported to the NFZ was considered a first-time patient if it appeared with a given diagnosis of an acute respiratory disease for the first time in the system in 2014.

Results

Respiratory diseases were the most common group of general paediatric diagnoses in Poland in 2014, constituting 32.4% of all hospitalisations across the country. A total of 101,000 children were hospitalised due to acute respiratory diseases (1554 hospitalisations per 100,000 children). Relative to the total number of hospitalisations of children in Poland, the percentage of hospitalisations due to acute respiratory diseases was 7.30%, and 1.45% relative to the size of the Polish paediatric population [3]. The most common reason for hospitalisation was pneumonia (68%), bronchitis or bronchiolitis (30% in total). The shortest average length of stay (ALOS) was 5.21 days and concerned hospitalisation due to bronchitis. Basic data (by sex and age group) on children hospitalised due to pneumonia, bronchitis and tuberculosis are presented in Table 1.

Based on available data, the deaths and death rate in children due to acute respiratory diseases were analysed. Summary results are presented in Table 2.

Multifactorial analysis of variance test was used for a comparison of the percentage of deaths among children, depending on the voivodship and age group. Multifactorial ANOVA test were applied for the leading causes of deaths among acute respiratory disease (pneumonia, bronchitis and acute respiratory failure). Test results are presented in Table 3.

In the pneumonia group, death was statistically often observed in the youngest analysed group (0–1), however, there were no differences according to the treatment in the analysed province. Among the death because of acute respiratory failure, statistical significance was observed between the provinces. In case of bronchitis, neither the main effects (province $P = 0.563$, age group $P = 0.664$) nor the province age group interaction ($P = 0.997$) were statistically significant.

Pneumonia in children

Pneumonias were the most common cause of hospitalisation due to acute respiratory diseases, both in adults and children. In 2014, 73,255 hospitalisations due to pneumonia were reported among children and adolescents up to 18 years of age (by comparison, there were 59,790 hospitalisations in adults). The calculated incidence per 100,000 was 956.11 in children and 235.96 in adults. It was observed, both in children and adults, that in-

Table 3. Results of multifactorial ANOVA for the percentage of deaths by province and age group

Disease group	Source of Variation	df	Sums of squares	Mean square	F statistic	P
Pneumonias	Province	15	0.00157	0.0001044	1.100	0.35160
	Age group	2	0.00127	0.0006362	6.700	0.00128
	Province∗Age group	30	0.00215	0.0000717	0.755	0.82751
	Residuals	1114	0.10508	0.0000943		
Bronchitis	Province	15	0.00062	0.0000413	0.901	0.56300
	Age group	2	0.00004	0.0000188	0.409	0.66400
	Province∗Age group	30	0.00060	0.0000200	0.437	0.99700
	Residuals	1057	0.04846	0.0000459		
Acute respiratory failure	Province	15	3.06700	0.2044600	2.528	0.00157
	Age group	2	0.25200	0.1262000	1.560	0.21190
	Province∗Age group	30	1.60300	0.0534400	0.661	0.91395
	Residuals	277	22.40400	0.0808800		

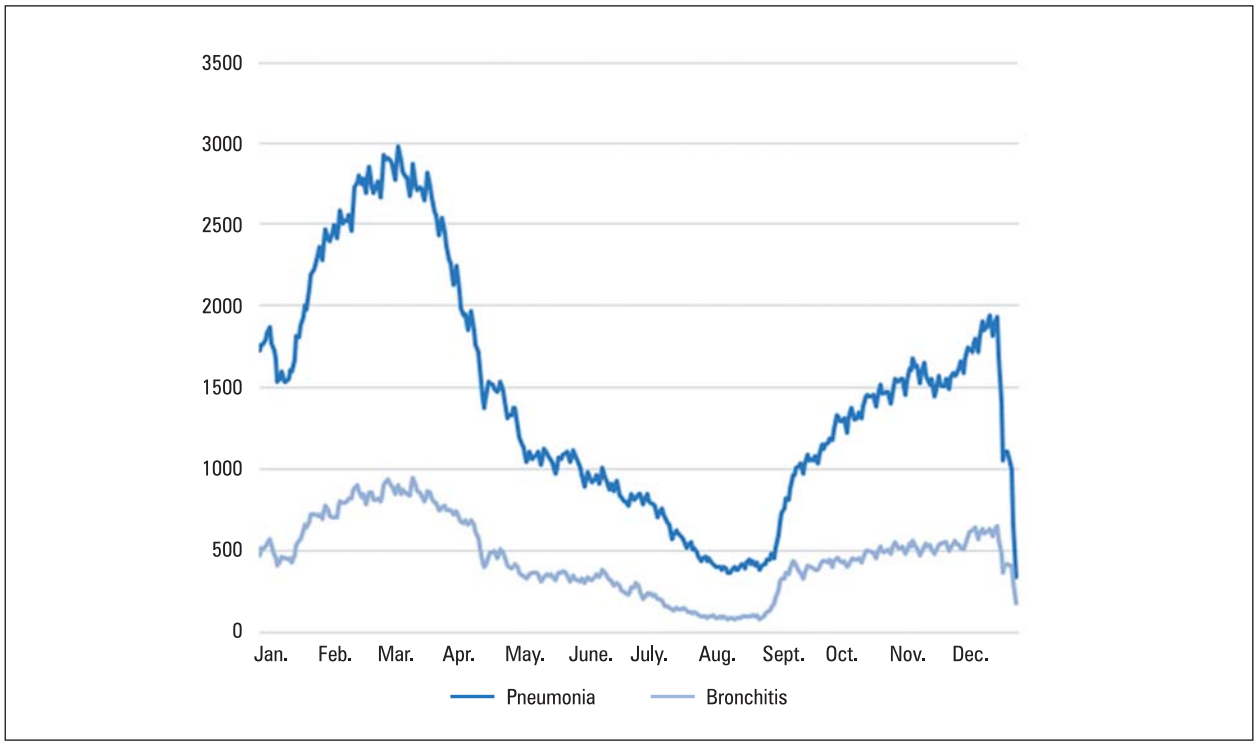


Figure 1. Daily number of hospitalisations due to pneumonia and bronchitis/bronchiolitis in children

cidence and hospitalisations due to pneumonia were seasonal, with the nadir in the summer season (June to August) and increased incidence in the autumn and winter season (Figure 1). ALOS for pneumonia is presented in Table 1.

Analysed was also the registered incidence of pneumonia by age group in all of Poland. The highest rate was calculated for the group of infants (3847.26 per 100,000), among children 2 to 5 years of age (1572.72 per 100,000) and above 6 years of age (270.59 per 100,000). The percentage share relative to the entire paediatric population was as follows — children up to 1 year of age constituted as much as 42.7%, children 2 to 5 years of age — 38.7%, and children above 5 years of age — 18.6%. In each age group, boys required hospitalisation more often (Table 1). The average age of a paediatric patient

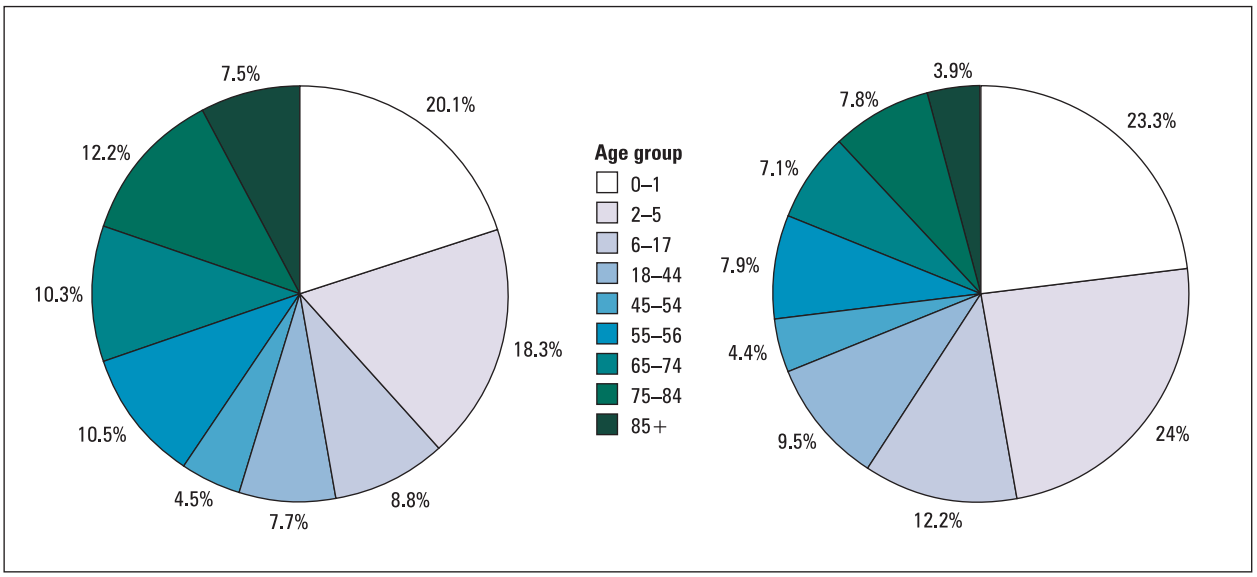


Figure 2. Structure of registered incidence of pneumonia (left) and bronchitis (right) by age group

requiring hospitalisation due to pneumonia was 3.25 years. Figure 2 summarises the structure of registered incidence of pneumonia and bronchitis by age group.

Bronchitis

In 2014 in Poland, there were 46,241 hospitalisations due to acute bronchitis identified by the ICD-10 codes J20-J22. Seventy percent of all hospital stays (32,366) were hospitalisations of children and adolescents up to 18 years of age. In the adult population, only 13,875 hospitalisations were reported (most were exacerbations of chronic obstructive pulmonary disease). The number of emergency admissions was 26,875 (83%) in children and adolescents, and 11,592 (84%) in adults. As in the case of pneumonia, a seasonality of incidence and hospital admissions was also observed (Figure 1). The calculated ALOS due to bronchitis/bronchiolitis is presented in Table 1. Code ICD-10: J21 (bronchiolitis) was isolated from among the overall coding data. 1,754 children under 1 year of age and 196 children aged 2 to 5 were hospitalised, and 11 patients above 6 years of age were diagnosed with bronchiolitis. The most commonly hospitalised due to bronchitis were children up to 1 year of age, irrespective of their place of residence. The registered incidence rate in this age group was 2633.4 per 100,000. In the group of children aged 2 to 5 years, registered incidence was calculated to be 1220.3 per 100,000, and for children above 6 years of age — only 221.9 per 100,000. For adults, this rate was 108.68 per 100,000. The structure of registered incidence, including the adult population, is presented in Figure 2. The calculated percentage share relative to the paediatric population only was as follows — children up to 1 year of age: 39.2%, children 2 to 5 years of age: 40.3%, children 6 years of age and older: 20.5%. In each of the analysed age groups, boys were hospitalised more often (Table 1), and the average age was 2.93 years.

Tuberculosis

In 2014, 467 children were hospitalised in Poland with the ICD-10 code for tuberculosis. The average length of stay was longest in the group of acute respiratory diseases (14.3 days). The structure of registered tuberculosis incidence in children by age and province is presented in Table 4. IGiChP data for 2014 are provided for the sake of comparison [4].

Univariate analysis of variance (ANOVA) test was used to differentiate the incidence of tuberculosis between province. Test results are presented in Table 5.

ANOVA test results showed group differences to be significant at $p < 0.05$ for all the age groups except the group aged 0 to 1 year.

Registered incidence of tuberculosis by age group was also analysed. Tuberculosis incidence in the paediatric population constituted only a small percentage (4.1%) relative to other age groups (Figure 3). The average age of a paediatric patient requiring hospitalisation due to tuberculosis was 8.91 years.

Table 4. Structure of registered incidence of tuberculosis per 100,000 children by age and province together with data published by IGiChP

Province	0– 1 year of age	2–5 years of age	6–17 years of age	IGiChP data	
				0– 14 years of age	15–19 years of age
Dolnośląskie	11.4	2.6	5.3	1.2	2.8
Kujawsko-pomorskie	5.1	4.5	7.4	0.6	1.7
Lubelskie	–	–	4.2	0.6	4.0
Lubuskie	–	–	–	–	–
Łódzkie	13.5	12.0	16.2	0.6	8.6
Małopolskie	17.5	14.6	10.9	0.8	1.0
Mazowieckie	17.1	13.6	15.0	3.4	7.0
Opolskie	–	–	1.8	–	9.5
Podkarpackie	–	2.3	2.6	0.6	3.1
Podlaskie	14.1	8.5	13.4	1.2	2.9
Pomorskie	6.2	17.7	11.6	0.3	1.6
Śląskie	2.4	2.2	5.0	2.8	6.2
Świętokrzyskie	–	–	4.8	–	4.2
Warmińsko-mazurskie	–	14.5	6.6	–	3.5
Wielkopolskie	–	5.0	3.0	0.7	3.6
Zachodniopomorskie	39.1	30.6	18.4	–	3.2
Poland	8.8	8.6	8.5	0.2	2.8

Table 5. Results of 1-Way ANOVA for the incidence of tuberculosis by province for all age groups

Age group	Source of variation	df	Sums of squares	Mean square	F statistic	P
0–1	Province	15	1795	119.67	0.6021	0.8733
	Residuals	364	72342	198.74		
2–5	Province	15	11305	753.68	3.5252	< 0.0001
	Residuals	364	77823	213.80		
6–17	Province	15	10491	699.40	5.5555	< 0.0001
	Residuals	364	45825	125.89		

Pleural diseases

Pleural diseases were the cause of hospitalisation of 370 children, who required 494 hospital stays (number of hospitalisations per patient: 1.34). The calculated average patient age was 10.51 years, and ALOS was 11.2 days. Pneumothorax was diagnosed in 145 children requiring hospitalisation (incidence rate of 2 per 100,000 children). In this group, as many as 133 children (92%) were older than 6 years of age. 225 children (including only 16 infants) were hospitalised due to diagnosed pleural empyema/effusion. As part of the implementation of the project, the 10 most commonly reported ICD-9 procedures were selected from the databases, of which radiological examination, pleural drainage, and chest ultrasound, essential for pleural diseases, were reported 311, 163, and 123 times, respectively.

Acute respiratory failure

Acute respiratory failure was diagnosed in 929 children (996 hospitalisations). The average patient age was 4.19 years, and ALOS was 7.24 days. After analysing the accompanying codes of acute respiratory failure, the ICD-10 codes most commonly accompanying it were identified. The most common accompanying diagnoses included G71.0 (muscular dystrophy)

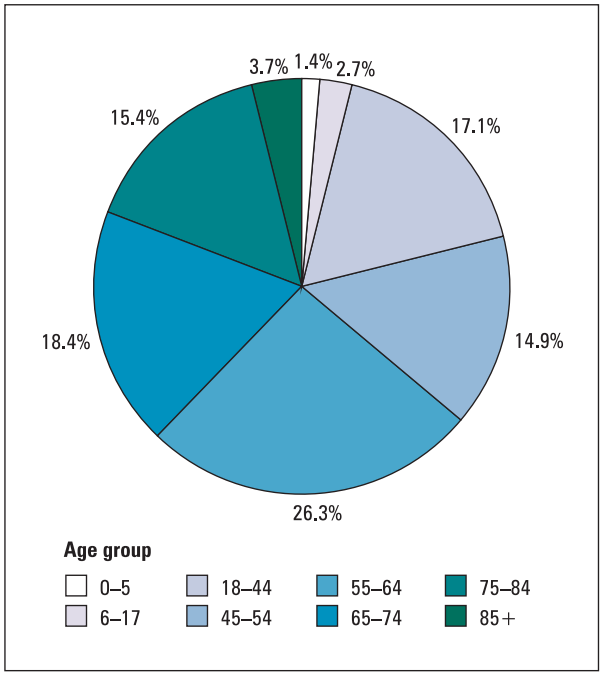


Figure 3. Structure of registered incidence of tuberculosis by age group

and G80.9 (cerebral palsy), both reported in the case of 8% of all hospitalisations. Among the 10 most commonly reported ICD-9 procedures in patients hospitalised with diagnosed acute respiratory failure, there was no invasive or non-invasive ventilation. Oxygen therapy was reported 215 times in 929 patients (23%) and pulse oximetry and gasometry were reported 278 (30%) and 121 times (12.6%), respectively.

Other acute respiratory diseases

In this diverse set of diseases (ICD-10 codes — J68, J95, R05, T81.8), 143 hospitalisations were reported in 140 children. It amounted to only 0.1% of all hospital stays due to acute respiratory diseases, and therefore, no detailed analysis of the available data was conducted.

Discussion

Acute respiratory diseases in the paediatric population are a significant problem in all countries. They are a common cause of hospitalisation and a reason for necessary out-of-hospital medical services. In 2014, acute respiratory diseases constituted 32.4% of all hospitalisations among children. Similar results were obtained by Nguyen *et al*. The authors found that respiratory diseases in a tertiary hospital in Hanoi were the most frequent, accounting for 37.7% of all hospital admissions [5]. By comparison, in 2012 in the United States, this percentage for children up to 17 years of age (excluding the neonatal period) was 22 [6]. Each year in Poland, about 7 to 8% of children with respiratory infections are hospitalised. According to Pancer *et al*., hospitalisation is required more often in infants (15 to 17%) and in children up to 4 years of age (about 30%) [7]. In the Hanoi population, 45.8% of the hospitalised children with a respiratory disease were infants. Hospital admissions for the same reason in the group of children from 5 to 17 years were 19.6% [5]. Similarly, in our data, a decreasing tendency has already been observed in the population of children above 2 years of age, and especially among children above 6 years of age. The recommended vaccination against pneumococcus may contribute to this, however, the lack of reliable data on the aetiology of pneumonias and on the percentage of children vaccinated in 2014 only enables a casual hypothesis in our reports. According to earlier data of the National Institute of Public Health — National Institute of Hygiene (NIZP-PZH) from 2010, children under 1 year of age and persons above 65 years of age were the most often hospitalised. In the population up to 18 years of age, the most often hospitalised due to respiratory diseases were children under 10 years of age, however, the highest percentage were patients up to 5 years of age [8]. Gajewska *et al*. also pointed out in their studies that the incidence rates decrease with the child's age [9, 10]. Nguyen *et al*. found that in the infant group, the hospitalisation rate in 2014 due to pneumonia was 34 per 1,000 children and only 5 per 1,000 for children aged 1 to 4 years [5]. In the same time frame in Poland, 56,070 children under 5 years of age were hospitalised in Poland due to pneumonia, which allows us to calculate the prevalence rate at 0.02 per child per year. This complies with the data coming from other developed countries [11]. In our analyses, older children required hospitalisation 4 times less often. The average length of stay due to pneumonia was 7.29 days. Children up to 1 year of age were hospitalised for the longest time (7.96 days). In the Vietnamese population, the average length of stay due to pneumonia was 6.42 [5]. In a paper by Gajewska *et al*., LOS was 10.1 in 2007 and 8.2 in 2011. Children up to 2 years of age were hospitalised for the longest time (nearly 11 days in 2007 and 9 days in 2011). A study of numerous papers from the subsequent years shows that the length of stay becomes shorter with age. By comparison, the average length of stay in the United States — irrespective of the cause — was

3.9 days in 2012. The shortening of the length of hospitalisation may also result from a different system of insurance, which in as much as 43.6% of all cases is based on private insurance, and from a system of insurance settlements, which is different from that in Poland [6]. Moreover, a decrease in length of stay observed in another country was associated with a decreased threshold for hospital admission. On the other hand, an increase in unplanned admissions or an increase in short-stay admissions, which was observed in Poland, may result from primary health care inefficiencies [12].

Another equally common acute respiratory disease requiring hospitalisation was bronchitis/bronchiolitis. Incidence of these diseases in 2014 in the group of children under 1 year of age was 2633.4 per 100,000. The data published in the ERS White Book 2011 recorded incidence in this age group at 2773.7 per 100,000. Similar data comes from Finland, the Czech Republic, Austria, Switzerland, and the United Kingdom [11]. A separate analysis of the ICD-10 code: J21 (bronchiolitis) made it possible to calculate registered incidence in the group of children up to 1 year of age, hospitalised with bronchiolitis at 238.34 per 100,000. Ten times and one hundred times lower values were calculated respectively for the age groups 2 to 5 years of age and above 6 years of age. The obtained results match the data concerning the diagnosis of bronchiolitis as a disease characteristic for the infant population. As in the case of pneumonias, in each of the age groups analysed, boys were hospitalised due to bronchitis more often. Similar conclusions were reached by De Lusignan *et al*. General practitioners in England more often diagnosed (in outpatient clinics) lower respiratory tract infections, mainly bronchitis, in boys up to 15 years of age [13].

Both in pneumonia and bronchitis, incidence is seasonal, with the nadir in the autumn and winter season. It corresponds with infections common in a moderate climate, mainly viral infections, during the "colder" seasons. The number of hospitalisations is affected by, in the case of bronchitis, infections caused by the respiratory syncytial virus (RSV), and in the case of pneumonia, infections caused by the influenza virus. Peak hospitalisations due to pneumonia in March 2014 coincided with the peak flu incidence recorded at that time by the National Institute of Hygiene (PZH) [14]. In a population of 236 children under 16 years of age, Finianos *et al*. observed that the majority of positive results of tests for viral infections were recorded between December and March [15]. Ramaekers *et al*. observed a clear increase in the number of viral infections between 2011 and 2016, mainly caused by RSV and the influenza virus, during the winter season [16]. According to our data, a reduced number of hospitalisations, both in the pneumonia and bronchitis group, was observed during Easter (20 April 2014) and Christmas. In accordance with observations resulting from the authors' experience, in these special periods, children remaining at hospitals are those most ill and requiring treatment continuation in closed health care conditions. Summing up, it must be emphasised that the seasonality of respiratory infections and the periods of church holidays affect the variations in the use of resources (such as hospital beds and medical staff), which is a challenge for the organisation of flexible health care, irrespective of the system in place.

Another issue analysed was an evaluation of death rates due to acute respiratory diseases. According to our data, in 2014 a total of 117 deaths due to pneumonia were reported to the National Health Fund (NFZ), however, only 19 children died during hospitalisation. Multifactorial analysis of variance showed that in those cases, a province was not relevant, but interestingly, we observed statistically significant differences according to the age. The highest death rate was observed in the youngest children, although deaths did not depend on treatment in the provinces. No inpatient deaths due to bronchitis or bronchiolitis were reported. At the same time, death due to acute respiratory failure (ICD-10- J96) during hospitalisation was reported in 46 patients under 18 years of age, and 36 additional children died within 90 days after discharge. We observed that the province has an impact on death due to acute respiratory failure. There is no simple explanation of that because we analysed namely registered incidence of each disease and also deaths. Children with complication due to many reasons, finally with acute respiratory failure were probably hospitalised not only in the district hospital but were transported to the voivodship hospital, however, there is no simply data in the system on that. In accordance with the available data by the World Health Organisation (WHO) and Europe Mortality Databases, the rate of deaths in Poland in 2011 — including deaths due to bronchiolitis, bronchitis and pneumonia — was 14.36 per 100,000 in the population of children up to 1 year of age, and the death rate in severe pneumonia among children up to 15 years of age was 1.91 per 100,000 [17]. According to the data

by the Polish Central Statistical Office (GUS), the reduction in the death rate among children 1 to 14 years of age in Poland is a positive phenomenon, observed constantly for several years now. In 2014, 3,114 children up to 19 years of age died [3] of which 5.7% (178 children) were deaths due to pneumonia [18]. The highest death rate due to this reason was recorded in a group of infants (1.6%) and the lowest in the group of children 10 to 14 years of age (0.38%) [8, 18]. The hard-to-explain differences in the reports presented in this paper and by the Central Statistical Office (GUS) may result, for example, from incorrectly completed death reports by doctors or from incorrectly identified (coded) causes of death. Cardiac or respiratory arrests as a consequence of acute respiratory failure, notoriously entered into the death reports, are after all not the cause of death but a consequence of the underlying cause. Code J96 (respiratory failure) belongs to the extended list of the so-called "garbage codes" which fail to precisely and accurately describe various conditions and diseases, thus preventing a precise determination of the cause of death.

Interesting but difficult to interpret, are the data reported to the NFZ concerning tuberculosis. According to our study, 467 children were hospitalised in Poland in 2014 with such a diagnosis. The data differ considerably from the data published in the IGiChP 2014 Bulletin. Korzeniewska-Koseła states that in 2014, a total of 70 cases of tuberculosis were reported in the group of children up to 14 years of age, and 86 cases were reported in the age group of 15 to 19 years of age [19]. Similarly, divergent are the data coming from individual provinces. The highest incidence was registered in the Zachodniopomorskie Province, although according to the IGiChP data, there was not a single report to the Central Register in the group of children up to 14 years of age, and details of only 3 patients were entered among children aged 15 to 19. Data most similar to those coming from IGiChP were obtained in the Śląskie Province. Beside of our findings, for clarification we used univariate analysis of variance to differentiate the incidence of tuberculosis between voivodships. We observed, that there is a significant difference between the incidence of tuberculosis depending on the province. ANOVA test results showed group differences to be significant at $p < 0.05$ for all age groups except the youngest one. One of the explanations why there is no significance in children up to the 1year of age is that in this special group, tuberculosis was recognised very rarely. The important question is why data vary so greatly in most provinces? It is difficult to explain, because a doctor in Poland is obliged to report each infection to the State District Sanitary Inspector or to the State Border Sanitary Inspector appropriate for the site of identification. Reporting flu incidence is mandatory under the Infectious Diseases Act of 5 December 2008 [20]. One of the most rational explanation may be that ICD-10 tuberculosis diagnosis codes are used for the purpose of financial settlements with the NFZ when it is suspected, and therefore, when it is necessary to carry out examinations to confirm it or to rule it out. The final report to IGiChP — which translates into the data published in the bulletin — is made only when the disease is confirmed bacteriologically or clinically and not when it is suspected.

Pleural diseases were also included in the acute respiratory diseases group. Half in this group was pneumothorax, which in as much as 92% was the cause of hospitalisation in the group of children above 6 years of age. It corresponds with the reports by both national and foreign centres [21, 22] as spontaneous pneumothorax occurs most often in the group of older children and in adolescents. According to our data, incidence in Poland in 2014 may be assessed at 2 per 100,000 children. Among the analysed procedures reported during hospitalisation due to pleural diseases, there were no biochemical, cytological and microbiological tests of pleural effusion — all essential from the point of view of medical treatment. Also, no thoracentesis (pleural tap) was listed — a procedure less invasive than surgical drainage. In a group of 370 patients, pleural drainage was reported in 44% of patients, and chest ultrasound in only 30% of patients. It should be stressed that these are essential procedures in managing patients with pleural effusion. For children, the percentage of pleural ultrasound should be close to 100%.

When analysing the issue of acute respiratory failure, it was observed that the use of oxygen therapy (only in 23% of all children) and of invasive and non-invasive ventilation were reported relatively rarely. It should be stressed that supporting ventilation by means of various methods and/or oxygen therapy are vital therapeutic procedures in the treatment of respiratory failure. It is therefore not possible that these methods were not used in such diagnosis. Such a low percentage results from failure to include these procedures in reports.

The strength of this paper is that it comprises data coming from one source in the same period of time, which makes it possible to compare it

with data from other European health systems. Its weakness is the lack of accurate data concerning performed ICD-9 procedures, which may result, among others, from the fact that the statistical records are not accurately completed. In 2014, in most hospitals, this data was entered by doctors or medical secretaries themselves. Automatic data entering will contribute positively to the reliability of available data.

The analysis performed by the authors of this study raises several questions for future investigations. First of all, why are there still so many hospitalisations due to respiratory diseases? Second, what is the importance of the distance between the place of residence and hospitals, insurance and hospital LOS? Thirdly, how to shorten LOS, increase the efficiency of the hospital system and reduce costs without jeopardising the quality of care? Understanding these factors will provide the information needed to plan and implement evidence-based prevention and treatment strategies.

Summary

The presented data on acute respiratory diseases reported in 2014 to the NFZ seem quite reliable and do not differ significantly from those reported in other European countries. The tuberculosis incidence rates, and acute respiratory disease death rates are a clear exception which requires, above all, improved reporting. Based on results obtained from data analysis, it seems that a skilful use of the reported data in combination with appropriate communication between the service provider and the payer will make it possible to appropriately assess the needs with respect to both hospital and outpatient care in acute respiratory diseases in children.

Significance for public health

Acute respiratory diseases in the paediatric population are one of the most common causes of paediatrician or general practitioner visits, both in outpatient and hospital care. The demand for epidemiological data on this group of diseases in children results from the need to implement well-thought-out systemic solutions which cover above all the assessment of health needs of this age group. Epidemiological knowledge is necessary for planning an appropriate level of contracting, both in hospital and outpatient care, and for assessing the institutional and staff needs in order to secure them. Clinical information from the databases is relevant to the development of local health needs.

Conflict of interest

None declared.

Funding

This paper has been prepared within the project Maps of Health Needs — Database of Systemic and Implementation Analyses. The project is co-financed by the European Union from the European Social Fund under the Operational Programme Knowledge Education Development and it is being carried out by the Analyses and Strategies Department of the Polish Ministry of Health.

References:

1. Safran C, Chute C. Exploration and exploitation of clinical databases. International Journal of Bio-Medical Computing. 1995; 39(1): 151–156, doi: 10.1016/0020-7101(94)01094H.
2. Ben-Arieh A. The child indicators movement: past, present, and future. Child Indicators Research. 2007; 1(1): 3–16, doi: 10.1007/s12187-007-9003-1.
3. Central Statistical Office. Demographic Yearbook of Poland Warsaw, 2015. Available at: https://stat.gov.pl/obszary-tematyczne/roczniki-statystyczne/roczniki-statystyczne/rocznik-demograficzny-2015,3,9.html. [Last accessed at: 14.02.2020].
4. Instytut Gruźlicy i Chorób Płuc. Biuletyn 2015. Available at: http://igichp.edu.pl/IGIChP. [Last accesed at: 14.02.2020].
5. Nguyen N, Dien T, Schindler C, et al. Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014. BMJ Open. 2017; 7(7): e015260, doi: 10.1136/bmjopen-2016-015260.
6. Witt WP, Weiss AJ, Elixhauser A. Overview of hospital stays for children in the United States, 2012. HCUP Statistical Brief #187. December 2014. Agency for Healthcare Research and Quality, Rockville, MD. Available at: https://hcup-us.ahrq.gov/reports/statbriefs/sb187-Hospital-Stays-Children-2012.pdf. [Last accessed at: 14.02.2020].
7. Pancer K, Gut W, Abramczuk E, et al. Czynniki wirusowe ostrych zakażeń dróg oddechowych u małych dzieci. Wzrost zachorowań wywołanych przez metapneumowirusy podczas pandemii grypy 2009 w Polsce. Przegl Epidemiol. 2014; 68: 729–733.
8. Raport „Sytuacja zdrowotna ludności Polski i jej uwarunkowania". Wotyniak B, Goryński P (ed.). Narodowy Instytut Zdrowia Publicznego, Warszawa 2016.
9. Gajewska M. Goryński P, Seroka W. Hospitalization of children and adolescents in Poland between 2004-2008. Probl Hig Epidemiol. 2013; 94(1): 71–8.
10. Gajewska M, Lewtak K, Scheres J, et al. Trends in hospitalization of children with bacterial pneumonia in Poland. Central European Journal of Public Health. 2016; 24(3): 188–192, doi: 10.21101/cejph.a4164.
11. European Lung White Book. Chapter 16 Paediatric Respiratory Diseases. Available at: https://www.erswhitebook.org/chapters/paediatric-respiratory-diseases/. [Last accessed at 14.02.2020].
12. Saxena S, Bottle A, Gilbert R, et al. Increasing short-stay unplanned hospital admissions among children in england; time trends analysis '97–'06. PLoS ONE. 2009; 4(10): e7484, doi: 10.1371/journal.pone.0007484.
13. de Lusignan S, Correa A, Pebody R, et al. Incidence of lower respiratory tract infections and atopic conditions in boys and young male adults: royal college of general practitioners research and surveillance centre annual report 2015–2016. JMIR Public Health and Surveillance. 2018; 4(2): e49, doi: 10.2196/publichealth.9307.
14. National Institute of Public Health — National Institute of Hygiene. Available at: wwwold.pzh.gov.pl/oldpage/epimeld/grypa/index.htm. [Last accessed 14.02.2020].

15. Finianos M, Issa R, Curran M, et al. Etiology, seasonality, and clinical characterization of viral respiratory infections among hospitalized children in Beirut, Lebanon. Journal of Medical Virology. 2016; 88(11): 1874–1881, doi: 10.1002/jmv.24544.
16. Ramaekers K, Keyaerts E, Rector A, et al. Prevalence and seasonality of six respiratory viruses during five consecutive epidemic seasons in Belgium. Journal of Clinical Virology. 2017; 94: 72–78, doi: 10.1016/j.jcv.2017.07.011.
17. Eurostat. Causes of death — deaths by country of residence and occurrence. Available at: https://ec.europa.eu/eurostat/web/products-datasets/-/hlth_cd_aro. [Last accessed at. 14.02.2020].
18. Central Statistical Office. Demographic Yearbook of Poland. Warsaw, 2016. Available at: https://stat.gov.pl/en/topics/statistical-yearbooks/statistical-yearbooks/demographic-yearbook-of-poland-2016,3,10. [Last accessed at: 14.02.2020].
19. Korzeniewska-Koseła M. Tuberculosis in Poland 2014. Przegl Epidem. 2016; 70(2): 261–272.
20. Journal of laws. Available at: http://prawo.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20082341570. [Last accessed at: 14.02.2020].
21. Matuszczak E, Dębek W, Hermanowicz A, et al. Spontaneous pneumothorax in children — management, results, and review of the literature. Polish Journal of Cardio-Thoracic Surgery. 2015; 4: 322–327, doi: 10.5114/kitp.2015.56782.
22. Žganjer M, Čizmić A, Pajić A, et al. Primary spontaneous pneumothorax in pediatric patients: our 7-year experience. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2010; 20(2): 195–198, doi: 10.1089/lap.2009.0070.

Phuuwadith Wattanachayakul[1], Pongprueth Rujirachun[1], Nipith Charoenngam[2], Patompong Ungprasert[3]

[1]Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2]Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[3]Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Chronic obstructive pulmonary disease is associated with a higher level of serum uric acid. A systematic review and meta-analysis

Abstract

Introduction: Recent studies have suggested that patients with chronic obstructive pulmonary disease (COPD) may have a higher level of serum uric acid compared with individuals without COPD, although the data are still limited. The current systematic review and meta-analysis was conducted to summarize all available data.

Material and methods: A systematic review was performed using the MEDLINE and EMBASE databases from their inception to July 2019. Studies that were eligible for the meta-analysis must have consisted of two groups of participants, patients with COPD and individuals without COPD. The eligible studies must have reported either mean or median level of serum uric acid and its standard deviation (SD) or interquartile range of participants in both groups. Mean serum uric acid level and SD of participants in both groups were extracted from each study and the mean difference (MD) was calculated. Pooled MD was then computed by combining MDs of each study using random effects model.

Results: A total of eight studies with 1,612 participants met the eligibility criteria and were included in the data analysis. The serum uric acid level among patients with COPD was significantly higher than individuals without COPD with the pooled MD of 0.91 mg/dL (95% CI: 0.45–1.38; $I^2 = 89\%$).

Conclusions: The current study found a significantly higher level of serum uric acid among patients with COPD than individuals without COPD.

Key words: chronic obstructive pulmonary disease, serum uric acid, meta-analysis

Adv Respir Med. 2020; 88: 215–222

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common pulmonary disorders worldwide. The disease is characterized by persistent respiratory symptoms due to airflow limitation. Airway and/or alveolar abnormalities of COPD are usually caused by significant exposure to noxious particles or gases [1]. COPD is currently the fourth leading cause of death globally according to the World Health Organization (WHO) and is predicted to become the third leading cause of mortality by 2030 [2]. Mechanisms that lead to airway destruction include oxidant/antioxidant imbalance, unopposed protease activity, inflammation, autoimmunity and enhanced apoptosis [3–6].

Hyperuricemia is a common metabolic abnormality that can lead to various clinical phenotypes, ranging from asymptomatic incidental laboratory abnormality to acute gouty arthritis and urate nephropathy [7–8]. Recent studies have suggested that serum uric acid level could be used as a marker of tissue hypoxia, particularly among patients with pulmonary diseases [9–10]. The increased level of serum uric acid is thought

Address for correspondence: Phuuwadith Wattanachayakul, Department of Microbiology Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; e-mail: phuuwadith.wat@gmail.com

DOI: 10.5603/ARM.2020.0119
Received: 15.03.2020

ISSN 2451–4934

to be a consequence of increased purine catabolism in the presence of tissue hypoxia [11]. The current systematic review and meta-analysis was conducted to compare serum uric acid level between patients with COPD, a common hypoxemic disorder, and individuals without COPD [12–19].

Material and methods

Search strategy

Three investigators (P.W., P.R., N.C.) independently searched for published studies indexed in EMBASE and MEDLINE from their inception to July 2019. Search terms were compiled from terms related to COPD and uric acid. The detailed search strategy is provided in the supplementary data 1. No language limitation was applied. References of the included studies were also manually reviewed for additional eligible studies. This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which is available as supplementary data 2.

Inclusion criteria

Studies that were eligible to be included into the meta-analysis must have consisted of two groups of participants, patients with COPD and individuals without COPD, and have reported either mean or median level of serum uric acid of participants in both groups and its standard deviation (SD), standard error of the mean (SE) or interquartile range, regardless of study design.

Study eligibility was independently determined by the three investigators (P.W., P.R., N.C.). Different opinions were resolved by conference with the senior investigator (P.U.). The quality of each study was jointly evaluated by all investigators using the Newcastle-Ottawa quality assessment scale for cohort studies [20] and the modified Newcastle-Ottawa quality assessment scale as described by Herzog *et al.* for cross-sectional studies [21].

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, country where the study was conducted, study design, year of publication, total number of participants, recruitment of patients with COPD and individuals without COPD, average age of participants, percentage of females and methods used to diagnose COPD. This data extraction was independently performed by the same three investigators (P.W., P.R., N.C.) to minimize error. Any discrepancies found in the case record forms were resolved by referring back to the original articles.

Statistical analysis

Mean serum uric acid level and SD of participants in both groups were extracted from each study and the mean difference (MD) was calculated. Pooled MD was then computed by combining MDs of each study using random effects model. If the study provided median and interquartile range instead of mean and SD, median would be used as an estimate for mean and SD would be estimated from interquartile range divided by 1.35. The heterogeneity of the MDs across the included studies was quantified using the Q statistic, which is complemented with I^2 statistics. A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76–100% high heterogeneity [22]. Visual inspection of funnel plots was used to assess for the presence of publication bias. Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom).

Results

The systematic search identified 526 potentially relevant articles (412 articles from EMBASE and 114 articles from MEDLINE). After the exclusion of 100 duplicated articles, 426 articles underwent title and abstract review. A total of 406 articles were excluded at this stage as they clearly did not fulfill the eligibility criteria based on the type of article, study design, participants and outcome of interest. A total of 20 articles were retrieved for full-length article review and 12 articles were excluded at this stage as they did not report the level of serum uric acid among participants with and without COPD. Finally, eight studies [12–19] with 1,612 participants were eligible for the meta-analysis. The literature retrieval, review and selection process are shown in Figure 1. The characteristics of the included studies and their quality assessment are described in Table 1.

Serum uric acid level among patients with COPD versus individuals without COPD

The pooled analysis found a significantly increased serum uric acid level among patients with COPD compared with individuals without COPD with the pooled MD of 0.91 mg/dL (95% CI: 0.45–1.38). The between-study heterogeneity was high with an I^2 of 89%. Figure 2 demonstrated the forest plot of the included studies.

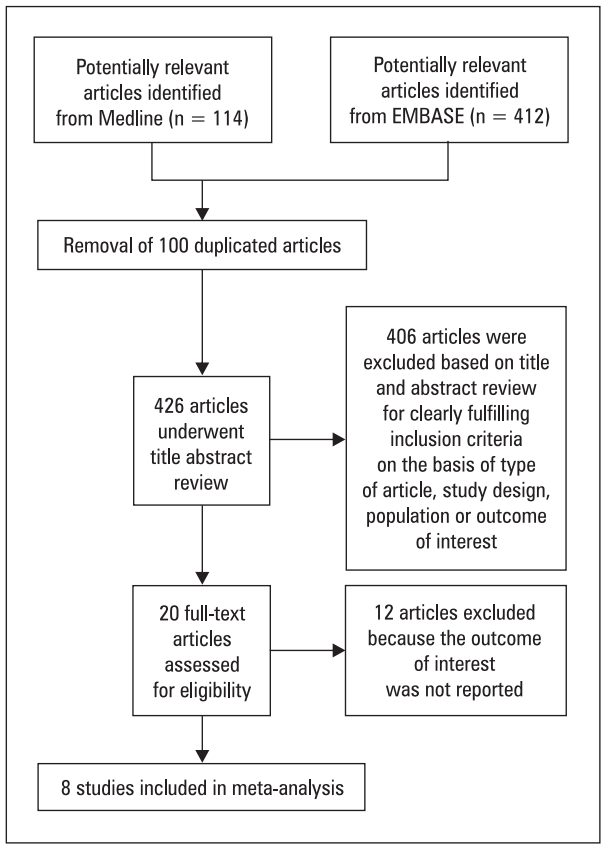


Figure 1. Literature review process

Evaluation for publication bias

Funnel plot was used to evaluate for the presence of publication bias as shown in Figure 3. The plot was relatively asymmetric and may suggest the presence of publication bias.

Sensitivity analysis

A sensitivity analysis was conducted to exclude two studies [17–18] that reported median and interquartile range and, thus, mean and SD had to be approximated using the technique described under Methods. Exclusion of these two studies from the pooled analysis only slightly increased pooled MD to 1.16 and remained statistically significant (95% CI: 0.57–1.75; I^2 88%), suggesting that the approximation did not have a substantial impact on the pooled result (supplementary data 3).

Discussion

The current study is the first systematic review and meta-analysis that summarized data from all available studies that compared the level of serum uric acid among patients with COPD versus individuals without COPD. We found that, on average, patients with COPD had a higher level of serum uric acid level than individuals without COPD with the difference of almost 1 mg/dL, which is approximately the same as the magnitude of uric acid reduction clinicians can expect from patients with gout/hyperuricemia who follow low-purine diet [23]. This observation may reinforce the hypothesis that tissue hypoxia can increase the rate of purine catabolism. In fact, *in vitro* and animal studies have indicated that hypoxic state can reversibly enhance oxidation of xanthine dehydrogenase into xanthine oxidase [12, 24–26]. Since significant number of patients with COPD has systemic hypoxia at rest or during acute exacerbation as a result of decreased oxygen diffusion capacity and alveolar hypoventilation, higher xanthine oxidase activity and increased serum uric acid level could be expected.

Another possible explanation is associated with an increased oxidative stress, which is a prominent feature of COPD [27]. Uric acid is classified as a low molecular weight water soluble antioxidant [12] that takes part in protecting the lungs from oxidative stress by inhibiting lipid peroxidation and scavenging reactive oxygen species and reactive nitrogen species [28]. Therefore, it is possible that the higher level of serum uric acid is a counter-response to a higher burden of oxidative stress among patients with COPD [3, 29].

Because of the observational nature of the included studies, it is also possible that the observed association between COPD and higher serum uric acid level is not causal with no direct mechanistic link. A recent systematic review found that metabolic syndrome is common among patients with COPD that is found in about one-third of them [30]. Since there is a strong association between insulin resistance, metabolic syndrome and hyperuricemia, [31] the observed higher level of serum uric acid level could be confounded by co-morbidities rather than COPD itself.

The results of this systematic review and meta-analysis may suggest that patients with COPD could be at a higher risk of hyperuricemia and serum uric acid may be worth checking for patients with COPD who exhibit signs and symptoms of complications of hyperuricemia, such as acute arthritis and kidney stones.

Few limitations of this systematic review and meta-analysis should be noted. First, between-study heterogeneity was high in this analysis, suggesting that the results of the primary studies could be too heterogeneous to combine together. The difference in background popula-

Table 1. Baseline characteristics of studies included in the meta-analysis

Study	Country	Study design	Study subjects	Number of subjects	Baseline characteristics of subjects	Quality assessment
Nicks *et al.* 2011 [12]	United States	Cohort study	**Cases:** Cases were smokers (at least a 10-pack year smoking history) with COPD who were recruited from the community of Denver, Colorado. Diagnosis of COPD was made based on GOLD criteria. **Comparators**: Comparators were smokers (at least a 10-pack year smoking history) without COPD who were recruited from the same community	Cases: 367 Comparators: 136	Mean age: Cases: 66.0 years Comparators: 57.0 years Percentage of female: Cases: 44.0% Comparators: 55.0% BMI Cases: 27.2 Comparators: 29.2 Smoking (Pack-Years) Cases: 57.0 Comparators: 42.0 Predicted FEV_1% Cases: 50.0% Comparators: 80.0% FEV_1/FVC Cases: 0.48 Comparators: 0.77	Selection: 4 stars Comparability: 1 star Outcome: 3 stars
Kocak *et al.* 2016 [14]	Turkey	Cohort study	**Cases:** Cases were patients with stable COPD (i.e., not in current COPD exacerbation or had history of exacerbation during the previous four weeks) who were recruited from the outpatient clinic of the study center between August 2014 and April 2015. Diagnosis of COPD was made based on GOLD criteria. **Comparators:** Comparators were subjects without COPD who were recruited from the same center. Subjects with chronic renal failure (serum creatinine levels > 3 mg/dL or glomerular filtration rate < 30 mL/min), gout disease or those who used any drugs that might affect serum UA levels, including allopurinol, febuxostat, probenecid, losartan, fenofibrate, pyrazinamide, ethambutol, cyclosporine and heparin, were excluded	Cases: 110 Comparators: 52	Mean age: Cases: 65.4 years Comparators: 62.7 years Percentage of female: Cases: 16.3% Comparators: 28.8% Current smoker: Cases: 18.1% Comparators: 26.9% Smoking (pack-years): Cases: 34.2 Comparators: 13.6 BMI (kg/m^2): Cases: 27.0 Comparators: 27.5 Urea (mg/dL): Cases: 27.1 Comparators: 31.1 Creatinine (mg/dL): Cases: 0.9 Comparators: 0.8	Selection: 4 stars Comparability: 1 star Outcome: 3 stars

Table 1. Baseline characteristics of studies included in the meta-analysis [cont.]

Study	Country	Study design	Study subjects	Number of subjects	Baseline characteristics of subjects	Quality assessment
Ozanturk *et al.* 2016 [13]*	Turkey	Cohort study	**Cases:** Cases were patients with COPD who were recruited from the study center. COPD was diagnosed from a history of ≥ 10 pack-years of smoking or a history of biomass exposure AND FEV_1 of < 80% of the predicted value after bronchodilator AND FEV_1/FVC of ≤ 0.7 after bronchodilator use. **Comparators:** Comparators were subjects without COPD who were recruited from the same center. Subjects with the following conditions were excluded: gout, diabetes mellitus, hemolytic anemia, myelolymphoproliferative disease, psoriasis, Paget's disease, glucose-6-phosphatase deficiency, glycogen storage disease, renal failure, acidosis, sarcoidosis, lead intoxication, berylliosis, use of some medication (salicylic acid, diuretic,cyclosporine, levodopa, phenylbutazone, ethambutol, pyrazinamide, nicotinic acid,nitroglycerin, theophylline, and allopurinol)	Cases: 15 Comparators: 15	Mean age: Cases: 58.0 years Comparators: 46.2 years Percentage of female: Cases: 6.6% Comparators: 60.0% Current smoker: Cases: 40.0% Comparators: 20.0% BMI (kg/m^2): Cases: 27.2 Comparators: 27.5	Selection: 4 stars Comparability: 1 star Outcome: 3 stars
Antus *et al.* 2017 [16]	Hungary	Cohort study	**Cases:** Cases were patients with stable COPD who were recruitedthe study center. **Comparators:** Comparators were subjects without COPD who were recruited from the same center	Cases: 34 Comparators: 29	NA	Selection: 2 stars Comparability: 0 star Outcome: 2 stars
Sarangi *et al.* 2017 [15]	India	Cohort study	**Cases:** Cases were patients with stable COPD who were recruited from the study center between 1st June 2016 and 31st July 2016. Diagnosis of COPD was made based on presence of persistent cough with or without sputum production and breathlessness, followed by spirometric evaluation (post bronchodilator FEV_1 to FVC ratio less than 0.7). **Comparators:** Comparators were nonsmoker, nonalcoholic subjects who came for routine health checkup at the same center. Comparators had no history of any respiratory signs or symptoms in the last three months. They were age and sex matched to cases	Cases: 39 Comparators: 46	Mean age: Cases: 62.97 years Comparators: 48.76 years Percentage of female: Cases: 46.2% Comparators: 43.4%	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars
AbdelHalim *et al.* 2018 [19]	Egypt	Cohort study	**Cases:** Cases were male patients with stable COPD (i.e., no exacerbation within 4 weeks prior to recruitment) who were recruited from the study center between August 2014 and April 2015. Diagnosis of COPD was made based on GOLD criteria. **Comparators:** Comparators were males without COPD who were recruited from the same center. Subjects with the following conditions were excluded: other chronic lung diseases, gouty arthritis, chronic renalfailure, malignancies, and use ofmedications that may affect the serum level of either UA or Cr, for example, allopurinol, ethambutol, pyrazinamide, cyclosporine, probenecid, heparin, fenofibrate and losartan	Cases: 283 Comparators: 123	Mean age: Cases: 55.9 years Comparators: 56.1 years Percentage of female: Cases: 0.0% Comparators: 0.0% BMI (kg/m^2): Cases: 25.9 Comparators: 25.3 CRP (mg/dl): Cases: 3.2 Comparators: 0.6	Selection: 4 stars Comparability: 1 star Outcome: 2 stars

↓

Table 1. Baseline characteristics of studies included in the meta-analysis [cont.]

Study	Country	Study design	Study subjects	Number of subjects	Baseline characteristics of subjects	Quality assessment
Bačura *et al.* 2018 [18]	Croatia	Cohort study	**Cases:** Cases were patients with stable COPD who were recruited from the study center. **Comparators:** Comparators were subjects without COPD who were recruited from the same center	Cases: 137 Comparators:95	NA	Selection: 3 stars Comparability: 1 star Outcome: 2 stars
Lee *et al.* 2018 [17]	South Korea	Cohort study	**Cases:** Cases were never-smokers with COPD who were recruited from 6 administrative districts of South Korea in the Kangwon and Chungbuk provinces between October 2012 and November 2014. Diagnosis of COPD was made based on clinical presentation and evidence ofairflow limitation (post-bronchodilator FEV_1 to FVC of $< 70\%$). **Comparators:** Comparators were never-smokers without COPD who were recruited from the same areas	Cases: 77 Comparators : 54 Comparators: 54	Mean age: Cases: 74.0 years Comparators: 73.0 years Percentage of female: Cases: 57.0% Comparators: 38.0% BMI (kg/m^2): Cases: 24.1 ± 3.1 Comparators: 23.9 ± 3.2 Extra-pulmonary comorbidities Diabetes mellitus: Cases: 11.7% Comparators: 13.0% Cerebrovascular disease: Cases: 9.1% Comparators: 9.3% Malignancy: Cases: 3.9% Comparators: 5.6% Chronic liver disease: Cases: 3.9% Comparators: 3.7% Chronic kidney disease: Cases: 1.3% Comparators: 3.7%	Selection: 4 stars Comparability: 1 star Outcome: 3 stars

*The study by Ozanturk E. *et al.* reported serum uric acid level in several groups of participants but only data from two groups of participants, individuals without COPD and obstructive sleep apnea and patients with COPD without nocturnal hypoxemia, were used for the meta-analysis. BMI — body mass index; Cr — creatinine; COPD — chronic obstructive pulmonary disease; $D_{LCO}\%$ — diffusing capacity for carbon monoxide percentages; FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; GOLD — Global Initiative for Chronic Obstructive Lung Disease; NA — not available; UA — uric acid

Study or subgroup	COPD Mead	COPD SD	COPD Total	Comparators Mean	Comparators SD	Comparators Total	Weight	Mean difference IV, Random, 95% CI	Year	Mean difference IV, Random, 95% CI
Nicks *et al.*	9.3	5	367	9.4	4.7	136	9.4%	-0.10 [-1.04, 0.84]	2011	
Ozanturk *et al.*	5.5	1.1	15	4.8	1.2	15	10.4%	0.70 [-0.12, 1.52]	2016	
Kocak *et al.*	5.9	1.5	110	4.6	1.2	52	13.6%	1.30 [0.87, 1.73]	2016	
Sarangi *et al.*	4.9	1.7	39	2.3	0.9	46	12.3%	2.60 [2.01, 3.19]	2017	
Antus *et al.*	5.4	0.3	34	4.6	0.3	29	15.2%	0.80 [0.65, 0.95]	2017	
Lee *et al.*	4.7	1.3	77	4.7	1.3	54	13.5%	0.00 [-0.45, 0.45]	2018	
Bacura *et al.*	5.4	1.6	137	4.9	1.3	95	14.0%	0.50 [0.13, 0.87]	2018	
AbdelHalim *et al.*	6.2	1.3	283	4.8	3.7	123	11.6%	1.40 [0.73, 2.07]	2018	
Total			**1062**			**550**	**100.0%**	**0.91 [0.45, 1.38]**		

Heterogeneity: $Tau^2 = 0.36$, $Chi^2 = 61.44$, df = 7 ($P < 0.0001$); $I^2 = 89\%$
Test for overall effect: $Z = 3.89$ ($P = 0.0001$)

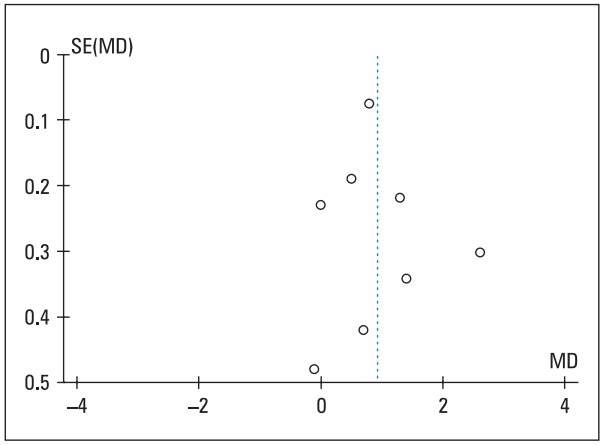


Figure 3. Funnel plot o1.1f the meta-analysis

Figure 2. Forest plot of the meta-analysis

tions of patients with COPD was the most likely explanation for the variation. Second, funnel plot of this analysis was relatively asymmetric and may suggest the presence of publication bias in favor of studies that report positive results. Third, the quality of some included studies was fairly low as reflected by low Newcastle-Ottawa scores.

Conclusions

In conclusion, this study found a higher level of serum uric acid among patients with COPD. Tissue hypoxia and increased oxidative burden are the possible explanations as well as confounding effect of co-morbidities.

Contributors

All authors designed the study. PW, NC and PR collected data and drafted the manuscript. PU performed statistical analysis and made critical revisions. All authors revised and approved the final manuscript.

Conflict of interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices or materials described in this report.

References:

1. Singh D, Agusti A, Anzueto A, *et al.* Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. European Respiratory Journal. 2019; 53(5): 1900164, doi: 10.1183/13993003.00164-2019.
2. Mathers C, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Medicine. 2006; 3(11): e442, doi: 10.1371/journal.pmed.0030442.

3. Bowler R, Barnes P, Crapo J. The role of oxidative stress in chronic obstructive pulmonary disease. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2004; 1(2): 255–277, doi: 10.1081/copd-200027031.
4. Mroz RM, Holownia A, Chyczewska E, *et al.* Cytoplasm-nuclear trafficking of CREB and CREB phosphorylation at Ser133 during therapy of chronic obstructive pulmonary disease. J Physiol Pharmacol. 2007; 58(Pt 2): 437–444.
5. Hogg J, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. New England Journal of Medicine. 2004; 350(26): 2645–2653, doi: 10.1056/nejmoa032158.
6. Hageman G. Systemic poly(ADP-ribose) polymerase-1 activation, chronic inflammation, and oxidative stress in COPD patients. Free Radical Biology and Medicine. 2003; 35(2): 140–148, doi: 10.1016/s0891-5849(03)00237-5.
7. Alvarez-Lario B, MacArron-Vicente J. Is there anything good in uric acid? QJM. 2011; 104(12): 1015–1024, doi: 10.1093/qjmed/hcr159.
8. Charoenngam N, Ponvilawan B, Ungprasert P. Sat0452 vitamin D insufficiency and deficiency are associated with a higher level of serum uric acid: a systematic review and meta-analysis. Saturday, 15 June 2019. 2019, doi: 10.1136/annrheumdis-2019-eular.696.
9. Viglietta L, Ferravante A, Berardino A, *et al.* Association between obstructive sleep apnea and serum uric acid levels in obese women. Eur Resp J. 2014; 44(Suppl 58): P2243.
10. Kadowaki T, Hamada H, Yokoyama A, *et al.* Significance of serum uric acid in patients with chronic respiratory failure treated with non-invasive positive pressure ventilation. Internal Medicine. 2007; 46(11): 691–698, doi: 10.2169/internalmedicine.46.6120.
11. Aida Y, Shibata Y, Osaka D, *et al.* The relationship between serum uric acid and spirometric values in participants in a health check: the takahata study. International Journal of Medical Sciences. 2011; 8(6): 470–478, doi: 10.7150/ijms.8.470.
12. Nicks M, O'Brien M, Bowler R. Plasma antioxidants are associated with impaired lung function and COPD exacerbations in smokers. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011; 8(4): 264–269, doi: 10.3109/15412555.2011.579202.
13. Ozanturk E, Ucar ZZ, Varol Y, *et al.* Urinary uric acid excretion as an indicator of severe hypoxia and mortality in patients with obstructive sleep apnea and chronic obstructive pulmonary disease. Revista Portuguesa de Pneumologia (English Edition). 2016; 22(1): 18–26, doi: 10.1016/j.rppnen.2015.06.002.
14. Kocak ND, Sasak G, Akturk UA, *et al.* Serum uric acid levels and uric acid/creatinine ratios in stable chronic obstructive pulmonary disease (COPD) patients: are these parameters efficient predictors of patients at risk for exacerbation and/or severity of disease? Medical Science Monitor. 2016; 22: 4169–4176, doi: 10.12659/msm.897759.
15. Sarangi R. Serum uric acid in chronic obstructive pulmonary disease: a hospital based case control study. Journal of clinical and diagnostic research. 2017, doi: 10.7860/jcdr/2017/29300.10605.
16. Antus B, Drozdovszky O, Barta I, *et al.* Assessment of serum uric acid in COPD exacerbations. Monitoring Airway Disease. 2017, doi: 10.1183/1393003.congress-2017.pa1086.
17. Lee H, Hong Y, Lim M, *et al.* Inflammatory biomarkers and radiologic measurements in never-smokers with COPD: A cross-sectional study from the CODA cohort. Chronic Respiratory Disease. 2017; 15(2): 138–145, doi: 10.1177/1479972317736293.
18. Bacura AS, Rajković MG, Rogić D, *et al.* Uric acid/creatinine ratio as a biomarker of severity of chronic obstructive pulmonary disease. Biochemia Medica. 2018; 28: S125–126.
19. AbdelHalim H, AboElNaga H. Serum uric acid levels and uric acid/creatinine ratios: affordable biomarkers for predicting chronic obstructive pulmonary disease severity and exacerbations. The Egyptian Journal of Chest Diseases and Tuberculosis. 2018; 67(3): 231, doi: 10.4103/ejcdt.ejcdt_39_18.
20. Wells GA, Shea B, O'Connell D, *et al.* The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. The Ottawa Hospital 2000. ; 2000.
21. Herzog R, Álvarez-Pasquin M, Díaz C, *et al.* Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? a systematic review. BMC Public Health. 2013; 13(1), doi: 10.1186/1471-2458-13-154.
22. Higgins J. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414): 557–560, doi: 10.1136/bmj.327.7414.557.
23. Peixoto M, Monego E, Jardim P, *et al.* Diet and medication in the treatment of hyperuricemia in hypertensive patients. Arquivos Brasileiros de Cardiologia. 2001; 76(6): 468–472, doi: 10.1590/s0066-782x2001000600004.
24. Kang DH, Ha SK. Uric acid puzzle: dual role as anti-oxidantand pro-oxidant. Electrolytes & Blood Pressure. 2014; 12(1): 1, doi: 10.5049/ebp.2014.12.1.1.
25. Stirpe F. Della Corte E. The regulation of rat liver xanthine oxidase — conversion in vitro of the enzyme activity from dehydrogenase (type D) to oxidase (type O). J Biol Chem. 1969; 244(14): 3855–3863.
26. Berry C, Hare J. Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications. The Journal of Physiology. 2004; 555(3): 589–606, doi: 10.1113/jphysiol.2003.055913.
27. Kirkham P, Barnes P. Oxidative stress in COPD. Chest. 2013; 144(1): 266–273, doi: 10.1378/chest.12-2664.
28. Halliwell B, Gutteridge J. Free radicals in biology and medicine. 2015, doi: 10.1093/acprof:oso/9780198717478.001.0001.
29. MacNee W. Oxidants and COPD. Current Drug Target — Inflammation & Allergy. 2005; 4(6): 627–641, doi: 10.2174/156801005774912815.
30. Lipovec NC, Beijers R, Borst Bv, *et al.* The prevalence of metabolic syndrome in chronic obstructive pulmonary disease: a systematic review. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2016; 13(3): 399–406, doi: 10.3109/15412555.2016.1140732.
31. Adnan E, Rahman I, Faridin HP. Relationship between insulin resistance, metabolic syndrome components and serum uric acid. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2019; 13(3): 2158–2162, doi: 10.1016/j.dsx.2019.04.001.

Rita Georges Nohra[1], Rola Bou Serhal[2], Hala Sacre[3], Pascale Salameh[3, 4], Monique Rothan-Tondeur[1]

[1]Nursing Sciences Research Chair, Laboratory Educations and Health Practices, Université Sorbonne Paris Nord, Bobigny, France
[2]Clinical Research Center, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon
[3]National Institute of Public Health, Clinical Epidemiology adn Toxycology (INSPECT-LB), Beirut, Lebanon
[4]Faculty of Pharmacy, Faculty of Medicine, Lebanese University, Hadath, Lebanon

Effective components of self-management programs for chronic obstructive pulmonary disease patients: scoping review

Abstract

Introduction: To date, little guidance is available to support the development of effective programs for improving self-management in chronic obstructive pulmonary disease (COPD) patients. Yet, given the global burden of this disease, it seems important to identify the components of a self-management program that are effective in terms of health outcomes for COPD patients.

Objectives: This review aims to identify effective elements of a self-management program for COPD patients, the ones that may impact quality of life, emergency visits, and rehospitalization rates.

Material and methods: A systematic literature search of three databases (Medline, Cochrane, and CINHAL) was conducted to identify studies on self-management of COPD, with three limiting parameters: published in twelve years prior to November 2019, in English or French, and including patients over 40 years old. Prisma was used to guide the work process.

Results: The search yielded 361 studies from the three electronic databases by applying limiting criteria, and after removing duplicates. Sixty-five articles were identified as relevant based on their titles and abstracts. However, 16 documents were retained after full reading. The analysis of the included articles identified 4 components in self-management programs for COPD patients: initiation stage of the intervention, educational sessions, support and monitoring methods.

Conclusions: Although the combination of self-management program initiation, educational sessions, support and monitoring methods were effective, further research is needed to identify the components that have better impact on COPD patients' skills and quality of life.

Key words: COPD, self-care, self-management, program components

Adv Respir Med. 2020; 88: 223–232

Introduction

The burden of non-communicable diseases is increasing rapidly worldwide, and by 2020, they would account for nearly three-quarters of global deaths [1]. The World Health Organization (WHO) has called on all countries to provide interventions, including self-care interventions, to address this global epidemic [2].

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide [2]. Although the WHO had predicted in 2004 that COPD would become the third leading cause of death in the world by 2030, this threshold has already been reached in 2010 [3]. Moreover, COPD is associated with a significant economic burden [4], and exacerbations account for most of the costs associated with the disease [5].

Complete recovery from the disease is currently not achievable and as it progresses, patients experience a reduced breathing capacity and disability to carry out activities of daily living, thus deterioration in their quality of life [6]. Therefore, researchers are increasingly interested in maintaining the quality of life of COPD patients [7]. Nonpharmacological interventions, such as smoking cessation, and self-management

Address for correspondence: Rita Georges Nohra, Nursing Sciences Research Chair, Laboratory Educations and Health Practices, Université Sorbonne Paris Nord, Bobigny, France; e-mail: ritag.nohra@gmail.com
DOI: 10.5603/ARM.2020.0117
Received: 06.03.2020

ISSN 2451–4934

are considered an integral component of the chronic care model of COPD management [2]. COPD self-management interventions was defined as structured but personalized and often multicomponent interventions, with the goal of motivating, engaging and helping patients to positively adapt their behavior(s) and develop their skills to better manage their disease [8]. Better self-management could improve the quality of life and reduce emergency visits and hospital admissions for COPD patients [9]. This study aims to identify effective components of a self-management program for COPD patients, the ones that may affect quality of life, emergency visits, and rehospitalization rates.

Material and methods

Study type

This scoping review was carried out using the following databases: Cochrane, Medline and CINHAL. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was applied to guide the work process [10].

Eligibility criteria for the work

The inclusion criteria were based on the "PICOTS" criteria [11, 12].

— Population: Adult COPD patients aged 40 years and over, with no restriction on the stage of the disease;
— Intervention: Self-management program for non-hospitalized COPD patients;
— Comparisons: No comparator defined;
— Outcomes: At least one of the following: impact on the quality of life, rehospitalization rate and emergency visits;
— Type of the study: Quantitative (RCT, NRCT) and all types of qualitative studies;
— Setting: Outside.

In addition, the studies included had to be in English or French and published in the twelve years prior to November 2019.

The summaries were read, as was the full article when in doubt about the inclusion criteria.

In the first analysis, the studies that met the inclusion criteria and generated new insights into the components of a COPD self-management program in patients over 40 years were selected as the prevalence of COPD is rare under the age of 40 (0.1%) [13].

The studies not meeting the inclusion criteria, not including COPD patients or study protocols were excluded.

Source of information

The Medline, Cochrane and CINHAL databases were queried, and the reference lists of the included studies analyzed.

Research strategy

A literature search strategy was developed using the Medical Subject Headings (MeSH) thesaurus and key words related to COPD. After the strategy was finalized, it was adapted to the syntax of other databases. The research in the three databases was conducted with the same search and limiting parameters.

Search equation

The search was based on the use of Medical Subject Headings (MeSH terms). That included: Pulmonary Disease, Chronic Obstructive, Lung Disease, Obstructive, Self-Care, Self-Management, Disease Management, Program Evaluation, and Program Development.

The research equation used was: ["program evaluation" (MeSH Terms) OR "program development" [MeSH Terms)] AND ["self-care" (MeSH Terms) OR "self-management" (MeSH Terms)] AND "pulmonary disease, chronic obstructive" (MeSH Terms) AND ["2007/01/01" (PDAT): "2019/12/31" (PDAT)] .

Selection of literature

The study selection process involved several essential steps based on the PRISMA 2009 model [10]. A first screening took into consideration the title; a second identification was carried out on the basis of the abstract of each bibliographic reference retained by the documentary research to eliminate the publications not in the scope of the present study. Finally, the selection of the studies to be included relied on the full text, by applying the eligibility criteria.

Two reviewers independently reanalyzed the titles and abstracts generated by the research equation, then reviewed the full-text reports and decided whether they met the inclusion criteria. The references of included studies were also screened and checked for eligibility. Any disagreements were resolved by discussion between the two reviewers.

Data extraction

The information extracted was as follows: topic of research, publication year, country of the study and participants' characteristics (age,

Table 1. Analysis criteria of retained articles*

Sections	Number	Control criteria	Yes	No
		Introduction		
Objectives	1	The goals and objectives of the study are clearly reported		
Methods				
Eligibility Criteria	2a	An adequate description of the sample and the methods by which the sample has been identified and recruited is present		
	2b	The intervention is specific to COPD patient		
Source of information	3a	The methods used to collect data are described		
	3b	The study used appropriate data collection methods to help understand which components of the self-management program has a positive impact on the expertise of COPD patients		
Process	4a	The intervention process is indicated		
	4b	The components of self-management programs are clearly described		
		Results		
Data	5a	The results are consistent with the objective of the study		
	5b	Results specific to each action of the self-management program are present		
		Discussion		
Summary of results	6a	An adequate description of the methods used to analyze the data is present		
	6b	The study used appropriate methods to ensure that the data analysis is based on the specific components of a self-management program for COPD patients		
		Limitations		
Risk of bias inherent in each of the studies	7	Possible biases or limitations are assessed including biases in outcome, study methodology, or both		
		Total	7 sections 12 sub sections	

*We evaluated the quality of articles as follows: **A.** High quality if it meets 10 or more criteria; **B.** Average quality if it meets 5–10 criteria; **C.** Low quality if it meets fewer than 5 criteria

severity of illness and comorbidities). Information on the features of intervention quality of life rehospitalization rates, and visits to emergency services was also retrieved.

Data analysis

The principal investigator analyzed the content of each article according to a grid designed to examine the intrinsic qualities of the different parts, based on the PRISMA criteria.

The quality of items was evaluated as follows (Table 1, 2):

— High quality if it meets 10 or more criteria;
— Average quality if it meets 5–10 criteria;
— Low quality if it meets less than 5 criteria.

Results

This scoping review aimed to summarize the different components of a self-management program that positively impact the quality of life of patients with COPD. Such information is essential to the design of effective and specific program for this population.

The search yielded 361 articles from the three electronic databases by applying limiting criteria. Of those, 159 articles were excluded based on the title, and 76 based on the abstract and 53 duplicated articles. The remaining 65 papers were identified as relevant taking into account both the title and the abstract but only 16 were retained after reading the full text (Figure 1).

Table 2. Quality score of retained articles

Articles sections	Sanchez-Nieto *et al.* 2016 [14]	Turner A. *et al.* 2014 [24]	Cosgrove D. *et al.* 2013 [27]	Apps D. L. *et al.* 2013 [25]	Taylor S.J. *et al.* 2012 [9]	Wood-Baker R. *et al.* 2012 [19]	Chuang C. *et al.* 2011 [15]	Efraimsson O.E. *et al.* 2008 [23]	Bischoff W.M.A.E *et al.* 2012 [28]	Paneroni M. *et al.* 2013 [26]	Hamar B. *et al.* 2010 [16]	Lomundal K.B. *et al.* 2007 [17]	Khdour M.R. *et al.* 2009 [18]	Oancea C. *et al.* 2015 [20]	Yu S. *et al.* 2014 [22]	Rose L. *et al.* 2018 [21]
Objectives	1	1	1	1	1	—	1	1	1	1	1	1	1	1	1	1
Eligibility criteria	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2
Source of information	—	1	2	2	1	1	—	1	1	1	1	1	1	1	1	1
Approach	2	2	2	2	2	1	1	2	1	1	—	2	2	1	1	1
Data	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1
Summary of results	1	1	2	1	1	1	—	1	1	1	—	1	1	1	1	1
Risk of bias inherent in each of studies	1	1	—	—	1	1	—	1	1	1	1	1	1	1	1	1
Total	8	9	11	9	9	7	4	9	8	8	6	9	9	8	8	8
Mode	8															
Median	8															
Mean	8.13															
Variance	2.4															
Standard deviation	1.54															

The 16 included studies were published between 2007 and 2019. Five studies were undertaken in the United Kingdom, and one each in the United States, Australia, Canada, Sweden, Italy, Germany, Norwey, Romania, Spain, Netherlands and China. Two studies were qualitative, two were pilot randomized controlled trials, six were observationad and six experimental studies (Table 3). Of the 16 programs analyzed, 8 had a follow-up of 1 year [14– 21], 4 had a follow-up of 6 months [9, 22–24], and the remaining had a follow-up of 6 weeks [25], 10 months [26], 15 months [27] and 2 years [28]. Only one study excluded patients with very severe COPD [28].

Synthesis of the results

After reading and summarizing the articles, eight intervention components were identified (Table 4): individualized initiation session, group education session, individual training, phone calls, action plan, educational material, daily diary, and text messaging.

These components were grouped into 4 modalities. The first modality, **"the initiation stage of the intervention"**, is characterized by individualized initiation sessions. The second modality, **"the educational sessions"**, includes individual or group education sessions with the caregiver. The third modality, **"the support material"** encompasses the action plan, educational materials, and text messaging. The fourth modality **"the monitoring method"** uses a daily diary and, in some cases, telephone calls that are also used as a follow-up method, among other ways of support, and sometimes as a training tool.

- Modality I: Initiation into the self-management program: Individualized initiation sessions;
- Modality II: Educational sessions: Group education sessions, individual training, phone calls [16];
- Modality III: Support method: action plan, educational materials, text messaging and telephone calls [17, 21, 25, 28];
- Modality IV: Monitoring method: diary and telephone calls [15, 18, 19, 22].

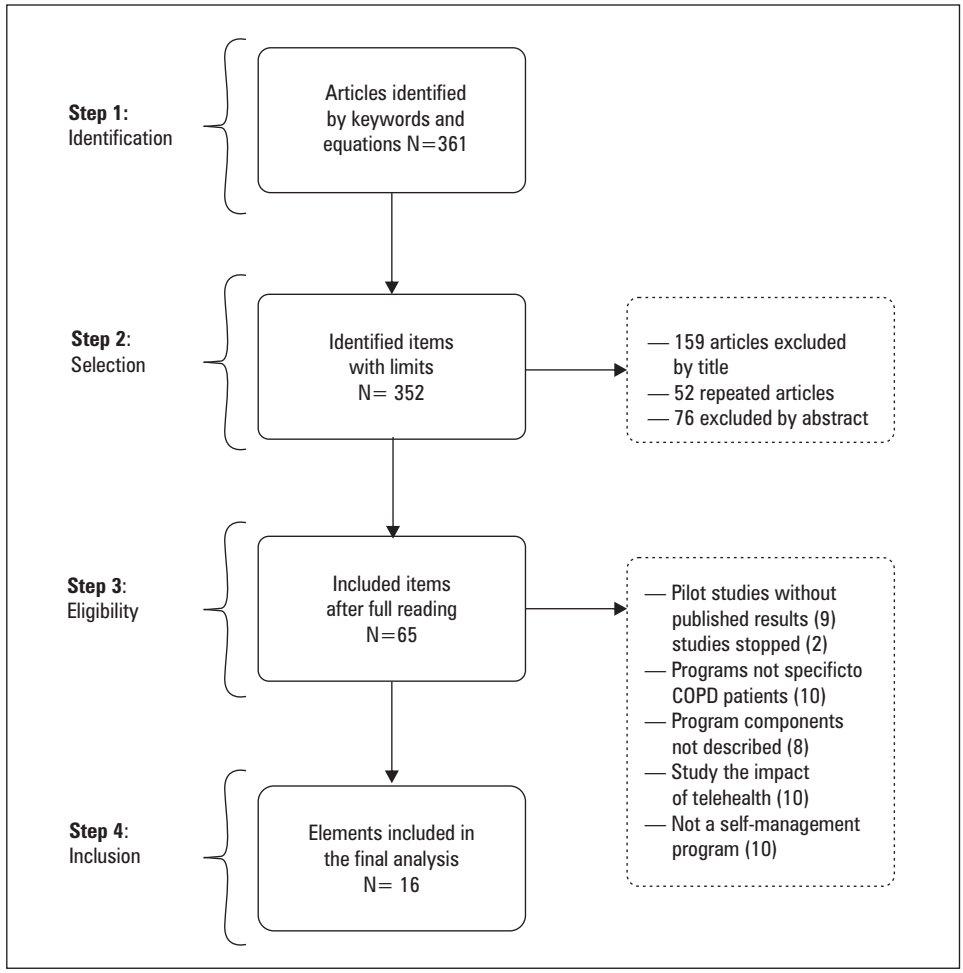


Figure 1. Flowchart for article selection strategy

Modality I: Initiation into the self-management program

Of the 16 selected studies, 5 included the initiation into the self-management program [15, 18, 19, 21, 25]. In 2009, a preliminary assessment of patients participating in the intervention was conducted to determine individual needs [18]. It included data on knowledge of the disease, smoking status, adherence to medication, self-efficacy in managing breathing difficulty, exercise and diet. In another study conducted in 2011 [15], the intervention group received a first face-to-face nursing assessment, during which a spirometry test and a health assessment were performed. At a later stage, an individualized one-hour initiation was conducted for participants in the self-management program; the discussion helped to determine participants' willingness to start a self-management program, explore immediate educational needs, and set objectives [25]. Similarly, in another study, mentors visited the patients at home one week after they were recruited to perform a general assessment and discuss the main clinical or social problems and set a medium-term goal [19].

Studies showed a decrease in hospital admissions [15, 18, 19], emergency visits [15, 18] and improvement in quality of life [18, 19, 25].

Therefore, the focus and the importance of this first step is to assess the patients' health status, explore their motivation to participate in the program, identify educational difficulties, and finally, set goals. In other words, the purpose of this first step is to adapt and individualize the interventions to each patient.

Modality II: Educational sessions

In all 16 studies that adopted Modality II, educational sessions were delivered by health professionals: five of the interventions were led by nurses [15, 16, 19, 23, 28], four were performed by a multidisciplinary team including nurses [1, 14, 17, 26], one intervention was conducted by a trained tutor with COPD [9], and others were

Table 3. Type of study

Type of study		Articles	Number of participants	Average age	Stage of COPD
Quantitative	Experimental (randomized/ non-randomized)	Chuang C. *et al.* 2011 (United States)	Control (C) = 141 Intervention (I) = 141	75	NA
Qualitative	Pilot	Taylor JC S. *et al.* 2012 (United Kingdom)	C = 38 I = 78	69.5 (9.8)	Moderate to severe (number not available)
Qualitative	Pilot	Apps D. L. *et al.* 2013 (United Kingdom)	20 patient	68	NA
Qualitative	Pilot	Cosgrove D. *et al.* 2013 (United Kingdom)	53 patient	65 (10)	Moderate (II) = 21 Severe (III) = 19 Very severe (IV) = 8
Quantitative	Observational	Oancea C. *et al.* 2015 (Romania)	C = 24 I = 52	C = 62.7 (4.9) I = 61.2 (5.7)	NA
Quantitative	Observational	Lomundal K.B. *et al.* 2007 (Norway)	30 self-management 30 pulmonary rehabilitation	67.2 self-management 62.8 pulmonary rehabilitation	NA
Quantitative	Experimental (randomized/ non-randomized)	Wood-Baker R. *et al.* 2012 (Australia)	C = 51 I = 55	69.1 (9.7)	II = 17 III = 49 IV = 39
Quantitative	Experimental (randomized/ non-randomized)	Turner A. *et al.* 2014 (United Kingdom)	18 patients	NA	NA
Quantitative	Experimental (randomized/ non-randomized)	Efraimsson O. E. *et al.* 2008 (Sweden)	C = 26 I = 26	C = 67 I = 66	I = 5 GI/5 GC II = 9 GI/9 GC III = 6 GI/ 5GC IV = 6 GI/7GC
Quantitative	Experimental (randomized/ non-randomized)	Bischoff W.M.A.E *et al.* 2012 (Netherlands)	Self-management = 55 Routine monitoring = 55 Usual care = 55	Self-management = 65.5 (11.5) Routine monitoring = 65.8 (8.3) Usual care = 63.5 (10.3)	Patients with very severe COPD were excluded (number not available)
Quantitative	Experimental (randomized/ non-randomized)	Paneroni M. *et al.* 2013. (Italy)	158	71.1 (8.3)	I = 3.4% II = 29.7% III = 21.4% IV = 45.5%
Quantitative	Experimental (randomized/ non-randomized)	Hamar B. *et al.* 2010 (German)	C = 5,668 I = 17,319	I = 71.2 C = 72.5	(3 less severe — 1 more severe) 3 ≥ 29.7 I 41 C 2 ≥ 46.4 I 37.1 C 1 ≥ 24 I 21.9 C
Quantitative	Experimental (randomized/ non-randomized)	Khdour M.R. *et al.* 2009 (United Kingdom)	C = 87 I = 86	C = 67.3 (9.2) I = 65.63 (10.1)	C ≥ I = 11 II = 34 III = 27 I ≥ I = 13 II = 37 III = 21
Quantitative	Experimental (randomized/ non-randomized)	Sanchez-Nieto *et al.* 2016 (Spain)	C = 38 I = 47	C = 67.6 ±6.9 I = 68.4±7.3	IV ≥ C = 71% I = 61.7% II-III ≥ C = 10.5% I = 6.3%
Quantitative	Experimental (randomized/ non-randomized)	Yu S. *et al.* 2014 (China)	C = 42 I = 42	68.29 (7.09)	NA
Quantitative	Experimental (randomized/ non-randomized)	Rose L. *et al.* 2018 (Canada)	C = 191 I = 207	71 (9.5)	Moderate to severe (number not available)

COPD — chronic obstructive pulmonary disease; NA — not available

Table 4. Intervention components

Article modality	Qualitative	Pilot	Quantitative														
	Apps D. L. *et al.* 2013 [25]	Cosgrove D. *et al.* 2013 [27]	Taylor JC S. *et al.* 2012 [9]	Chuang C. *et al.* 2011 [15]	Sanchez-Nieto *et al.* 2016 [14]	Turner A. *et al.* 2014 [24]	Wood-Baker R. *et al.* 2012 [19]	Efraimsson O. E. *et al.* 2008 [23]	Bischoff W.M.A.E *et al.* 2012 [28]	Paneroni M. *et al.* 2013 [26]	Hamar B. *et al.* 2010 [16]	Lomundal K.B. *et al.* 2007 [17]	Khdour M.R. *et al.* 2009 [18]	Oancea C. *et al.* 2015 [20]	Yu S. *et al.* 2014 [22]	Rose L. *et al.* 2018 [21]	Total
Individualized initiation session	×			×			×						×			×	5
Group education session		×	×		×	×			×	×		×		×			8
Individual training					×			×					×		×		4
Phone calls	×			×			×		×		×	×	×		×	×	9
Action plan	×	×			×		×		×			×	×			×	8
Educational material	×			×					×	×	×	×	×		×		8
Daily diary	×						×								×		3
Text messaging															×		1

done by a physician [20], a pharmacist [18], or a health professional whose discipline was not specified [21, 22, 25, 27].

Components of educational sessions

The intervention programs analyzed were either group education sessions or one-on-one training sessions. The content of the sessions varied and only one study included both a self-management program designed to provide one-on-one training in inhalation techniques and a group education session [14]. Other researchers examined the effect of programs with individual training sessions [18, 21, 22, 23]. In two studies, patients in the intervention group received education emphasizing self-care capacity, and the education focused on how to support the individuals based on their unique needs and coping skills [21, 23]. In another study, patients were individually educated by a clinical pharmacist, their prescribed medications, the importance of adherence, the inhaler technique and the management of COPD symptoms [18]. In the fourth study, the subjects were trained individually on how to use inhalation devices and maintain the appropriate position, in addition to training on breathing techniques [22].

In summary, the content of the individual training was mainly focused on: anatomy and physiology of the respiratory tract and the effects of COPD, respiration techniques, physical activity, compliance, and other educational topics, such as smoking cessation and dietary counseling.

One of those studies [21] did not result in differences in terms of the quality of life, reduction in frequency of emergency department visits or hospital admissions but contributed to a reduction in mortality of almost half, compared with the usual care group. This intervention did not include a respiratory rehabilitation or formal exercise program.

Finally, one study adopting the group education session showed that a multidisciplinary educational program for patients with COPD is feasible and effective in improving knowledge about disease management [26]. The results from this study also showed that the patients most likely to benefit from education are those with high compliance, low comorbidities, and at least minimal knowledge of the disease and related problems.

Follow-up time

Taylor's study showed that there was no difference between the intervention and control

groups at 2 months' follow-up, but at 6 months, differences appeared in favor of the intervention group with regard to levels of self-reported exercise and quality of life [9]. In Turner's study that used group education sessions, health status and health-related quality of life improved significantly 6 months after program completion [24]. Similarly, in the Lomundal study, participants in the self-management program made a statistically and clinically significant improvement in health-related quality of life (HRQOL) that was maintained over the last six months of the program and during the following year [17]. On the other hand and with respect to the key findings of the Oancea study, the positive effects were observed during six months but no difference between the groups was recorded after this period [20]. Following these results, the training proposed in this study should be repeated once every 6 months to maintain the positive medical effect.

In the 24-month Bischoff study, neither self-management nor routine monitoring showed significant benefits over usual care in terms of the quality of life, frequency of exacerbation or self-efficacy in patients with COPD. In contrast, compared to usual care, patients in the self-management group appeared to be more able to take appropriate measures to manage their exacerbations [28].

Modality III: Support methods

The supportive methods included action plans, educational materials, text messaging and phone calls.

Action plans

Action plans has to do with the exacerbation phase of COPD. In Sanchez-Nieto's study, the action plan consisted of a folder containing written material with four types of colored sheets [14]. The exacerbation sheet explained the symptoms of bronchial infection for which patients had to start taking antibiotics and oral glucocorticoids. Apps *et al*. used a sputum color chart describing normal and flare-up symptoms, and participants were encouraged to follow the advice on the action plan if they feared an outbreak of symptoms [25]. In the other research work, the exacerbation action plan was individualized, covering early recognition and rapid action during an exacerbation [28]. Actions included increasing the use of bronchodilators, initiating permanent prescriptions for prednisone, antibiotics, or both, and contacting the nurse or the general practitioner. In Roses's study, an individualized action plan was distributed to both intervention and usual care [21], and it was the only study from all 8 that included action plans in their interventions [14, 17–19, 25, 27, 28] that did not reveal an impact on the quality of life, emergency department visits or hospital admissions.

Educational materials, text messaging, and phone calls

All 8 studies that had adopted the educational material used written information [15–18, 22, 25, 26, 28] in form of e-mails [16], manuals [25], papers [28], booklets [17], and brochure [18, 22, 26]. Several support methods were used: interactive tables and tasks to be completed by the participants to make sure knowledge and skills are well acquired (25), summary of all lectures at the end of the course [17], and weekly standardized text message after discharge from the hospital [22]. In all those 8 studies [15–18, 22, 25, 26, 28], the results showed that a structured self-management education program, including educational materials provided an effective method for the management of patients with COPD.

Modality IV: Monitoring methods

The monitoring methods consisted of a daily diary and phone calls. A daily diary was used in 3 studies and participants had to record their walking progress [25], shortness of breath, coughing, spitting, well-being, physical activity, and the use of relieving medications [19, 22]. Those interventions improved compliance, reduced the need for hospital care and improved some aspects of participants' quality of life. Moreover, 5 studies relied on phone calls to followup on patients [15, 18, 19, 21, 22], which gained health benefits through self-management.

Discussion

Among the 16 studies analyzed, 2 were qualitative and tested the effectiveness of a self-management program from both patients' and health professionals' perspectives, and 2 were pilot studies and examined the feasibility, effectiveness and cost-effectiveness of a self-management support program for COPD patients. The remaining studies were randomized or non-randomized and assessed the effect of a self-management program on skills, quality of life, emergency room visits, and hospitalization rates in patients with COPD.

In this paper, we were able to identify studies that assessed different methods of self-management in COPD patients.

Characteristics of participants

Only one study excluded patients with very severe COPD (28); a meta-analysis later demonstrated the effectiveness of self-management programs in patients with severe COPD, while no significant effects were observed in studies that enrolled individuals with moderate symptoms [29].

Duration of follow-up

Of the 16 programs analyzed, 8 had a follow-up of 1 year [14–21], 4 had a follow-up of 6 months [9, 22–24], and the remaining had a follow-up of 6 weeks [25], 10 months [26], 15 months [27] and 2 years [28].

Researchers suggested that an improvement in the quality of life may take a long time, from 6 to 12 months [30], and that a longer duration of self-management interventions correlates with a reduced number of hospitalizations in patients with COPD [31].

Action

Our research aims to identify the components that have proven effective for a specific self-management program for patients with COPD. In analyzing the articles and their results, the interventions varied but had points in common:

— The initiation intervention sessions adopted in several studies can have a positive effect because they tested the patients' motivation for the intervention, a factor that could contribute to a better outcome of self-management programs [17];
— Action plans engaged patients in the management of their disease;
— Educational materials helped patients in the self-management process;
— The phone calls had intended to motivate, engage, and accompany patients throughout the intervention.

The results of the studies analyzed confirmed that learning is not achieved by a single action or method and requires time. The learning modalities must be varied to consolidate the acquired knowledge in different domains: cognitive, psychomotor, and emotional (including social), in addition to the knowledge acquired on the actions to be undertaken. However, the methods used to collect and analyze data, as presented in the analyzed studies, did not help us understand what components of the self-management program had a positive impact on the expertise of patients with COPD, and this may be the greatest limitation in our paper. On the other hand, the results of another study showed that the patients most likely to benefit from educational interventions are those with high compliance, low comorbidities, and at least minimal knowledge of the disease and related problems [26]. Other studies [9, 22] showed that the effect of self-management education was not evident at three months but gradually increased over time and was apparent at six months. Some researchers have even suggested that training should be repeated once every 6 months to maintain the positive medical effect [20].

Similarly, Jonkaman *et al*. recommend long-lasting self-management strategies rather than brief interventions [31]. Moreover, Newham *et al*. showed a significant improvement in the quality of life in patients with COPD in both individual and group-based self-management programs, and positive effects of multiple-session interventions versus single-session self-management programs [29]. This meta-analysis also showed that self-management programs targeting mental health and physical activity were more effective than those focused solely on symptom management [29].

Conclusions

To date, little guidance is available to support the development of effective programs for improving self-management in COPD patients. It seems obvious that interventions involving only one component, such as written action plans or training sessions, do not produce the desired effects. In this scoping review, 4 components described in 15 studies were identified as having a positive impact on patients' skills and knowledge, quality of life, hospitalization rates and emergency room visits: initiation into the self-management program, educational sessions, support methods and monitoring methods.

However, further research is needed to identify the components that have the best cost/benefit ratios and have a greater impact on patients' skills and lifestyle.

Conflict of interest

The authors report no conflicts of interest in this work.

References:

1. World Health Organization. The World Health Report 1998: Life in the 21st century. WHO, Geneva 1998: 241.
2. GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD [Internet]. Global Initiative for Chronic Obstructive Lung Disease — GOLD. Available at: https://

goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. [Last accessed at: 05.06.2020].
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet Lond Engl. 2012; 380(9859): 2095–2128.
4. WHO. OMS. Charge de morbidité due à la bronchopneumopathie chronique obstructive (BPCO). 2018 . Available from: www.who.int/respiratory/copd/burden/fr/. [Last accessed at: 05.06.2020].
5. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006; 3(11): e442, doi: 10.1371/journal.pmed.0030442, indexed in Pubmed: 17132052.
6. Alcazar B, de Lucas P, Soriano JB, et al. The evaluation of a remote support program on quality of life and evolution of disease in COPD patients with frequent exacerbations. BMC Pulm Med. 2016; 16(1): 140, doi: 10.1186/s12890-016-0304-3, indexed in Pubmed: 27821164.
7. Jonkman NH, Westland H, Trappenburg JCa, et al. Do self-management interventions in COPD patients work and which patients benefit most? An individual patient data meta-analysis. Int J Chron Obstruct Pulmon Dis. 2016; 11: 2063–2074, doi: 10.2147/COPD.S107884, indexed in Pubmed: 27621612.
8. Gregersen TL, Green A, Frausing E, et al. Do telemedical interventions improve quality of life in patients with COPD? A systematic review. Int J Chron Obstruct Pulmon Dis. 2016; 11: 809–822, doi: 10.2147/COPD.S96079, indexed in Pubmed: 27143872.
9. Taylor SJC, Sohanpal R, Bremner SA, et al. Self-management support for moderate-to-severe chronic obstructive pulmonary disease: a pilot randomised controlled trial. Br J Gen Pract. 2012; 62(603): e687–e695, doi: 10.3399/bjgp12X656829, indexed in Pubmed: 23265228.
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009; 6(7): e1000100, doi: 10.1371/journal.pmed.1000100, indexed in Pubmed: 19621070.
11. Haynes RB. Haynes RB. Clinical Epidemiology: How to Do Clinical Practice Research. Lippincott Williams & Wilkins 2012: 516.
12. Riva JJ, Malik KMP, Burnie SJ, et al. What is your research question? An introduction to the PICOT format for clinicians. J Can Chiropr Assoc. 2012; 56(3): 167–171, indexed in Pubmed: 22997465.
13. Khelafi R, Aissanou A, Tarsift S, et al. Épidémiologie de la bronchopneumopathie chronique obstructive dans la wilaya d'Alger. Revue des Maladies Respiratoires. 2011; 28(1): 32–40, doi: 10.1016/j.rmr.2010.06.026.
14. Sánchez-Nieto JM, Andújar-Espinosa R, Bernabeu-Mora R, et al. Efficacy of a self-management plan in exacerbations for patients with advanced COPD. Int J Chron Obstruct Pulmon Dis. 2016; 11: 1939–1947, doi: 10.2147/COPD.S104728, indexed in Pubmed: 27574418.
15. Chuang C, Levine SH, Rich J. Enhancing cost-effective care with a patient-centric chronic obstructive pulmonary disease program. Popul Health Manag. 2011; 14(3): 133–136, doi: 10.1089/pop.2010.0015, indexed in Pubmed: 21214417.
16. Hamar B, Wells A, Gandy W, et al. The impact of a proactive chronic care management program on hospital admission rates in a German health insurance society. Popul Health Manag. 2010; 13(6): 339–345, doi: 10.1089/pop.2010.0032, indexed in Pubmed: 21091374.
17. Lomundal BK, Steinsbekk A. Observational studies of a one year self-management program and a two year pulmonary rehabilitation program in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2007; 2(4): 617–624.
18. Khdour MR, Kidney JC, Smyth BM, et al. Clinical pharmacy-led disease and medicine management programme for patients with COPD. Br J Clin Pharmacol. 2009; 68(4): 588–598, doi: 10.1111/j.1365-2125.2009.03493.x, indexed in Pubmed: 19843062.
19. Wood-Baker R, Reid D, Robinson A, et al. Clinical trial of community nurse mentoring to improve self-management in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2012; 7: 407–413, doi: 10.2147/COPD.S32220, indexed in Pubmed: 22848153.
20. Oancea C, Fira-Mladinescu O, Timar B, et al. Impact of medical education program on COPD patients: a cohort prospective study. Wien Klin Wochenschr. 2015; 127(9-10): 388–393, doi: 10.1007/s00508-015-0712-z, indexed in Pubmed: 25851721.
21. Rose L, Istanboulian L, Carriere L, et al. Program of integrated care for patients with chronic obstructive pulmonary disease and multiple comorbidities (PIC COPD): a randomised controlled trial. Eur Respir J. 2018; 51(1), doi: 10.1183/13993003.01567-2017, indexed in Pubmed: 29326330.
22. Yu SH, Guo AM, Zhang XJ. Effects of self-management education on quality of life of patients with chronic obstructive pulmonary disease. International Journal of Nursing Sciences. 2014; 1(1): 53–57, doi: 10.1016/j.ijnss.2014.02.014.
23. Efraimsson EO, Hillervik C, Ehrenberg A. Effects of COPD self-care management education at a nurse-led primary health care clinic. Scand J Caring Sci. 2008; 22(2): 178–185, doi: 10.1111/j.1471-6712.2007.00510.x, indexed in Pubmed: 18489687.
24. Turner A, Anderson JK, Wallace LM, et al. An evaluation of a self-management program for patients with long-term conditions. Patient Educ Couns. 2015; 98(2): 213–219, doi: 10.1016/j.pec.2014.08.022, indexed in Pubmed: 25441096.
25. Apps LD, Mitchell KE, Harrison SL, et al. The development and pilot testing of the self-management programme of activity, coping and education for chronic obstructive pulmonary disease (SPACE for COPD). Int J Chron Obstruct Pulmon Dis. 2013; 8: 317–327, doi: 10.2147/COPD.S40414, indexed in Pubmed: 23874093.
26. Paneroni M, Clini E, Crisafulli E, et al. Feasibility and effectiveness of an educational program in Italian COPD patients undergoing rehabilitation. Respir Care. 2013; 58(2): 327–333, doi: 10.4187/respcare.01697, indexed in Pubmed: 22782190.
27. Cosgrove D, Macmahon J, Bourbeau J, et al. Facilitating education in pulmonary rehabilitation using the living well with COPD programme for pulmonary rehabilitation: a process evaluation. BMC Pulm Med. 2013; 13: 50, doi: 10.1186/1471-2466-13-50, indexed in Pubmed: 23915179.
28. Bischoff EW, Akkermans R, Bourbeau J, et al. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. BMJ. 2012; 345: e7642, doi: 10.1136/bmj.e7642, indexed in Pubmed: 23190905.
29. Newham JJ, Presseau J, Heslop-Marshall K, et al. Features of self-management interventions for people with COPD associated with improved health-related quality of life and reduced emergency department visits: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2017; 12: 1705–1720, doi: 10.2147/COPD.S133317, indexed in Pubmed: 28652723.
30. Jonkman NH, Schuurmans MJ, Groenwold RHH, et al. Identifying components of self-management interventions that improve health-related quality of life in chronically ill patients: Systematic review and meta-regression analysis. Patient Educ Couns. 2016; 99(7): 1087–1098, doi: 10.1016/j.pec.2016.01.022, indexed in Pubmed: 26856778.
31. Jonkman NH, Westland H, Trappenburg JCA, et al. Characteristics of effective self-management interventions in patients with COPD: individual patient data meta-analysis. Eur Respir J. 2016; 48(1): 55–68, doi: 10.1183/13993003.01860-2015, indexed in Pubmed: 27126694.

Gil Gonçalves[1], Haitham Saeed[2], Mohamed E Abdelrahim[2], Hadeer S Harb[2], Yasmin M Madney[2], Kevin Eng[3], Habib MR Karim[4], Mohamad El-Khatib[5], Bushra Mina[6], Szymon Skoczyński[7], Irena Sarc[8], Vânia Caldeira[9], Sara M Cabral[1], Bruno Cabrita[10], Miguel Guia[11], Jun Duan[12], Igor Barjaktarevic[3], Giuseppe Fiorentino[13], Edoardo Piervincenzi[14], Güniz Köksal[15], Sibel O Sarin[16], Peter J Papadakos[17], Benan Bayrakci[18], Vijay Hadda[19], Gerhard Laier-Groeneveld[20], Karen EA Burns[21], Raffaele Scala[22], Andres C Alcaraz[23], Antonio M Esquinas[23]

[1]Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[2]Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
[3]Division of Pulmonary and Critical Care, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, United States
[4]Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India
[5]Department of Anesthesiology, American University of Beirut-Medical Center, Beirut, Lebanon
[6]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Northwell Health, Lenox Hill Hospital, New York, United States
[7]Department of Pulmonology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[8]Noninvasive Ventilation Department, University Clinic for Pulmonary and Allergic Diseases, Golnik, Slovenia
[9]Pulmonology Department, Santa Marta Hospital, Lisbon, Portugal
[10]Pulmonology Department, Pedro Hispano Hospital, Matosinhos, Portugal
[11]Pulmonology Department, Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal
[12]Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[13]Respiratory Unit, AO Ospedali dei Colli Monaldi, Naples, Italy
[14]Department of Anaesthesiology and Intensive Care Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[15]Department of Anaesthesiology and Reanimation, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey
[16]Internal Medicine, Istanbul Umraniye Research Hospital, Istanbul, Turkey
[17]Department of Anesthesiology, University of Rochester, Rochester, United States
[18]Pediatric Intensive Care Department, Hacettepe University, Ankara, Turkey
[19]Department of Pulmonary, Critical Care & Sleep Medicine, All India Institute of Medical Sciences, New Delhi, India
[20]Pneumology, Clinical and Home Ventilatory Support and Sleep, Schellstrasse, Bochum, Germany
[21]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
[22]Pulmonology and Respiratory Intensive Care Unit, S Donato Hospital, Arezzo, Italy
[23]Intensive Care and Noninvasive Ventilatory Unit, Hospital Morales Meseguer, Murcia, Spain

Non-invasive ventilation in patients with an altered level of consciousness. A clinical review and practical insights

Abstract

Non-invasive ventilation has gained an increasingly pivotal role in the treatment of acute hypoxemic and/or hypercapnic respiratory failure and offers multiple advantages over invasive mechanical ventilation. Some of these advantages include the preservation of airway defense mechanisms, a reduced need for sedation, and an avoidance of complications related to endotracheal intubation.

Despite its advantages, non-invasive ventilation has some contraindications that include, among them, severe encephalopathy. In this review article, the rationale, evidence, and drawbacks of the use of noninvasive ventilation in the context of hypercapnic and non-hypercapnic patients with an altered level of consciousness are analyzed.

Key words: non-invasive ventilation, altered consciousness, encephalopathy, coma

Adv Respir Med. 2020; 88: 233–244

Address for correspondence: Gil Gonçalves, Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; e-mail: bgilgoncalves@gmail.com
DOI: 10.5603/ARM.2020.0110
Received: 27.03.2020

ISSN 2451–4934

Introduction

The utility of non-invasive ventilation (NIV) has been fully proven and well documented in several categories of patients with acute respiratory failure (ARF) [1–3]. Recent ERS/ATS and ISCCM guidelines reported a high level of evidence in favor of the use of NIV in acute acidic hypercapnic respiratory failure due to a COPD exacerbation, in acute pulmonary edema, in immunosuppressed hosts, and as a facilitating tool for transitioning from invasive ventilation to spontaneous breathing [4, 5].

By preventing endotracheal intubation (ETI), NIV confers many advantages over invasive mechanical ventilation (IMV). NIV is more comfortable and does not require the use of sedation in most cases [6]. It also allows patients to continue oral nutrition. The non-invasive interface allows positive pressure to be delivered while keeping the airway patent, thus preserving natural defense mechanisms. As such, NIV reduces morbidity and mortality by avoiding many complications associated with IMV including nosocomial ventilator-associated pneumonia, sepsis, and additional infectious sequelae [7].

Although NIV is an effective treatment, there are important limitations and contraindications to its use. In 2001, the International Consensus Conference on NIV [8] recommended against its use in the setting of cardiac or respiratory arrest, hemodynamic instability, unstable cardiac arrhythmias, severe encephalopathy (Glasgow coma scale < 10), severe upper gastrointestinal bleeding, facial surgery or trauma, upper airway obstruction, and in patients who are at high risk for aspiration who are unable to protect their airway or to cooperate or clear respiratory secretions.

Most studies use the Glasgow coma scale (GCS) or the Kelly-Matthay score (KMS) to assess the level of consciousness. Although GCS is the tool which has been mostly used in the clinical setting, this 15-point scoring system in which a lower score corresponds to a lower level of consciousness was originally developed to assess and monitor changes in the level of consciousness after head trauma [9]. The 6-level KMS is a tool specifically designed to evaluate neurological alterations in patients ventilated in the intensive care unit (ICU) [10]. With the KMS, a higher score corresponds to a lower level of consciousness.

In this article, we reviewed the rationale, evidence, and pitfalls regarding use of NIV in hypercapnic and non-hypercapnic ARF in patients with an altered level of consciousness.

Material and methods

We performed a search in the PubMed National Library with the keywords “non-invasive ventilation”, “hypercapnic”, “hypoxemic”, “altered consciousness”, “encephalopathy”, and “coma”. Articles were selected according to their relevance to the topic of this review. Backward reference searching from selected articles was also performed. In addition, other articles were reviewed and included based on the authors’ judgment of their relevance. Studies were limited to the English language.

Rationale for NIV use in patients with hypercapnic ARF encephalopathy

The pathophysiology of hypercapnic encephalopathy may be explained by the acidosis of cerebrospinal fluid and brain interstitial tissue. Acute respiratory acidosis has a greater impact on cerebrospinal fluid pH than metabolic acidosis does because CO_2 crosses the blood-brain barrier easily and quickly due to its high liposolubility. Accordingly, symptoms of hypercapnic encephalopathy (i.e. cognitive defects, delirium, and coma) correlate more strongly with changes in cerebrospinal pH than with those in arterial pH and/or $PaCO_2$ [11]. Although several pulmonary and extrapulmonary factors are involved as well, it is safe to assume that by normalizing arterial pH by diminishing arterial $PaCO_2$, cerebrospinal pH can be normalized as well.

The rationale for using NIV in hypercapnic encephalopathy is based on the reduction in $PaCO_2$ levels and its advantages over IMV. Firstly, its efficacy on respiratory muscles, improvement in gas exchange, and in in-hospital mortality in patients with respiratory acidosis due to acute exacerbations of COPD with the use of NIV is comparable to that of IMV [11, 12].

Secondly, the absence of ETI and other invasive devices reduces the risk of ventilator-associated pneumonia [13].

Thirdly, the risk of gastric distension and aspiration is probably overestimated due to the physiological barriers of the upper (resting pressure between 60–139 cm H_2O) [14] and lower sphincters (resting pressure between 14–41 cm H_2O) [15]; it is uncommon to use NIV pressures higher than 30 cm H_2O, thus minimizing this risk.

Fourthly, NIV has an important role as a form of salvage therapy in frail patients with end-stage chronic respiratory failure and do-not-intubate orders, especially in cases of hypercapnic coma [16].

Finally, NIV has been shown to reduce the length of ICU and hospital stays and can lead to more effective resource utilization [17]. These important quality metrics translate into improved patient outcomes and reduced financial burden [11].

Current evidence for the use of NIV in hypercapnic ARF encephalopathy

We reviewed the published literature examining the use of NIV in patients with hypercapnic encephalopathy. Most reports showed an improvement in the GCS score within a few hours after NIV initiation (Figure 1, Table 1).

Corrado *et al.* [18] were the first to evaluate patients with hypercapnic coma of various etiologies treated with NIV (iron lung). In their study, the mean arterial pH was 7.13 ± 0.3 and $PaCO_2$ was 112 ± 21 mm Hg. Of the 150 patients analyzed, treatment was successful in 70%, ranging from 0% in patients with a GCS of 3 to 85% with a GCS of 8. Five patients had aspiration complications, but all were successfully treated without intubation. Through multivariate analysis, a GCS of ≤ 6 and age ≥ 70 years were the only variables associated with NIV failure.

In a study by Briones *et al.* [19], the effectiveness of positive pressure NIV compared to IMV was assessed in two cohorts of twelve patients each with similar baseline characteristics (GCS < 8, arterial pH < 7.25, APACHE II scores). Both groups presented to the Emergency Department with severe hypercapnia secondary to an acute exacerbation of COPD. NIV was considered successful when the following parameters were met: respiratory rate of < 24 breaths/min, heart rate of < 90 beats/min, improvement in consciousness level (GCS 15/15), and compensated arterial pH with adequate oxygen saturation at room air or with the use of a low percentage of inspired oxygen (FiO_2 < 31%). The authors identified a lower 30 day mortality (16.7% *vs* 33.3%, p = 0.01), fewer days on mechanical ventilation (3.6 ± 1.1 *vs* 5.6 ± 1.2, p = 0.006), and a shorter hospital stay (6.5 ± 1.9 *vs* 11.1 ± 4.7 days, p = 0.001) in the NIV (*vs* IMV) group, but no differences in survival at 6 months (80% *vs* 71.4%, p = 0.80). This study noted that improvements in $PaCO_2$, pH, and GCS measured at 3 hours after NIV initiation were predictive of continued success of NIV therapy. Important differences, measured and unmeasured, may have existed between the cohorts and may in part explain the observed differences in outcomes.

Diaz *et al.* [20] prospectively examined patients with hypercapnic coma (GCS ≤ 8) secondary

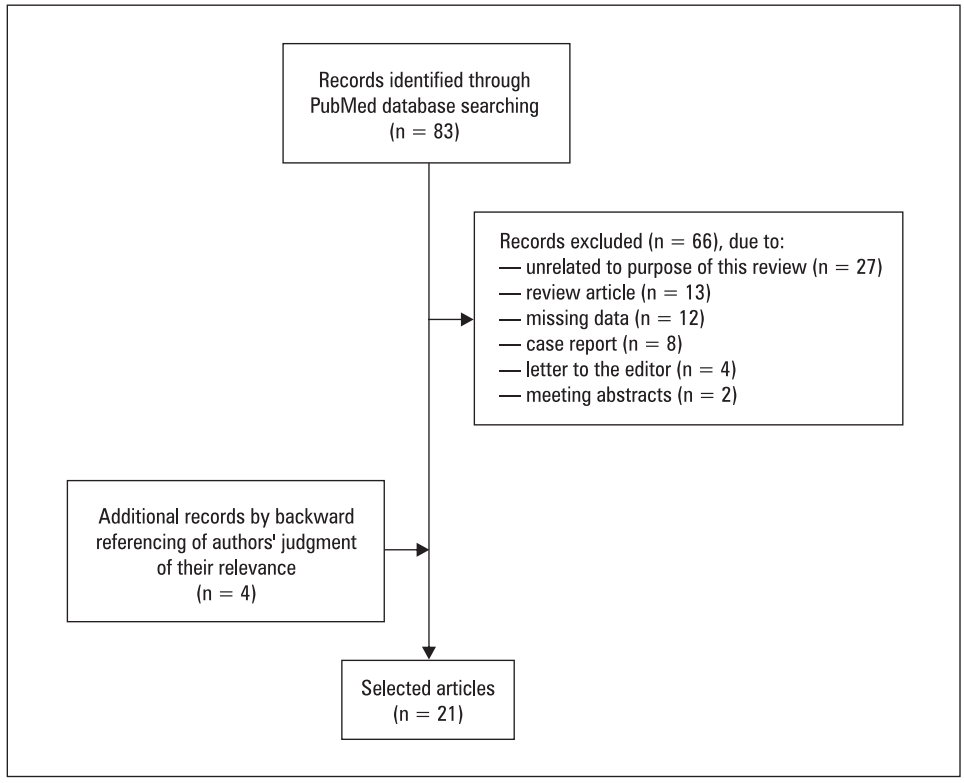


Figure 1. Flowchart of the study selection process for using non-invasive ventilation in hypercapnic acute respiratory failure encephalopathy

Table 1. Current evidence for using NIV in hypercapnic ARF encephalopathy

Author, year	Patients and aim of the study	Level of consciousness	Type of study	Results	Limitations
Lemyze 2019 [16]	86 DNI patients, NIV in hypercapnic coma *vs* NIV in hypercapnic ARF without coma	Comatose group with KMS ≥ 5	Prospective observational case-control study	70% survived to hospital discharge and half survived 6 months, with similar outcomes to controls	Selection bias could not be ruled out
Corrado 1996 [18]	150 patients, evaluate NIV (iron lung) success in hypercapnic coma	All GCS 3–8	Retrospective, uncontrolled study	NIV failure in 30%. GCS ≤ 6 had negative prognostic value	Retrospective study, limited availability of iron lung
Briones 2008 [19]	24 patients, NIV *vs* IMV in hypercapnic coma	All GCS < 8	Prospective interventional study	Less days on mechanical ventilation, days of stay and 30-day mortality	Small group of patients
Diaz 2005 [20]	958 patients, determine NIV success in hypercapnic coma *vs* NIV while awake	All GCS ≤ 8	Prospective, open, noncontrolled study	No increase in failure or mortality relative to non-comatose patients	Observational design, lack of control subjects
Scala 2007 [21]	40 patients, NIV *vs* IMV in hypercapnic encephalopathy	All KMS ≥ 3	Prospective matched case-control study	Shorter duration of mechanical ventilation and lower rate of complications. Mortality similar in both groups	Case-control design and lack of randomization
Zhu 2007 [22]	68 patients, evaluate the effectiveness and safety of NIV for severe hypercapnic encephalopathy	GCS < 10 *vs* GCS ≥ 10	Prospective case-control study	Similar results in hospital mortality and NIV success *vs* control group	Different levels of pressure support and NIV time between groups
Stefan 2015 [24]	2577 patients, compare outcomes of acute exacerbation of COPD, NIV *vs* IMV	GCS in NIV group of 15 (IQR 14–15)	Retrospective, multicenter cohort of prospectively collected data	Lower GCS was predictive of NIV failure	Patients received ventilatory support for an exacerbation of COPD and not necessarily hypercapnic acidotic exacerbation
Confalonieri 2005 [25]	1033 patients, assess the risk of NIV failure in acute exacerbations of COPD	GCS 13.2 ± 2.3	Prospective study	GCS ≤ 14 was predictive of NIV failure; main factor influencing the outcome was the pH value	Absent
Fan 2014 [26]	261 patients, measure cough strength and outcomes in acute exacerbations of COPD on NIV	GCS 14.8±0.5 in NIV success *vs* GCS 13.8 ± 2.5 in NIV failure	Prospective observational study	APACHE II, semiquantitative cough strength score and total proteins were the only predictors of NIV failure	Accuracy of cough measurements based on the clinicians' experience
Wang 2017 [27]	164 patients, compare NIV and IMV combined with a non-invasive strategy for clearing secretions in hypercapnic encephalopathy	All KMS ≥ 3	Prospective cohort study	2 hours of NIV with clearance of secretions significantly improved KMS and arterial blood gases. Hospital mortality lower in the NIV group	Not a randomized controlled trial, single-center study, hospital setting between groups differed, did not include an additional group with NIV alone

Table 1. Current evidence for using NIV in hypercapnic ARF encephalopathy [cont.]

Scala 2010 [28]	30 patients, early fiberoptic bronchoscopy during NIV *vs* IMV-based strategy in hypercapnic encephalopathy	KMS 2–4	Prospective matched case-control study	Higher complication rates in the IMV group. Similar hospital mortality, hospital lengths of stay, and duration of ventilation in the two groups	NIV application with the concomitant use of fiberoptic bronchoscopy to remove secretions should be reserved for centers where all staff members have sufficient experience
Contou 2013 [51]	242 patients admitted for hypercapnic ARF, assess the rate of NIV failure	Included RASS < 0	Observational cohort study	Altered levels of consciousness at admission had no influence on outcome	Retrospective, single unit, longstanding experience in NIV practice
Briones 2013 [52]	22 patients, BiPAP S/T *vs* AVAPS mode	All GCS < 10	Prospective interventional match-controlled study	Rapid improvement in arterial blood gases and GCS in both groups	Small number of patients
Scala 2005 [53]	153 patients requiring NIV divided into 4 groups, according to level of consciousness	Groups: KMS 1, KMS 2, KMS 3 and KMS > 3	5-year case-control study with a prospective data collection	Significant improvement in arterial blood gases and KMS in all groups after 1 to 2 hours. NIV failure and 90-day mortality significantly increased with worse KMS	No randomization
Jatoi 2019 [54]	78 patients, predict NIV success in post-TB sequelae	GCS 8.4 $\pm$ 2.1 in nonresponders *vs* GCS 9.4 $\pm$ 1.8 in responders	Single center, prospective, cohort study	Lower GCS was a significant independent predictor of NIV failure	Single unit, no IMV group control, absence of long-term mortality or morbidity
Scarpazza 2013 [55]	78 patients, assess NIV success in hypercapnic ARF	GCS 7.2 $\pm$ 1.5 in non-responsive patients *vs* GCS 9.7 $\pm$ 2.9 in respondive patients	Single center, prospective, cohort study	Lower GCS was a significant independent predictor of NIV failure	Single unit, no IMV group control
van Gemert 2015 [56]	50 COPD patients, assess risk factors in transition from NIV to IMV	GCS 9–15	Retrospective cohort study	Lower GCS at presentation is associated with the transition from NIV to IMV in COPD patients with hypercapnic ARF	Retrospective study, small sample size
Ucgun 2006 [57]	151 patients, identify factors affecting mortality and intubation in COPD patients	GCS 14.1 $\pm$ 1.4 in nonintubated *vs* GCS 10.8 $\pm$ 3.4 in intubated	Single center, prospective study	Lower GCS was associated with intubation	Small sample size, low rate of NIV applications, inclusion of pneumonia and heart failure leading to acute exacerbation of COPD
Kida 2012 [58]	42 patients, identify predictors of NIV success in elderly	GCS 8.9 $\pm$ 2.4 in survivors *vs* 4.0 $\pm$ 1.7 in non-survivors	Single center, retrospective study	GCS < 9 was associated with higher mortality	Retrospective study, small sample size

ARF — acute respiratory failure; AVAPS — average volume-assured pressure support; BiPAP — bilevel positive airway pressure; COPD — chronic obstructive pulmonary disease; DNI — do not intubate order; GCS — Glasgow coma scale; ICU — intensive care unit; IMV — invasive mechanical ventilation; IQR — interquartile range; KMS — Kelly-Matthay score; NIV — non-invasive ventilation; RASS — Richmond Agitation-Sedation Scale; TB — tuberculosis

to respiratory failure of various causes and treated with NIV. At the beginning of ventilatory therapy, arterial pH was 7.13 ± 0.06 and $PaCO_2$ was 99 ± 19 mm Hg. Improvements in pH, GCS, $PaCO_2$, and PaO_2/FiO_2 within the first hour of NIV correlated with NIV success. A high rate of response to NIV was achieved in comatose patients with cardiogenic pulmonary edema, COPD, and obesity. Subjects with acute respiratory distress syndrome (ARDS) and pneumonia had a higher probability of not responding to NIV. These findings support that NIV success may be related to the type and nature of the underlying disease.

Scala *et al.* [21] conducted a prospective matched case-control study comparing 40 patients with neurological impairment (KMS ≥ 3) secondary to an acute exacerbation of COPD treated with NIV or IMV. In this study, the mean arterial pH and $PaCO_2$ in NIV patients was 7.22 ± 0.02 and 88 ± 15 mm Hg. In the control group, these same parameters were 7.22 ± 0.05 and 90 ± 10 mm Hg. They noted that consciousness improved from a mean of 3.4 ± 0.6 to 2.1 ± 0.8 points in NIV patients after 2 hours of treatment, and to 1.6 ± 1.0 at 24 hours. Compared to the IMV group, the NIV group showed a shorter duration of mechanical ventilation and a lower complication rate due to fewer cases of nosocomial pneumonia and sepsis despite similar (25%) in-hospital mortality rates between groups.

In a case control study, Zhu *et al.* [22] compared a group of 22 exacerbated COPD patients with GCS < 10 with a control group of 21 subjects with GCS ≥ 10. They noted similar rates of hospital mortality (14% *vs* 14%, $p > 0.05$) and NIV success (73% *vs* 68%, $p > 0.05$). However, pressure support, NIV time, and hospital length of stay were significantly higher in patients with GCS < 10.

These studies conclusively demonstrated that many of the consensus-based "absolute" contraindications to NIV should be viewed as "relative", although an increase in failure rates can be expected in the most severe forms of hypercapnic encephalopathy. Additionally, severe complications from NIV are rare. However, most published series have been submitted by teams with extensive experience in ventilatory support, and it is difficult to know whether these results can be extrapolated to other groups with less expertise.

Current evidence against the use of NIV in hypercapnic ARF encephalopathy

By contrast, there is also evidence that NIV can be harmful in certain settings. Some studies demonstrate high rates of NIV failure in patients with low consciousness levels. In these particular patients who initially receive NIV and then experience NIV failure, there is a subsequent need for them to be intubated in order to undergo IMV, which results in them being more likely to die in the hospital [23, 24]. One possible reason for the increased mortality can be due to an inappropriate initial selection of NIV candidates and/or delay in ETI.

In a study by Confalonieri *et al*, the risk of NIV failure in a large unselected population admitted to different hospital units with expertise in NIV was assessed. The authors used this data and built two risk charts for NIV failure; one at admission and the other after 2 hours. NIV failure occurred in 236 patients (22.9%); among those, 142 died (13.7%). Risk factors for NIV failure included APACHE II score ≥ 29, GCS ≤ 14, pH < 7.25, and respiratory rate ≥ 30 breaths/minute. At admission, in a patient with pH < 7.25, APACHE II ≥ 29 and GCS ≤ 11, the chart shows a predicted risk of failure > 70%. This risk increases to 90% if the same parameters are kept after 2 hours [25].

In addition, there is data that suggest additional harm in patients with excessive secretions. Most COPD exacerbations are triggered by pulmonary infections, and exacerbations are usually associated with copious secretions. A previous study has reported that COPD patients with low cough strength were more likely to experience NIV failure (up to 80%) [26]. In selected scenarios, a reduction in NIV failure may be achieved by initiating early suction of secretions with bronchoscopy performed during NIV by an expert team [27, 28]. In a matched case-control study by Scala *et al.* [28], bronchoscopy was performed 18.5 ± 6.9 minutes after NIV initiation and lasted 7.8 ± 3.1 minutes with the removal of 23 ± 18 mL of respiratory secretions. In these patients, although both KMS and cough efficiency significantly improved after two hours, NIV still failed in 3 of 15 patients (20%). Compared to the IMV group, hospital mortality, hospital length of stay, and duration of ventilation were similar to patients in the NIV group.

Finally, a lack of cooperation in agitated patients may limit NIV success [29]. Continuous infusion of a single sedative and analgesic titrated to obtain a "conscious sedation" may decrease patient discomfort and improve gas exchange, with no significant effects on respiratory drive or hemodynamic status [30]. However, larger and more controlled trials are needed to clarify the indications of sedation during NIV.

Rationale for NIV use in patients with hypoxemic ARF and an altered level of consciousness

In this section, we will consider non-hypercapnic patients with an altered level of consciousness who have symptoms related to impaired mental function that appeared as a result of hypoxia and sepsis. Hypoxemic non-hypercapnic patients with an altered level of consciousness refers to a syndrome marked by cerebral dysfunction caused by brain hypoxia and ischemia due to hypoxemic ARF. Similarly, septic encephalopathy is an impaired mental status syndrome with a clinical presentation ranging from clouded thinking/consciousness to deep coma as can be seen in patients with systemic inflammation. Pathophysiologic hallmarks are thought to comprise diffuse neuroinflammation, vascular dysfunction, and neurotransmitter imbalances leading to direct cellular neuronal damage, impaired autoregulation, and excitotoxicity [31].

The goal of using NIV is to improve oxygenation, to decrease dyspnea and the work of breathing, and to avoid intubation [32]. It is believed to be beneficial because it recruits collapsed alveoli, increases the functional residual capacity, and decreases intrapulmonary shunt which, as a result, improves respiratory mechanics and gas exchange [33].

Hypoxemic ARF is usually defined as significant hypoxemia ($PaO_2/FiO_2 \leq 200$ mm Hg) and tachypnea in a patient not diagnosed with COPD [4]. Thus, hypoxemic ARF represents the final result of a large number of different underlying pathologies [34]. Given the variety of the pathophysiology that leads to severe hypoxemia, drawing reasonable conclusions regarding the use of NIV for hypoxemia is associated with significant challenges.

The Berlin definition for ARDS is as follows: mild when PaO_2/FiO_2 is > 200 and < 300 mm Hg; moderate when PaO_2/FiO_2 is > 100 and ≤ 200 mm Hg; and as severe when $PaO_2/FiO_2 \leq 100$ mm Hg. Positive end-expiratory pressure (PEEP), which can be delivered through NIV, can markedly affect PaO_2/FiO_2. Therefore, a minimum level of PEEP (5 cm H_2O) was added to the definition [35].

In the LUNG SAFE Study, 2813 patients with ARDS were managed with NIV or IMV irrespective of the severity category. In this study, NIV failure occurred in 37.5% of patients with ARDS and in almost half of patients with moderate and severe ARDS. NIV was associated with a worse adjusted ICU mortality than IMV in patients with a $PaO_2/FiO_2 < 150$ mm Hg. However, there was no difference in hospital mortality [36].

Additionally, a new concept of patient self-inflicted lung injury can arise as spontaneous vigorous effort in non-intubated patients has been shown to worsen lung injury in moderate to severe ARDS. Higher EPAP through NIV can reduce the amount of atelectasis in the lung, decrease force generated by spontaneous effort, and often improves gas exchange. However, even in volume-controlled NIV mode, spontaneous effort can deteriorate lung injury by increasing local lung stress and overdistension [37].

As such, the use of NIV in patients with severe hypoxemic ARF is controversial [6, 38]. Most of the published literature has focused on common hypoxemic clinical conditions such as acute pulmonary edema and pneumonia [39]. Other investigations have focused on the use of NIV in severely hypoxemic patients due to ARDS [36, 40].

Current evidence for the use of NIV in hypoxemic ARF in patients with an altered level of consciousness

We reviewed published studies designed to assess the use of NIV as a first-line intervention in hypoxemic ARF to avoid ETI. However, the majority of studies excluded patients with altered levels of consciousness. Studies on altered mental status due to primitive neurological diseases (e.g. stroke) or metabolic/toxic causes were not included (Figure 2, Table 2).

Only one study compared NIV efficacy in hypoxemic ARF in patients with an altered level of consciousness (GCS 9–14) versus patients with full awareness [41]. Patients were divided into two groups according to the presence (66 patients) or absence (82 patients) of encephalopathy. Patients with encephalopathy were older (median of 72 *vs* 78 years, $p = 0.02$), had a higher APACHE II score (18 *vs* 19, $p = 0.02$), and received a higher level of IPAP. With the caveat of being a retrospective study with important baseline imbalances, there were no significant differences between groups in rates of NIV failure (24% *vs* 30%, $p = 0.4$) and in in-hospital mortality (13% *vs* 16%, $p = 0.3$).

Data from other studies must be cautiously taken into account as they did not exclude patients from their studies based simply on a certain level of awareness. Changes to the level of consciousness were not primary or secondary endpoints.

In a randomized clinical trial, Ferrer *et al.* [42] compared the efficacy of NIV versus the Venturi mask with FiO_2 of 50% based on survival

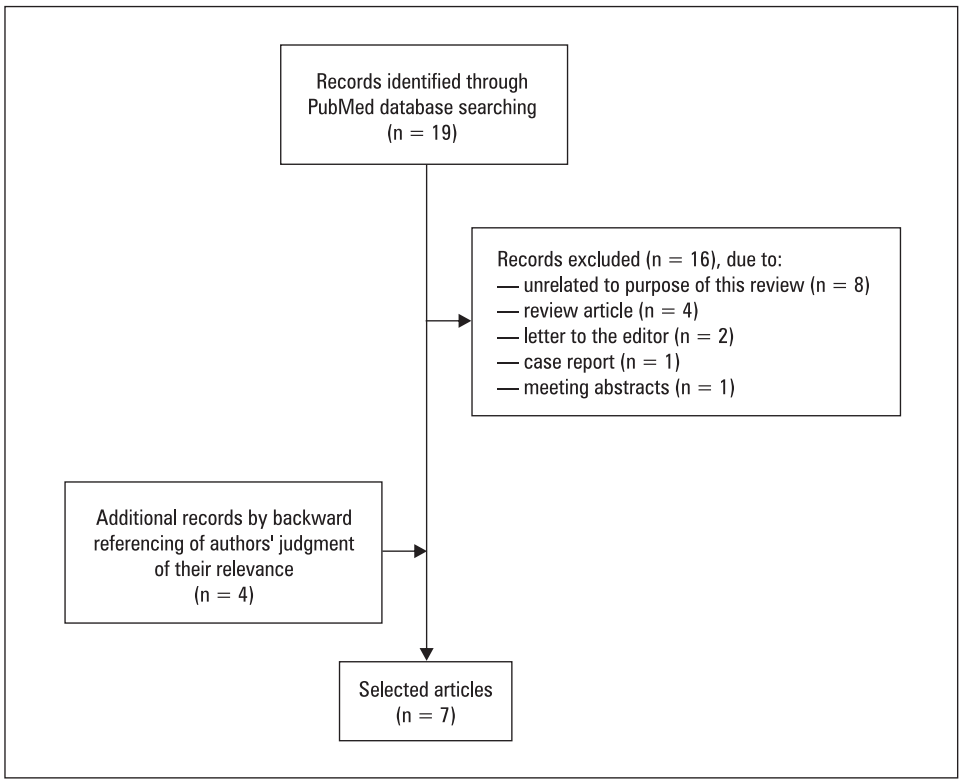


Figure 2. Flowchart of the study selection process for using non-invasive ventilation in hypoxemic acute respiratory failure in patients with an altered level of consciousness

and avoidance of ETI in 105 patients with GCS 12–15 and hypoxemic ARF. After multivariate analysis, NIV was independently associated with a decreased risk of ETI (OR 0.20, p = 0.003) and 90-day mortality (OR 0.39, p = 0.017).

In a study enrolling cardiogenic pulmonary edema patients with hypoxemic ARF who had a mildly altered level of consciousness (GCS 8–15), CPAP significantly improved 48-hour mortality (7% *vs* 24%, p = 0.017) and reduced the need for intubation (9% *vs* 30%, p = 0.001). However, there was no improvement in in-hospital mortality compared to that of standard medical care [43].

Patel *et al.* conducted a study of ARDS patients with GCS 8–15 randomized to treatment with NIV delivered by helmet or face mask. Patients in the helmet (*vs* face mask) group showed a lower need for ETI (18.2% *vs* 61.5%, p < 0.001) and an improved survival rate at 90 days from randomization (34.1% *vs* 56.4%, p = 0.02) [44]. That being said, the helmet group had significantly higher EPAP and lower pressure support results compared to the face mask group which may have influenced the final results.

Hilbert et al. published a study comparing the use of NIV to standard treatment with supplemental oxygen to treat immunosuppressed patients with hypoxemic ARF, including those with mildly altered levels of consciousness (GCS 9–15). This study showed that NIV can obviate the need for ETI in this population (46% *vs* 77%, p = 0.03) and diminish in-hospital mortality rates (50% *vs* 81%, p = 0.02) [45].

In summary, the current literature is insufficient to address the efficacy of NIV compared to other treatments in patients with hypoxemic non-hypercapnic ARF who also have an altered level of consciousness.

Current evidence against the use of NIV in hypoxemic ARF in patients with an altered level of consciousness

Delayed intubation in patients undergoing trials of NIV can lead to increased mortality [46, 47]. A previous study has reported a useful score (HACOR score) to predict NIV failure in patients with *de novo* hypoxemic ARF [48]. In this score, consciousness accounts for the highest weight among all risk factors for NIV failure. Patients with higher HACOR scores were more likely to experience NIV failure. Regarding consciousness, one assigns a HACOR score of 0 for GCS 15, 2 for

Table 2. Current evidence for using NIV in hypoxemic ARF in patients with an altered level of consciousness

Author, year	Patients and aim of the study	Level of consciousness	Type of study	Results	Limitations
Kogo 2018 [41]	148 patients, NIV efficacy in mildly altered consciousness	GCS 9–14 *vs* GCS 15	Retrospective study	No significant differences in NIV failure and in-hospital mortality	Retrospective study
Ferrer 2003 [42]	105 with severe ARF, NIV *vs* oxygen	GCS 12–15	Prospective, randomized controlled. Compares oxygen with NIV	NIV improves oxygenation, mortality, and decreases intubation rates	Difficulty for a correct blinding, relative heterogeneity of patients
L'Her 2004 [43]	89 patients with cardiogenic pulmonary edema, CPAP *vs* standard treatment	GCS 8–15	Prospective, randomized, concealed, and unblinded study	Reduction in early 48 h-mortality and ETI	Blinding impossible
Patel 2016 [44]	83 patients with ARDS, helmet *vs* face mask	GCS 8–15	Single-center randomized clinical trial	Reduction of intubation rates and 90-day mortality with helmet NIV	Blinding impossible
Hilbert 2001 [45]	52 immunosuppressed patients, NIV *vs* standard treatment	GCS –15	Prospective, randomized trial	Reduction in ETI, serious complications and mortality	Blinding impossible, single unit
Duan 2017 [48]	358 patients in the validation cohort, develop a scale to predict NIV failure in hypoxemic ARF	GCS in NIV success 14.8 ± 0.6 *vs* 14.3 ± 1.6 in the NIV failure group	Prospective observational study	NIV failure was associated with lower GCS	Observational study
Thille 2013 [49]	113 patients, assess rates and predictive factors of NIV failure	GCS in NIV success 14.9 ± 0.5 *vs* 14.6 ± 1.2 in the NIV failure group	Observational cohort study	NIV failure was associated with lower GCS	Single unit with longstanding experience in the use of NIV

ARDS — acute respiratory distress syndrome; ARF — acute respiratory failure; CPAP — continuous positive airway pressure; ETI — endotracheal intubation; GCS — Glasgow coma scale; NIV — non-invasive ventilation

GCS 13–14, 5 for GCS 11–12, and 10 for GCS ≤ 10. In this study, in patients with a HACOR score > 5, the risk for NIV failure reached up to 80%. Thus, the use of NIV in patients with low levels of consciousness must be done cautiously, especially in those with GCS ≤ 10.

In an observational cohort study, Thille *et al.* [49] assessed the rates and predictive factors of NIV failure in patients admitted to the ICU for hypoxemic ARF. Among 113 patients receiving NIV, 82 had ARDS and 31 had non-ARDS. Intubation rates significantly differed between ARDS and non-ARDS patients (61% *vs* 35%, p = 0.015) according to the clinical severity of ARDS. NIV failure was associated with active cancer, shock, moderate/severe ARDS, lower EPAP at NIV initiation, and lower GCS (p = 0.018).

In fact, the latest ERS/ATS clinical practice guidelines for NIV do not offer a recommendation about NIV use for *de novo* hypoxemic ARF [4]. This is justified, firstly, by the fact that as soon as NIV is ceased, the positive effects previously gained in terms of alveolar recruitment and oxygenation are lost. Secondly, during NIV, tidal volume results from the pressures given by the ventilator coupled with the respiratory muscle pressure generated by the patient's respiratory drive. Due to this mechanism, tidal volume is often high and may trigger ventilator-induced lung injury which contrasts with the intended lung protective ventilation strategies (low tidal volume of 6 mL/kg of predicted body weight) [32]. Finally, in a randomized controlled trial, the use of high-flow nasal cannula therapy has shown benefit in patient survival when compared with NIV and standard oxygen therapy in the treatment of hypoxemic ARF [50].

Conclusion

The overall analysis of the studies reviewed support the use of NIV as an adjunctive therapy in patients with hypercapnic encephalopathy because it decreases complication rates, the

Table 3. Advantages and disadvantages for using NIV over IMV in hypercapnic ARF encephalopathy

Advantages	Disadvantages
Less complication rates	Benefits decrease with lower levels of consciousness
Less cost	Benefits more significant in acute pulmonary edema, COPD, and obesity rather than ARDS or pneumonia
Less hospital and ICU length of stay	
Less mortality	

ARDS — acute respiratory distress syndrome; COPD — chronic obstructive pulmonary disease; ICU — intensive care unit

Table 4. Advantages and disadvantages for using NIV over IMV in hypoxemic ARF in patients with an altered level of consciousness

Advantages	Disadvantages
Less complication rates	NIV failure associated with active cancer, shock, moderate/severe ARDS Lower EPAP at NIV initiation and lower GCS
Less cost	Higher risk of NIV failure when GCS ≤ 10

ARDS — acute respiratory distress syndrome; EPAP — expiratory positive airway pressure; GCS — Glasgow coma scale; NIV — non-invasive ventilation

need for ETI, hospital length of stay, and mortality rate when compared to IMV. Patients with hypercapnic ARF and impaired consciousness can be treated with NIV, however, these results appear to be more relevant to specific patient populations including those with acute pulmonary edema, COPD, and obesity rather than conditions such as ARDS or pneumonia. Close monitoring is also mandatory as improvements in blood gas percentages within the first hours correlate with NIV success (Table 3).

Data regarding NIV effectiveness in hypoxemic ARF patients with an altered level of consciousness are more controversial given the heterogeneity of the studies identified and the fact that many studies excluded patients with alterations in mental status. Based on the examined studies, there is no evidence to either support or reject the routine use of NIV in patients with hypoxemic altered levels of consciousness due to ARF. However, NIV failure seems to increase with declining levels of consciousness. A multicenter, randomized, and controlled study trial is needed to clarify whether a benefit of NIV exists compared to other supportive treatments with regard to clinically important outcomes such as intubation rate, mortality, hospital/ICU length of stay, and other patient-centered outcome measures (Table 4).

In all cases, increased clinical experience in administering NIV, patient tolerance, and selection of the most appropriate interfaces are important considerations. The clinical status of the patient must be carefully monitored during NIV application. Clinicians must ensure that the use of NIV does not delay the need for ETI in patients who are deteriorating during NIV treatment. Proper patient monitoring is critical to ensure safe NIV initiation and titration. Skills in NIV application and limiting its use to highly monitored clinical settings are critical factors to consider to ensure optimal use of NIV and patient safety.

Conflict of interest

None declared.

References:

1. Keenan SP, Sinuff T, Cook DJ, et al. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. Ann Intern Med. 2003; 138(11): 861–870, doi: 10.7326/0003-4819-138-11-200306030-00007, indexed in Pubmed: 12779296.
2. Lightowler JV, Wedzicha JA, Elliott MW, et al. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003; 326(7382): 185, doi: 10.1136/bmj.326.7382.185, indexed in Pubmed: 12543832.
3. Lopez-Campos JL, Garcia Polo C, Leon Jimenez A, et al. Staff training influence on non-invasive ventilation outcome for acute hypercapnic respiratory failure. Monaldi Arch Chest Dis. 2006; 65(3): 145–151, doi: 10.4081/monaldi.2006.560, indexed in Pubmed: 17220104.
4. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017; 50(2), doi: 10.1183/13993003.02426-2016, indexed in Pubmed: 28860265.
5. Chawla R, Dixit SB, Zirpe KG, et al. ISCCM guidelines for the use of non-invasive ventilation in acute respiratory failure in adult icus. Indian J Crit Care Med. 2020; 24(Suppl 1): S61–S81,

doi: 10.5005/jp-journals-10071-G23186, indexed in Pubmed: 32205957.
6. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med. 1998; 339(7): 429–435, doi: 10.1056/NEJM199808133390703, indexed in Pubmed: 9700176.
7. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med. 2001; 163(2): 540–577, doi: 10.1164/ajrccm.163.2.9906116, indexed in Pubmed: 11179136.
8. Evans TW. International Consensus Conferences in icine: non-invasive positive pressure ventilation in acute respiratory failure. Organised jointly by the American Thoracic Society, the European Respiratory Society, the European Society of icine, and the Societe de Reanimation de Langue Francaise, and approved by the ATS Board of Directors, December 2000. Intensive Care Med. 2001; 27(1): 166–178.
9. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974; 2(7872): 81–84, doi: 10.1016/s0140-6736(74)91639-0, indexed in Pubmed: 4136544.
10. Kelly BJ, Matthay MA. Prevalence and severity of neurologic dysfunction in critically ill patients. Influence on need for continued mechanical ventilation. Chest. 1993; 104(6): 1818–1824, doi: 10.1378/chest.104.6.1818, indexed in Pubmed: 8252971.
11. Scala R. Hypercapnic encephalopathy syndrome: a new frontier for non-invasive ventilation? Respir Med. 2011; 105(8): 1109–1117, doi: 10.1016/j.rmed.2011.02.004, indexed in Pubmed: 21354774.
12. Honrubia T, García López FJ, Franco N, et al. Noninvasive vs conventional mechanical ventilation in acute respiratory failure: a multicenter, randomized controlled trial. Chest. 2005; 128(6): 3916–3924, doi: 10.1378/chest.128.6.3916, indexed in Pubmed: 16354864.
13. Gay PC. Complications of noninvasive ventilation in acute care. Respir Care. 2009; 54(2): 246--258.
14. Bitnar P, Stovicek J, Andel R, et al. Leg raise increases pressure in lower and upper esophageal sphincter among patients with gastroesophageal reflux disease. J Bodyw Mov Ther. 2016; 20(3): 518–524, doi: 10.1016/j.jbmt.2015.12.002, indexed in Pubmed: 27634073.
15. Pandolfino JE, Gawron AJ. Achalasia: a systematic review. JAMA. 2015; 313(18): 1841–1852, doi: 10.1001/jama.2015.2996, indexed in Pubmed: 25965233.
16. Lemyze M, De Palleja G, Guiot A, et al. Outcome of frail do-not-intubate subjects with end-stage chronic respiratory failure and their opinion of noninvasive ventilation to reverse hypercapnic coma. Respir Care. 2019; 64(9): 1023–1030, doi: 10.4187/respcare.06346, indexed in Pubmed: 30890633.
17. Mas A, Masip J. Noninvasive ventilation in acute respiratory failure. Int J Chron Obstruct Pulmon Dis. 2014; 9: 837–852, doi: 10.2147/COPD.S42664, indexed in Pubmed: 25143721.
18. Corrado A, De Paola E, Gorini M, et al. Intermittent negative pressure ventilation in the treatment of hypoxic hypercapnic coma in chronic respiratory insufficiency. Thorax. 1996; 51(11): 1077–1082, doi: 10.1136/thx.51.11.1077, indexed in Pubmed: 8958888.
19. Briones Claudett KH, Briones Claudett MH, Chung Sang Wong MA, et al. Noninvasive mechanical ventilation in patients with chronic obstructive pulmonary disease and severe hypercapnic neurological deterioration in the emergency room. Eur J Emerg Med. 2008; 15(3): 127–133, doi: 10.1097/MEJ.0b013e3282f08d08, indexed in Pubmed: 18460951.
20. Díaz GG, Alcaraz AC, Talavera JC, et al. Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. Chest. 2005; 127(3): 952–960, doi: 10.1378/chest.127.3.952, indexed in Pubmed: 15764781.
21. Scala R, Nava S, Conti G, et al. Noninvasive versus conventional ventilation to treat hypercapnic encephalopathy in chronic obstructive pulmonary disease. Intensive Care Med. 2007; 33(12): 2101–2108, doi: 10.1007/s00134-007-0837-2, indexed in Pubmed: 17874232.
22. Zhu Gf, Zhang W, Zong H, et al. Effectiveness and safety of noninvasive positive-pressure ventilation for severe hypercapnic encephalopathy due to acute exacerbation of chronic obstructive pulmonary disease: a prospective case-control study. Chin Med J (Engl). 2007; 120(24): 2204–2209, indexed in Pubmed: 18167203.
23. Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. Am J Respir Crit Care Med. 2012; 185(2): 152–159, doi: 10.1164/rccm.201106-1094OC, indexed in Pubmed: 22016446.
24. Stefan MS, Nathanson BH, Higgins TL, et al. Comparative effectiveness of noninvasive and invasive ventilation in critically ill patients with acute exacerbation of chronic obstructive pulmonary disease. Crit Care Med. 2015; 43(7): 1386–1394, doi: 10.1097/CCM.0000000000000945, indexed in Pubmed: 25768682.
25. Confalonieri M, Garuti G, Cattaruzza MS, et al. Italian noninvasive positive pressure ventilation (NPPV) study group. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. Eur Respir J. 2005; 25(2): 348–355, doi: 10.1183/09031936.05.00085304, indexed in Pubmed: 15684302.
26. Fan L, Zhao Q, Liu Y, et al. Semiquantitative cough strength score and associated outcomes in noninvasive positive pressure ventilation patients with acute exacerbation of chronic obstructive pulmonary disease. Respir Med. 2014; 108(12): 1801–1807, doi: 10.1016/j.rmed.2014.10.001, indexed in Pubmed: 25459451.
27. Wang J, Cui Z, Liu S, et al. Early use of noninvasive techniques for clearing respiratory secretions during noninvasive positive-pressure ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease and hypercapnic encephalopathy: A prospective cohort study. Medicine (Baltimore). 2017; 96(12): e6371, doi: 10.1097/MD.0000000000006371, indexed in Pubmed: 28328824.
28. Scala R, Naldi M, Maccari U. Early fiberoptic bronchoscopy during non-invasive ventilation in patients with decompensated chronic obstructive pulmonary disease due to community-acquired-pneumonia. Crit Care. 2010; 14(2): R80, doi: 10.1186/cc8993, indexed in Pubmed: 20429929.
29. Scala R. Non-invasive ventilation in acute respiratory failure with altered consciousness syndrome: a bargain or an hazard? Minerva Anestesiol. 2013; 79(11): 1291–1299, indexed in Pubmed: 23719655.
30. Huang Z, Chen Ys, Yang Zl, et al. Dexmedetomidine versus midazolam for the sedation of patients with non-invasive ventilation failure. Intern Med. 2012; 51(17): 2299–2305, doi: 10.2169/internalmedicine.51.7810, indexed in Pubmed: 22975538.
31. Tauber SC, Eiffert H, Brück W, et al. Fungal encephalitis in human autopsy cases is associated with extensive neuronal damage but only minimal repair. Neuropathol Appl Neurobiol. 2014; 40(5): 610–627, doi: 10.1111/nan.12044, indexed in Pubmed: 23517274.
32. Scala R, Pisani L. Noninvasive ventilation in acute respiratory failure: which recipe for success? Eur Respir Rev. 2018; 27(149), doi: 10.1183/16000617.0029-2018, indexed in Pubmed: 29997247.
33. Bello G, De Pascale G, Antonelli M, et al. Noninvasive ventilation for the immunocompromised patient: always appropriate? Curr Opin Crit Care. 2012; 18(1): 54–60, doi: 10.1097/MCC.0b013e32834e7c21, indexed in Pubmed: 22143051.
34. Narendra DK, Hess DR, Sessler CN, et al. Update in management of severe hypoxemic respiratory failure. Chest. 2017; 152(4): 867–879, doi: 10.1016/j.chest.2017.06.039, indexed in Pubmed: 28716645.
35. Ranieri VM, Rubenfeld GD, Thompson BT, et al. ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012; 307(23): 2526–2533, doi: 10.1001/jama.2012.5669, indexed in Pubmed: 22797452.
36. Bellani G, Laffey JG, Pham T, et al. LUNG SAFE Investigators, ESICM Trials Group. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. Am J Respir Crit Care Med. 2017; 195(1): 67–77, doi: 10.1164/rccm.201606-1306OC, indexed in Pubmed: 27753501.

37. Yoshida T, Grieco DL, Brochard L, et al. Patient self-inflicted lung injury and positive end-expiratory pressure for safe spontaneous breathing. Curr Opin Crit Care. 2020; 26(1): 59–65, doi: 10.1097/MCC.0000000000000691, indexed in Pubmed: 31815775.
38. Xu XP, Zhang XC, Hu SL, et al. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017; 45(7): e727–e733, doi: 10.1097/CCM.0000000000002361, indexed in Pubmed: 28441237.
39. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001; 27(11): 1718–1728, doi: 10.1007/s00134-001-1114-4, indexed in Pubmed: 11810114.
40. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med. 1994; 20(3): 225–232, doi: 10.1007/BF01704707, indexed in Pubmed: 8014293.
41. Kogo M, Nagata K, Morimoto T, et al. What is the impact of mildly altered consciousness on acute hypoxemic respiratory failure with non-invasive ventilation? Intern Med. 2018; 57(12): 1689–1695, doi: 10.2169/internalmedicine.9355-17, indexed in Pubmed: 29434147.
42. Ferrer M, Esquinas A, Leon M, et al. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med. 2003; 168(12): 1438–1444, doi: 10.1164/rccm.200301-072OC, indexed in Pubmed: 14500259.
43. L'Her E, Duquesne F, Girou E, et al. Noninvasive continuous positive airway pressure in elderly cardiogenic pulmonary edema patients. Intensive Care Med. 2004; 30(5): 882–888, doi: 10.1007/s00134-004-2183-y, indexed in Pubmed: 14991092.
44. Patel BK, Wolfe KS, Pohlman AS, et al. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2016; 315(22): 2435–2441, doi: 10.1001/jama.2016.6338, indexed in Pubmed: 27179847.
45. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med. 2001; 344(7): 481–487, doi: 10.1056/NEJM200102153440703, indexed in Pubmed: 11172189.
46. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004; 350(24): 2452–2460, doi: 10.1056/NEJMoa032736, indexed in Pubmed: 15190137.
47. Kikuchi T, Toba S, Sekiguchi Y, et al. Protocol-based noninvasive positive pressure ventilation for acute respiratory failure. J Anesth. 2011; 25(1): 42–49, doi: 10.1007/s00540-010-1051-x, indexed in Pubmed: 21153036.
48. Duan J, Han X, Bai L, et al. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. Intensive Care Med. 2017; 43(2): 192–199, doi: 10.1007/s00134-016-4601-3, indexed in Pubmed: 27812731.
49. Thille AW, Contou D, Fragnoli C, et al. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. Crit Care. 2013; 17(6): R269, doi: 10.1186/cc13103, indexed in Pubmed: 24215648.
50. Coudroy R, Frat JP, Ehrmann S, et al. REVA Network, REVA network, FLORALI Study Group, REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015; 372(23): 2185–2196, doi: 10.1056/NEJMoa1503326, indexed in Pubmed: 25981908.
51. Contou D, Fragnoli C, Córdoba-Izquierdo A, et al. Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit. Respir Care. 2013; 58(12): 2045–2052, doi: 10.4187/respcare.02456, indexed in Pubmed: 23737546.
52. Briones Claudett KH, Briones Claudett M, Chung Sang Wong M, et al. Noninvasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease and hypercapnic encephalopathy. BMC Pulm Med. 2013; 13: 12, doi: 10.1186/1471-2466-13-12, indexed in Pubmed: 23497021.
53. Scala R, Naldi M, Archinucci I, et al. Noninvasive positive pressure ventilation in patients with acute exacerbations of COPD and varying levels of consciousness. Chest. 2005; 128(3): 1657–1666, doi: 10.1378/chest.128.3.1657, indexed in Pubmed: 16162772.
54. Jatoi S, Akhter S, Rizvi N, et al. Standard factors predicting success of Non-invasive ventilation are useful in treating Patients with POST Tuberculosis sequel. J Pak Med Assoc. 2019; 69(8): 1146–1149, indexed in Pubmed: 31431769.
55. Scarpazza P, Incorvaia C, Melacini C, et al. Shrinking the room for invasive ventilation in hypercapnic respiratory failure. Int J Chron Obstruct Pulmon Dis. 2013; 8: 135–137, doi: 10.2147/COPD.S41374, indexed in Pubmed: 23516004.
56. van Gemert JP, Brijker F, van Gemert JP, et al. Intubation after noninvasive ventilation failure in chronic obstructive pulmonary disease: associated factors at emergency department presentation. Eur J Emerg Med. 2015; 22(1): 49–54, doi: 10.1097/MEJ.0000000000000141, indexed in Pubmed: 24637440.
57. Ucgun I, Metintas M, Moral H, et al. Predictors of hospital outcome and intubation in COPD patients admitted to the respiratory ICU for acute hypercapnic respiratory failure. Respir Med. 2006; 100(1): 66–74, doi: 10.1016/j.rmed.2005.04.005, indexed in Pubmed: 15890508.
58. Kida Y, Minakata Y, Yamada Y, et al. Efficacy of noninvasive positive pressure ventilation in elderly patients with acute hypercapnic respiratory failure. Respiration. 2012; 83(5): 377–382, doi: 10.1159/000328399, indexed in Pubmed: 21734354.

Małgorzata Czajkowska-Malinowska[1], Aleksander Kania[2], Paweł Kuca[3], Jacek Nasiłowski[4], Szymon Skoczyński[5], Rafał Sokołowski[6], Paweł Śliwiński[7]

[1]Department of Lung Diseases and Respiratory Failure, Centre of Sleep Medicine and Respiratory Care, Kujawy-Pomerania Pulmonology Centre, Bydgoszcz, Poland
[2]Jagiellonian University Medical College, Faculty of Medicine, Second Department of Medicine, Department of Pulmonology, Kraków, Poland
[3]Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
[4]Department of Internal Medicine, Pulmonary Diseases and Allergy, Medical University of Warsaw, Warsaw, Poland
[5]Department of Pneumonology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[6]Department of Internal Medicine, Pneumonology, Allergology and Clinical Immunology, Military Medical Institute, Warsaw, Poland
[7]2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

Treatment of acute respiratory failure in the course of COVID-19. Practical hints from the expert panel of the Assembly of Intensive Care and Rehabilitation of the Polish Respiratory Society

Abstract

In 2019, a pandemic began due to infection with a novel coronavirus, SARS-CoV-2. In many cases, this coronavirus leads to the development of the COVID-19 disease. Lung damage in the course of this disease often leads to acute hypoxic respiratory failure and may eventually lead to acute respiratory distress syndrome (ARDS). Respiratory failure as a result of COVID-19 can develop very quickly and a small percent of those infected will die because of it. There is currently no treatment for COVID-19, therefore the key therapeutic intervention centers around the symptomatic treatment of respiratory failure. The main therapeutic goal is to maintain gas exchange, mainly oxygenation, at an appropriate level and prevent the intensification of changes in the lung parenchyma. Depending on the severity of hypoxemia different techniques can be used to improve oxygenation. Medical staff dealing with COVID-19 patients should be familiar with both, methods used to treat respiratory failure and the epidemiological risks arising from their use. In some patients, conventional (passive) oxygen therapy alone is sufficient. In patients with worsening respiratory failure high flow nasal oxygen therapy (HFNOT) may be effective. The continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV) methods can be used to a limited extent. With further disease progression, invasive ventilation must be used and in special situations, extracorporeal membrane oxygenation (ECMO) can also be administered.

The authors of this article set themselves the goal of presenting the most current knowledge about the epidemiology and pathophysiology of respiratory failure in COVID-19, as well as the methods of its treatment. Given the dynamics of the developing pandemic, this is not an easy task as new scientific data is presented almost every day. However, we believe the knowledge contained in this study will help doctors care for patients with COVID-19. The main target audience of this study is not so much pneumonologists or intensivists who have extensive experience in the application of the techniques discussed here, but rather doctors of other specializations who must master new skills in order to help patients during the time of a pandemic.

Key words: acute respiratory failure, ventilatory support, non-invasive mechanical ventilation, high flow nasal oxygen therapy, COVID-19

Adv Respir Med. 2020; 88: 245–266

Introduction

The pandemic caused by the SARS-CoV-2 virus has, suddenly and unexpectedly, caused health services to be faced with previously unknown and difficult challenges. Since the main complication of this infection is severe viral pneumonia, pneumonologists and infectious disease specialists

Address for correspondence: Małgorzata Czajkowska-Malinowska, Department of Lung Diseases and Respiratory Failure, Centre of Sleep Medicine and Respiratory Care, Kujawy-Pomerania Pulmonology Centre, Bydgoszcz, Poland; e-mail: m.cz.malinowska@interia.pl
DOI: 10.5603/ARM.2020.0109
Received: 05.06.2020

ISSN 2451–4934

occupy a special place in the fight against this pandemic. At the turn of 2002–2003 a similar epidemic broke out, also due to the coronavirus, but only on a local scale (Southeast Asia). Some infected patients developed severe pneumonia, which was characterized by a rapid clinical course and a high mortality rate due to acute respiratory failure. For this reason, this disease was called SARS, an acronym made from the first letters of the English name: severe acute respiratory syndrome. During that outbreak, there were 8096 confirmed cases and 774 deaths, which signifies a high mortality rate of 9.5%. The epidemic at that time did not spread globally, and only single cases were reported in European countries [1]. In 2012 there was the second outbreak of epidemic caused by coronavirus, which took place in Middle East and Northern Africa regions. Due to location it was called Middle East Respiratory Syndrom (MERS). Till 2017 2040 cases and 712 deaths was noted [2, 3].

As in 2002 and 2012, the cause of the current pandemic is the coronavirus, hence the name SARS-CoV-2. The receptor for this virus in the human body is the angiotensin II converting enzyme, whose significant expression is present in, among others, the respiratory epithelial cells [4]. That explains why the virus has a special affinity for the lungs, among other organs. Since the world's first reported incident of infection with the SARS-CoV-2 virus, the number of infected people has grown exponentially and has now exceeded eight million, of which over 465,000 have died. Infected patients have been found in every country of the world [5]. The massive number of seriously ill patients suddenly requiring medical attention shocked and overwhelmed the health care systems of even the richest countries, with painful examples being Italy, Spain, and the USA. Compared to other Western European countries, the pandemic reached Poland with some delay giving authorities and health care workers time to take preventive measures and learn from the experiences of other countries that first faced this pandemic. In this study, the authors, members of the Intensive Care and Rehabilitation Assembly of the Polish Respiratory Society (PTChP), present knowledge about the clinical picture as well as the methods of treating respiratory failure in the course of COVID-19.

Clinical picture of COVID-19

The main source of information about patients infected with SARS-CoV-2 comes from Chinese reports, with some recent input also coming from Italy and the USA. Guan *et al.* [6] retrospectively described 1099 hospitalized patients. Contrary to popular belief, which stated the severe course of the disease affects only elderly patients, the average age of this group was 47 years old and almost 60% were men. Based on medical records, 173 patients (19%) were admitted in a severe condition. The risk factors for severe disease were advanced age and comorbidities. In the group of patients with a severe course, almost all patients (97%) had pathological changes in images produced by a CT scan of the chest on admission. Meanwhile, in the group of patients classified as having a mild course of the disease, only 19% had these changes. According to laboratory tests, severe patients had leukopenia and lymphocytopenia. 38% of severe patients required invasive ventilation, 15% required non-invasive mechanical ventilation (NIV), and 8% died. Zhou *et al.* analyzed a group of 191 hospitalized patients. Of these patients, 54% had respiratory failure and 2/3 of them developed ARDS, which was fatal in most cases. Respiratory acidosis was a rare phenomenon and was found in only 9% of all patients [7]. In an analysis of 201 hospitalized patients by Wu *et al.* [8], 82% of patients required oxygen therapy, including almost half (49% of the entire group) requiring low-flow oxygen supplementation through a nasal cannula. NIV was used in 30% of patients and 2.5% (5 patients) required intubation and invasive ventilation, including one patient who also needed extracorporeal blood oxygenation (ECMO). 53 patients (26%) required admission to the Intensive Care Unit (ICU), and 44 (22%) died. Risk factors for death, as in previous studies, were older age, coexistence of chronic diseases, as well as neutrophilia and high levels of LDH and d-dimer on admission. According to the results of the analysis of 73,000 COVID-19 cases in China, 81% of patients had a mild disease, 14% had a severe disease, and 5% had a critical disease. Mortality in this analysis was 2.3% [8] however, data on mortality vary from country to country. The highest rate of mortality (> 10%) was found in such countries as Italy, UK, and Belgium. One of the lowest rates was in Germany (< 1%) [9]. The mortality rate is most likely influenced by various factors ranging from healthcare organizations (i.e. number of beds in the ICU) to reporting methods and death qualifications.

Here we will discuss a typical course of severe COVID-19 [7]. The most commonly presented symptoms on admission are increased body temperature and dry cough. The temperature

does not have to be high as it can be < 37.5°C. On admission, changes in the CT scan of the lungs may be present. After five to seven days, dyspnea appears, which increases in the following days or even hours and may be the reason for urgent intubation and invasive ventilation. Since the disease progression rate may vary, each patient should be monitored constantly with a special focus on percutaneous measurement of the hemoglobin oxygen saturation (SpO_2).

An analysis of 1591 patients admitted to the ICU in Italy has recently been published [10] with 82% being male. Therefore, the male sex could be considered a risk factor for the development of severe disease. The average age of this group was 63 years, with 2/3 of patients having at least one comorbidity, most often being hypertension. Interestingly, COPD was present in only 8% of patients over 70 years of age and was rarer in younger patients (3%). In contrast, co-existing COPD is associated with up to a five-fold greater risk of severe COVID-19 [11]. Doctors should be aware that severe respiratory failure and ARDS may also occur in young people without any co-existing diseases. In a group of 1300 patients described by Grasselli *et al.*, data on the treatment of respiratory failure methods were presented. Almost everyone (98%) required ventilatory support; 1,150 (88%) patients needed invasive ventilation and only 137 (11%) were treated with NIV. 89% of patients required an oxygen supply with FiO_2 greater than 50% [10]. Data from the USA indicates a lower percentage of necessary intubation (71% of those treated in the ICU), but for now these are analyses of small groups of patients [12]. In China, the percentage of patients treated in the ICU and invasively ventilated ranged from 30% to 47% [13, 14], while NIV treated patients ranged from 14% to 62%. The varied data regarding the number of patients requiring invasive and non-invasive ventilation are probably due to different criteria for admission to the ICU, different criteria for invasive ventilation, and differing availability of medical equipment.

Pathophysiology of respiratory failure in COVID-19

As the SARS-CoV-2 pandemic continues, we are able to learn more about the pathophysiological aspects of COVID-19. The main complication of the severe course of this disease is viral pneumonia, which causes edema of the interstitium of the lungs, most often located in the sub-pleural areas. Therefore, CT scans of the chest reveal multifocal, diffuse, most often bilateral ground-glass opacities. Despite the relatively small amount of lung parenchyma involved, severe hypoxemia may occur during this phase of the disease. The cause is not entirely clear, but most likely is due to a disturbance in the regulation of pulmonary vascular tone (vasoplegia), which does not constrict despite alveolar hypoxia. This causes a significant inadequacy in ventilation to perfusion ratio (V/Q mismatch). Since lung compliance is likely to be normal or only slightly reduced with such small lesions, the patient usually has no difficulty increasing ventilation to improve PaO_2, often leading to hypocapnia. Some Italian researchers describe this clinical picture (relatively small changes in chest imaging, normal lung compliance, and significant hypoxemia) as the disease's "L" phenotype. This name comes from the first letter of the English terms for four characteristics: 1. **L**ow elastance (high compliance, normal or nearly normal in this case), 2. **L**ow V/Q ratio (low ventilation to perfusion ratio), 3. **L**ow lung weight, and 4. **L**ow lung recruitability (weak effect of alveolar recruitment with positive airway pressure). The optimal form of treatment at this stage is passive oxygen therapy. At this stage, the disease may either go into the regression phase and towards recovery or into the progression of lung lesions towards ARDS. If the latter scenario takes place, the lung changes evolve into massive parenchymal infiltrates covering large areas of the lung, a typical image of ARDS. This phenotype was named after the letter "H" from the first letter of English words describing the characteristic pathophysiological features: 1. **H**igh elastance (low compliance), 2. **H**igh right-to-left shunt, 3. **H**igh lung weight, and 4. **H**igh lung recruitability (good response to the use of positive airway pressure in the form of alveolar recruitment and improved gas exchange). For phenotype H, the main mechanism of hypoxemia is right-to-left intrapulmonary shunt. Areas of the lung parenchyma involved in the inflammatory process are not ventilated while the perfusion is still ongoing, therefore, there is no gas exchange. Blood that perfuses these areas returns to the systemic circulation as still poorly oxygenated venous blood. The greater the amount of blood that flows through the affected (unventilated) lung parenchyma, the greater the hypoxemia. Figure 1 presents the mechanism of hypoxemia by way of right-to-left intrapulmonary shunt. The use of positive airway pressure for ventilatory support (active oxygen therapy) is the treatment of choice in the H phenotype [15]. It is important to take into consideration

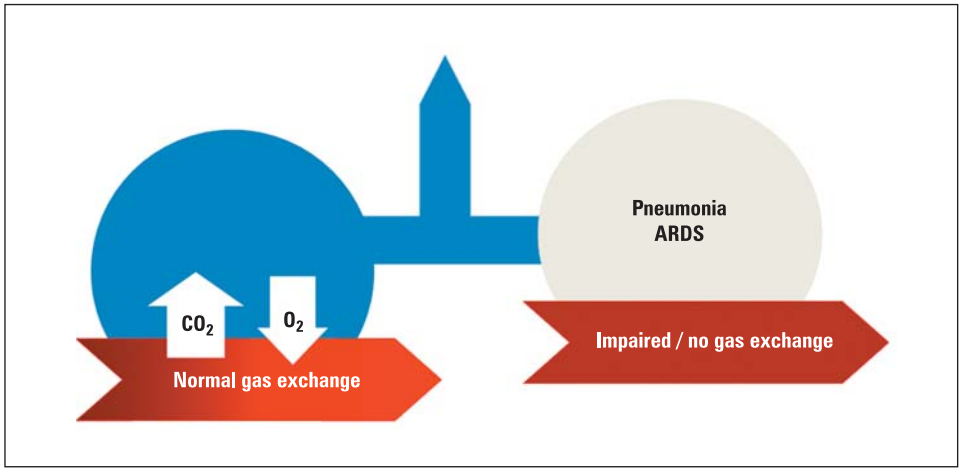


Figure 1. Schematic mechanism of hypoxemia (intrapulmonary shunt). On the left-hand side, a normal perfusion ventilation ratio can be seen, on the right-hand side, diseased lung area can be seen. In this area there is no ventilation, therefore no blood oxygenation may take place. In cases where the addition of non-oxygenated blood is large, the use of passive oxygen therapy will be probably ineffective, because the administered oxygen does not reduce intrapulmonary shunt, but only improves the oxygenation of blood passing through healthy pulmonary parenchyma

that prolonged strenuous respiratory effort may exacerbate (worsen) respiratory failure and cause a transition from "L" to "H" phenotype [15]. This phenomenon is called patient self-inflicted lung injury (P-SILI) and plays an important role in the pathophysiology of ARDS (caused not only by COVID-19). For this reason, ventilatory support (mechanical ventilation/CPAP/NIV) should not be delayed in patients with high respiratory effort. The described changes in lung parenchyma are presented in Figures 2 and 3.

In addition, hypercoagulability, which increases the risk of thrombosis, is also a characteristic of the severe course of COVID-19. Therefore, another mechanism by which hypoxemia can be caused and/or exacerbated is via pulmonary embolism. One report from a French center stated pulmonary embolism was found in 20% of 107 patients hospitalized in the ICU which, according to the authors, more than doubled the incidence of this complication among the general population of patients treated in the ICU [16].

Treatment of hypoxemia

Since there is no specific treatment for COVID-19, maintaining respiratory function by ensuring proper gas exchange and, above all, adequate oxygenation of blood is the most important therapeutic goal. Below, we will discuss methods of treating hypoxic respiratory failure starting with the simplest techniques allowing the use of a lower fraction of oxygen in inhalation gases (FiO_2) all the way up to advanced techniques that allow the supply of high fraction of oxygen, even up to 100% under positive pressure. This does not mean that every patient should be started with a nasal cannula and all oxygen therapy techniques should be used in succession. On the contrary, depending on the patient's initial state, severity of hypoxemia, respiratory effort, available equipment, possibility of patient isolation, and the possibility of implementing invasive ventilation, one should start with a treatment method that will ensure satisfactory oxygenation of blood while also taking the safety of the staff into account. Transcutaneous pulse oximetry should be used in the assessment of blood oxygenation due to its availability, ease of application, and possibility of continuous measurement of this vital parameter. Assessment of the partial pressure of oxygen (PaO_2) should only be used if there are doubts about the reliability of the SpO_2 measurement or if there is suspected hypercapnia. False SpO_2 measurements may occur in the following clinical situations: improperly fitted sensor (not fully covering the distal phalanx), peripheral hypoperfusion, hypotension, arrhythmia, damaged distal phalanx, or if a patient has dark nail polish covering their fingernail. There is no consensus among scientific bodies regarding the optimal SpO_2 value that should be achieved under the influence of treatment. The British Thoracic Society has recommended the SpO_2 target to be between 94–98% since 2008 [17]. Currently, the WHO also recommends maintaining $SpO_2 > 94\%$ in guidelines for the treatment of respiratory

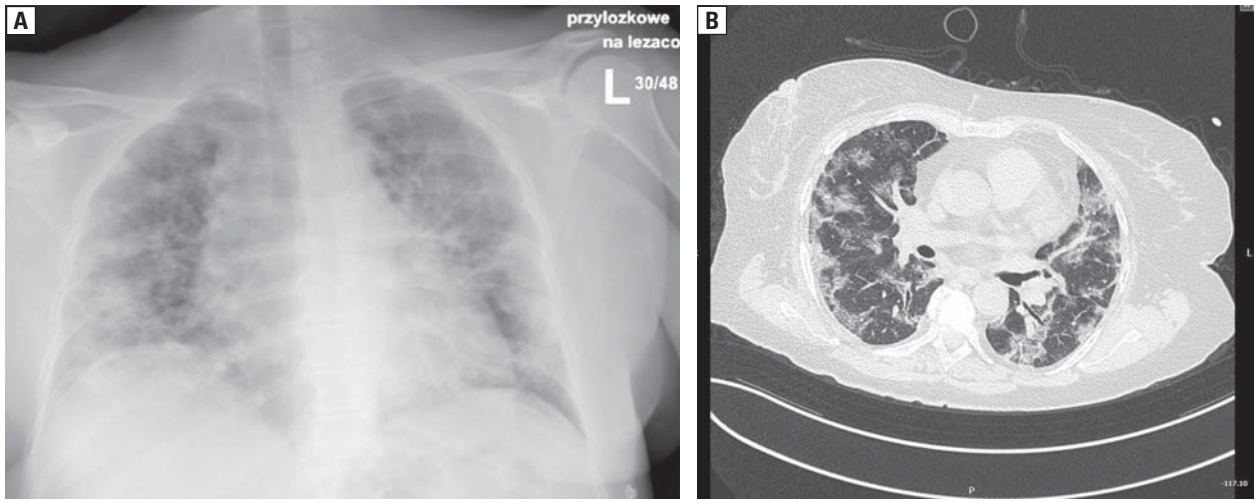


Figure 2. Picture of lung parenchyma involvement on the 4th day of treatment of 56-year-old woman infected with SARS-CoV-2. In chest anterior-posterior radiograph (**A**) and high resolution computer tomography (**B**) areas of grand glass opacities, mainly with sub-pleural predominance. Respiratory insufficiency. Treatment with Venturi mask — FiO_2 0.4 to be able to reach SpO_2 94%

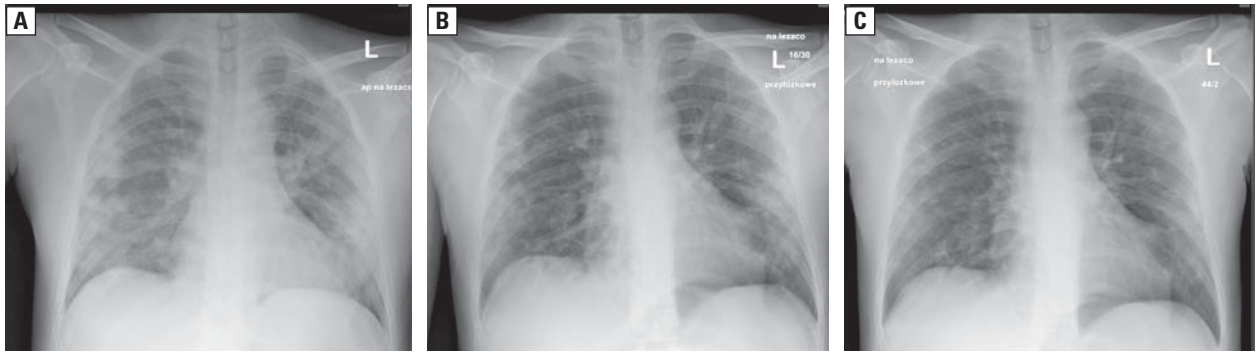


Figure 3. The course of COVID-19 in 37-year-old male in chest radiograph examinations. **A**. The admission day: disseminated parenchymal opacities in both lungs. **B**. 5th day of hospitalization. **C.** 16th day of hospitalization. Visible gradual regression of the lesions. The patient with respiratory failure — required the use of oxygen with nasal cannula (flow 5 L/min). On day 16th the patient without hypoxemia

failure in COVID-19 [18]. On the other hand, a panel of international experts in the field of intensive therapy draws attention to the harmful effects of hyperoxia (increased risk of death) and in a document issued in 2018, recommended maintaining SpO_2 at 90–94% [19]. The European Intensive Care Society also recommends that SpO_2 should not exceed 96% during the treatment of COVID-19 respiratory failure [20]. Regardless of which guidelines we adopt, treatment should never allow for SpO_2 to fall below 90%. It seems that the target SpO_2 should be between 92% and 96%. In the case of a patient with chronic hypercapnic respiratory failure, the recommendations are unambiguous. SpO_2 should be maintained within 88–92% so as not to weaken the hypoxic respiratory drive and to not increase hypercapnia.

Conventional (passive) oxygen therapy

Passive oxygen therapy refers to spontaneous breathing air with an increased oxygen content, which means a FiO_2 within a range of 0.22 to 1.0 (22% to 100%). This treatment can be performed with the use of devices described below:

A. Nasal cannula

The nasal cannula is the simplest device for oxygen administration (Figure 4). The oxygen fraction is titrated by changing oxygen flow through the cannula. Pure (100%) oxygen, which comes out of the cannula, is blended in the patient's nostrils with the inhaled air to form a mixture of air and oxygen. This method does not allow for the administration of an inspiratory gas with a precise FiO_2 value since it depends on

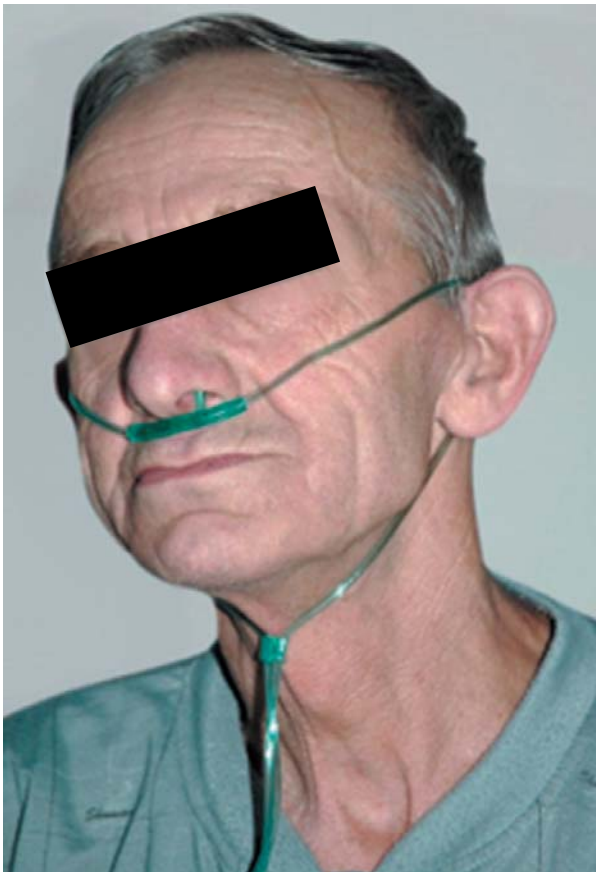


Figure 4. Oxygen therapy with nasal cannula. Flow range should be titrated between 0.5 L/min and 6 L/min. This interface provides FiO_2 up to 0.4. Breathing with open mouth does not reduce FiO_2 and is not a contraindication to use of nasal cannula

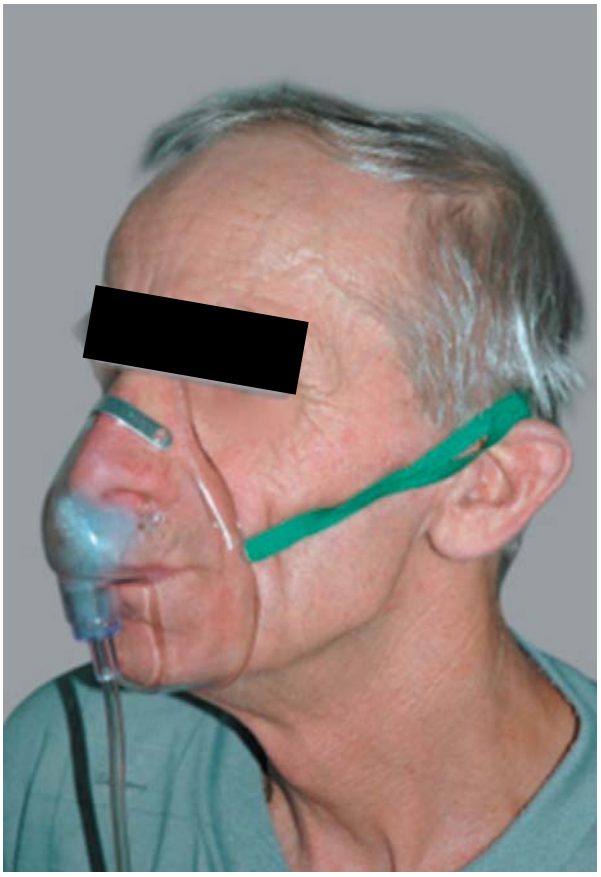


Figure 5. Oxygen therapy with the use of a simple oxygen mask

the patient's minute ventilation. The generally accepted FiO_2 estimation method (an increase of 4% with an increase in oxygen flow by 1 L/min) can be unreliable in patients with high respiratory drive and high minute ventilation. It is believed that the flow should not exceed 6 L/min as a further increase in oxygen supply no longer significantly increases FiO_2. For nasal cannula oxygen therapy, COVID-19 patients may be fitted with surgical masks to minimize the risk of dispersion of aerosol.

B. Simple oxygen mask

A simple oxygen mask is a frequently used interface in general wards (Figure 5). Its advantage lies in the possibility to provide higher FiO_2 [within 0.4–0.6 (40–60%)] compared to oxygen therapy via a nasal cannula. However, its disadvantage is the lack of strict control of FiO_2 administered and the risk of CO_2 re-inhalation. To avoid this risk, oxygen flow should not be less than 5 L/min. The maximum flow is considered to be 10 L/min.

C. Venturi mask

If the nasal cannula or simple oxygen mask cannot provide adequate blood oxygenation, a Venturi mask can be used (Figure 6). The advantage of this mask is the ability to administer a mixture of air and oxygen with a constant and precisely selected oxygen fraction in the range of 24% to 60%. The FiO_2 value is determined by selecting the appropriate sized port (Figure 7) and setting the appropriate oxygen flow assigned to the Venturi port. It should be remembered that the given oxygen flow rate is the minimum value that should be set. Therefore, it is not an error to set a higher flow rate when high minute ventilation is suspected. However, as the flow through the mask increases, the dispersion of exhaled gas in the room is also greater [21].

D. Non-rebreather mask

If oxygen therapy with a 60% Venturi mask is insufficient, a non-rebreather mask should be used (Figure 8). The principle mechanism of action of this mask is, with each breath, to inhale pure oxygen from the reservoir attached to the mask. The one-way valve system prevents the exhaled and

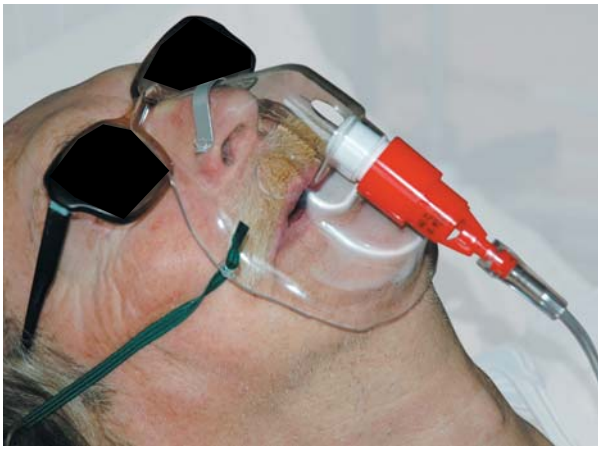


Figure 6. Oxygen therapy with the use of Venturi mask. The red item is a Venturi sized port, where air and oxygen is blended to provide exact FiO_2 between 24% and 60%

Figure 7. Venturi sized ports. In order to deliver certain FiO_2 the adequate port has to be implemented between mask and cannula, and indicated oxygen flow rate has to be set up

inhaled air from mixing. In order for this treatment to be effective, the mask must be tightly fitted to the face so the patient does not breathe in air from the room and the oxygen reservoir must be filled promptly so the entire inspiratory volume comes from it. With correct use, it is possible to achieve a FiO_2 of 0.8–0.95. The use of a non-rebreather mask is the safest method to avoid medical personnel being infected because the expiratory aerosol is dispersed the smallest distance from the patient's mouth, approximately 10 cm [22].

High-flow nasal oxygen therapy

A. Principle of operation

High-flow nasal oxygen therapy (HFNOT) refers to administering high flow air (10–60 L/min.) enriched with oxygen at a concentration ranging from 22% to 100% through dedicated nasal prongs (Figure 9). In addition, the gas mixture is saturated with moisture and heated to a temperature of 31–37°C, which closely mirrors the natural conditions in the nasal cavity. Thanks to this, the patient tolerates high airflow very well. This would not be possible with dry, cool gas [23]. HFNOT is an intermediate method between passive and active oxygen therapy. HFNOT has several beneficial effects on pathophysiology of respiratory failure. Firstly, high gas flow generates positive airway pressure (an increase in flow rate by 10 L/min results in an increase in airway pressure from 0.5–1.0 cmH_2O), which increases functional residual capacity (FRC) and causes alveolar recruitments, enhancing gas exchange. Secondly, reduction of expiratory gases retention in the dead space. Thirdly, in patients with obstruction, high inspiratory flow and positive airway pressure reduce the work of breathing [24]. Figure 10 shows the HFNOT device and explains its principle of operation.

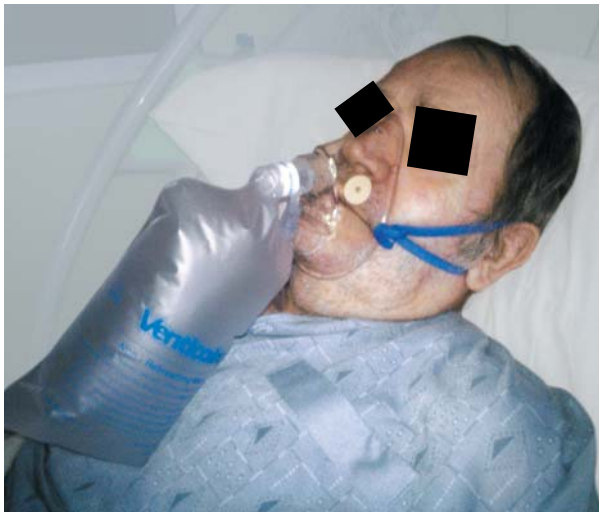


Figure 8. Non-rebreather mask. Fully expanded reservoir bag, which contains pure oxygen, means effective oxygen flow in. This interface provides FiO_2 at the level of 80–95%

B. Scientific evidence

To date, no randomized clinical trials have been conducted to assess the effectiveness of HFNOT in the treatment of COVID-19 respiratory failure, but this method has been commonly used in China. A retrospective analysis of 610 patients commonly treated with HFNOT found a lower necessity for intubation and lower mortality rate compared to data from neighboring regions of China where HFNOT was not used [25]. Earlier observations during the influenza epidemic in 2009 also pointed to the beneficial effects of HFNOT, although they were made on a small group of patients [26].

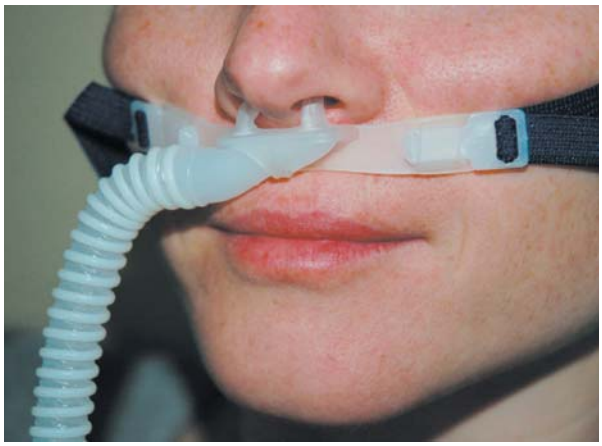


Figure 9. The interface for high-flow nasal cannula therapy

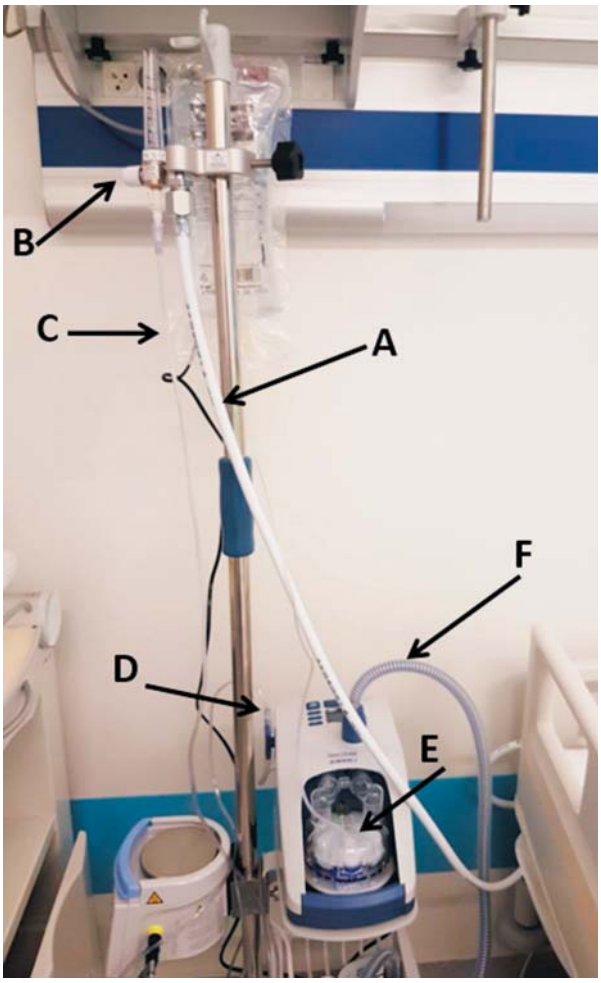


Figure 10. High-flow nasal cannula (HFNOT) device (AirVo2, Fisher&Paykel Healthcare, Auckland, New Zealand). **A.** High pressure oxygen circuit; **B.** High flowmeter (up 60 L/min); **C.** Oxygen cannula; **D.** Oxygen inlet with integreted blender and analyzer; **E.** Reservoir with distillated water supplied continuously (note the liquid bag on the top of rack), which serves as gas heater and humidifier; **F.** Inspiratory circuit leads the gas to nostrils

The randomized study assessing the effectiveness of HFNOT in the treatment of hypoxic respiratory failure showed a reduction in mortality in patients treated with HFNOT (PaO_2/FiO_2 < 300 mm Hg) compared to groups treated with conventional oxygen therapy (non-rebreather mask) or NIV [27]. This study also found a reduction in the risk of intubation in a subset of patients with an oxygenation index (PaO_2/FiO_2) < 200 mm Hg. These observations became the basis for recommending HFNOT in the treatment of acute hypoxemia in COVID-19 in the first place, prior to the use of NIV. It is worth noting, this study did not include patients with chronic respiratory diseases and cardiogenic pulmonary edema (clinical situations in which NIV has proven clinical efficacy). A meta-analysis of several randomized trials also confirmed that HFNOT reduces the risk of intubation [28] and the number of ICU admissions compared to conventional oxygen therapy [29]. These observations indicate that HFNOT can be used to treat hypoxic respiratory failure in COVID-19, especially where access to intensive care beds and ventilators is limited. WHO [18], the European Intensive Care Society [20], and numerous national scientific societies recommend this method.

C. Parameter titration

The optimal initial setting of gas flow (maximum or minimum) remains a matter of debate. Lower flow rates (35–40 L/min) are better tolerated [30], while a larger flow rate (40–60 L/min) achieves clinical benefits in a shorter time. These benefits include relieving shortness of breath, improving oxygenation, and preventing inspiratory muscle fatigue [27]. In the case of a more severe clinical condition, you can start with a higher flow rate (e.g. 60 L/min) at the beginning to achieve rapid improvement and then titrate according to therapeutic goals and patient comfort [31]. Initial settings should be regularly adjusted to the patient's current respiratory rate (so it reaches < 25–30 breaths/min), SpO_2 (> 90%), and treatment tolerance. If therapeutic goals are achieved, the flow rate should be reduced by 5–10 L/min every one to two hours. However, if the goals are not achieved, it is suggested to gradually increase the airflow rate by 5–10 L/min up to 60 L/min and then increase FiO_2. If the patient's clinical condition and SpO_2 improve, we do the opposite by first lowering the FiO_2 and then gradually reducing the amount of airflow by 5–10 L/min at a pace that is dependent on the patient's clinical condition. If

the patient remains stable for one to two hours at an $FiO_2 \leq 0.4$ and airflow rate < 15 L/min, HFNOT can be discontinued and passive oxygen therapy can be started.

If the patient needs to be intubated, HFNOT can initially be used to improve oxygenation during laryngoscopy. In this case, the maximum flows and FiO_2 (flow 60 L/min, FiO_2 1.0) should be used [32, 33]. HFNOT has been shown to minimize adverse events such as desaturation severity, arrhythmias, and cardiac arrest during intubation [33].

Unfortunately, in the age of the SARS-CoV-2 pandemic, the use of HFNOT may be associated with an increased risk of infection of medical personnel because during this process the exhaled air is dispersed in the form of aerosol droplets. However, research has shown that the distance of dispersion is not great. With an airflow of 60 L/min, the distance is less than 20 cm [34]. During the 2003 epidemic with SARS-CoV-1, reports do not indicate that the use of HFNOT was a risk factor for personnel infection [35]. In order to minimize this risk, the latest German guidelines recommend putting surgical masks on the patient's face [36].

Active oxygen therapy

If the use of passive oxygen therapy or HFNOT is ineffective and we do not achieve a $SpO_2 \geq 90$–92% or if the patient's respiratory effort is not reduced, active oxygen therapy should be initiated. It refers to the inhalation of inspiratory gases at a positive pressure (higher than atmospheric pressure). Positive airway pressure may be delivered invasively by intubating the patient and starting mechanical ventilation or may be provided in a non-invasive manner through various types of interfaces (masks) applied to the patient's face. The purpose of positive airway pressure is, among others, to recruit alveoli and increase the gas exchange area, as well as to prevent the occurrence of atelectasis in the lung parenchyma. The therapeutic effect is not always predictable and depends on the amount of pressure used and the nature and distribution of lung lesions. Positive airway pressure operation is demonstrated in Figure 11.

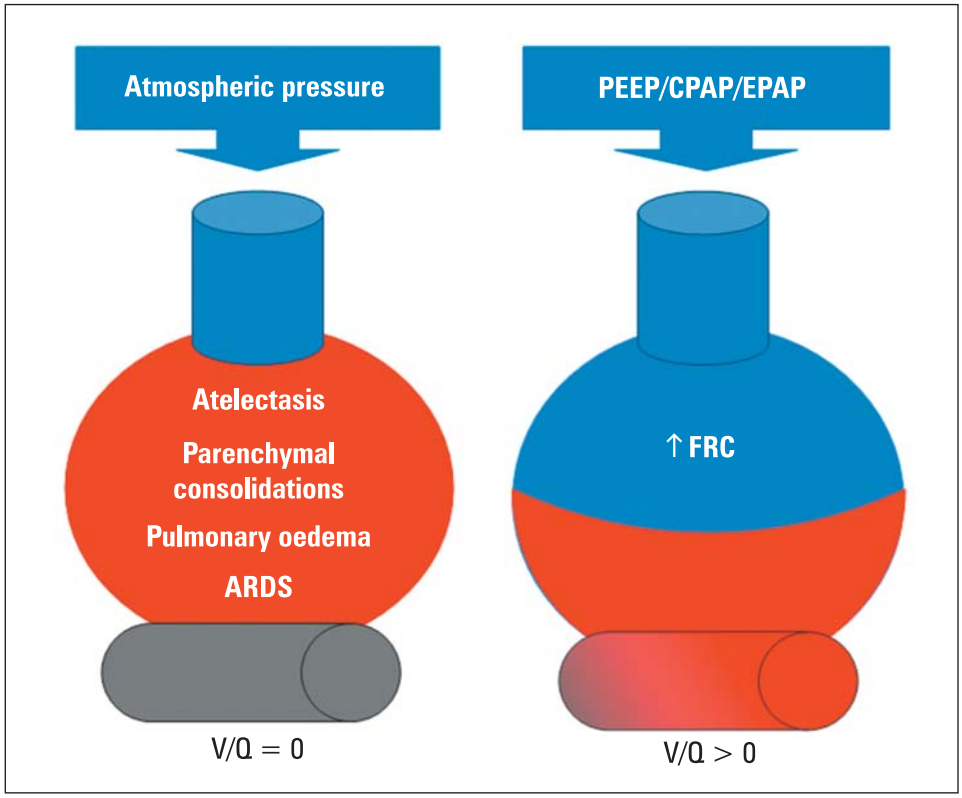


Figure 11. Schematic effect of the mechanism in which the positive airway pressure improves arterial blood oxygenation. The diagram on the left-hand side illustrates the part of the pulmonary parenchyma that is involved in the disease (**red color**), due to the lack of ventilation in these areas, the ratio of ventilation (**V**) to perfusion (**Q**) is zero. This means that there is no gas exchange between the blood and the alveoli (intrapulmonary shunt). The diagram on the right-hand side shows the use of positive airway pressure, which increases the gas exchange surface (so-called alveolar recruitment) (**blue**) and improves the ventilation to perfusion ratio, thanks to which gas exchange occurs in some of the blood

In most publications on the treatment of hypoxic respiratory failure, the authors use the common name for continuous positive airway pressure (CPAP) and describe it as non-invasive mechanical ventilation (NIV). This is justified by the fact that these patients require the application of positive airway pressure and not augmenting ventilation (i.e. bilevel positive airway pressure, BiPAP). However, from a physiological point of view, due to the fact that CPAP is not a method of ventilation in the literal sense, we will discuss both modes of non-invasive active oxygen therapy separately. CPAP will be understood as a mode of constant pressure and NIV understood as a mode of bi-level airway pressure (BiPAP).

A. Continuous positive airway pressure (CPAP)

The CPAP mode delivers gas into the respiratory system during inspiration and exhalation at a constant pressure higher than the atmospheric pressure. It is widely used in medicine, primarily in the treatment of obstructive sleep apnea [37]. PEEP (positive end-expiratory pressure) refers to positive airway pressure at the end of exhalation in intubated patients and is used in intensive care in the treatment of ARDS [38]. The possibility of using CPAP in the treatment of respiratory failure was already reported during the SARS-CoV-1 epidemic [39]. That being said, we do not have clinical trial results that allow us to provide clear guidelines on when and how to use CPAP in the treatment of patients infected with SARS-CoV-2. With this in mind, current clinical experience from doctors in Southern and Western Europe argue that this method can be effective in a certain group of patients. Constructed strategies for the treatment of COVID-19 also suggest taking this method into account [40], especially in patients without hypoventilation, which is typical for patients with COVID-19.

The advantages of CPAP therapy include high availability, low cost, no need to have high medical competence when using it, no patient-device asynchrony (possible when using ventilation), high safety of treatment, and the possibility of using the patient's own CPAP device (if the patient uses this method in treatment of sleep apnea). It should also be noted that the use of CPAP in improving oxygenation might be even more effective than when using NIV, as the mean respiratory pressure value during ventilation with bilevel positive airway pressure (BiPAP) is usually lower than the CPAP values, which are significantly higher. Moreover, a lack of increase in inspiratory volume through the use of CPAP, as opposed to NIV, may have additional significance in the treatment of this group of patients as it is part of the strategy of protecting lungs from overdistension (volutrauma and barotrauma) [41].

Indications for CPAP (non-invasive CPAP therapy)

We do not have clear guidelines based on strong scientific evidence determining the criteria for CPAP treatment. This therapy should be considered when passive oxygen therapy or HFNOT is ineffective and should be undertaken before invasive ventilation is started if the patient's status allows for this. A consultant intensivist makes this decision. The main purpose of using CPAP is to protect the patient against the need for intubation. The guidelines proposed by various scientific societies are based mainly on reports from regions with the most experience in the treatment of the COVID-19 disease. Decisions to initiate or discontinue this form of therapy should be taken individually and must take into account the following aspects:

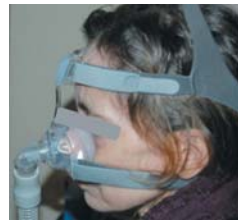
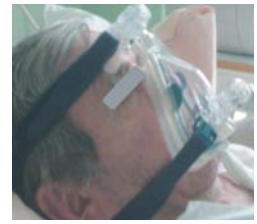
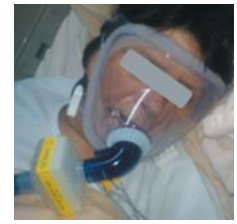
1. Patient's condition (risk of intubation);
2. Planned escalation of therapy (whether the patient would be qualified for invasive ventilation if his condition worsens or not);
3. Availability of medical equipment (i.e. CPAP devices, masks);
4. Experience of medical staff in its application;
5. Options for protecting medical staff against infection.

The British Thoracic Society (BTS) suggests starting CPAP therapy if the significant respiratory effort and respiratory rate ≥ 20 min persists and when, despite passive oxygen therapy with $FiO_2 \geq 0.4$, SpO_2 is below 94% [42]. In addition, the coexistence of obstructive sleep breathing disorders (it is worth considering unrecognized obstructive sleep apnea, especially in obese patients) may be an additional indication for early use of CPAP in patients hospitalized due to COVID-19.

How to use CPAP therapy in the treatment of COVID-19?

Interfaces. When choosing the type of interface, take into consideration both the possibility of conducting effective therapy as well as the safety of medical personnel. The characteristics of individual types of interfaces are presented in Table 1. Given this information and considering the quick and vast spread of the disease, as well as the danger that it poses, it seems the most

Table 1. Comparison of interfaces used in conducting non-invasive active oxygen therapy (CPAP or bi-level PAP)

	Helmet	Nasal mask	Oral-nasal mask	Full face mask
				
Unintentional leakage	Generally absent when the collar is inflated around the neck	Frequently excessive due to breathing through the open mouth	It is common but manageable in most patients	Usually relatively small and manageable in most patients
Pressure ulcers on patients face with prolonged use	Are not present	They are very common on the nose bridge	They occur in almost all patients on nasal bridge	Very rarely
The possibility of using high pressures	Unlimited	Usually poor tolerance and very large leaks	Often poor tolerance and large leaks	Often poor tolerance due to very large leaks
Ease to use by staff	Dedicated to handle by training and experienced staff	Relatively simple	Relatively simple	Relatively simple
Communication with the patient's environment	Possible, though difficult	Normal, the patient can communicate	Limited	Limited
Fluid oral intake	Possible through a special channel dedicated to carry the fluid probe	Convenient	Requires mask removal	Requires mask removal

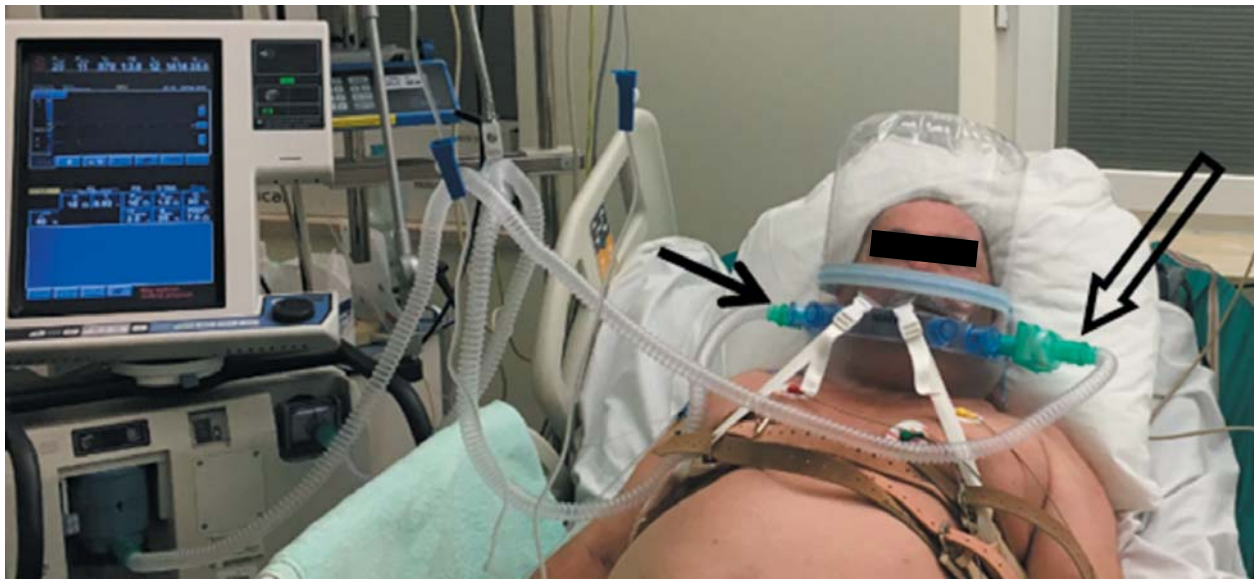


Figure 12. Non-invasive ventilation with the use of helmet and double limb respiratory circuit. On the left-hand side inspiratory arm of the circuit comes to the helmet (**black arrow**), on the right-hand side expiratory arm with antiviral filter (**empty arrow**)

optimal type of interface is a helmet. Despite the lack of hard scientific evidence, it is believed that it has the smallest risk of infection, due to the fact that the patient breathes in a closed space under the helmet and the air escaping from the helmet passes through a filter (Figure 12) [43]. In addition, the helmet is the best fitting interface available thanks to the flexible, cuffed collar

around the neck, which further reduces the risk of spraying aerosol droplets containing the virus. The helmet perfectly controls leaks in spite of a high pressure under it, which is extremely important in terms of effective treatment. Another advantage of the helmet is the possibility of long-term treatment. Since the helmet is not leaning on any part of the face, there are no pressure sores on the skin. However, an important side effect is the noise generated by the air flowing inside the helmet. It is recommended for the patient to wear earplugs when using this interface. In addition, a complication that may occur is swelling of the upper limbs, due to the pressure created by the belts supporting the helmet, which pass under the armpits. The solution to this problem is to attach straps to the harness on the patient's hips.

The second best option is to use a full-face or oral-nasal mask. Nasal masks are not applicable in the treatment of patients with severe shortness of breath. These patients breathe through their open mouths, which causes large leaks and an inability to maintain therapeutic pressure, thus exposing staff to infection. When using a mask with ventilator, the respiratory circuit should be composed in such a way that the patient exhales through the antiviral filter. Therefore, masks with a leak port located in the mask itself should not be used and we instead recommend using non-vented masks (without an exhalation port). There are three variants of respiratory circuits with non-vented masks:

1. A double-limb (Figure 13);
2. A single-limb with an exhalation valve (Figure 14);
3. A single-limb with a leakage port (whisper swivel type) located in the distal part of the circuit before the filter (Figure 15).

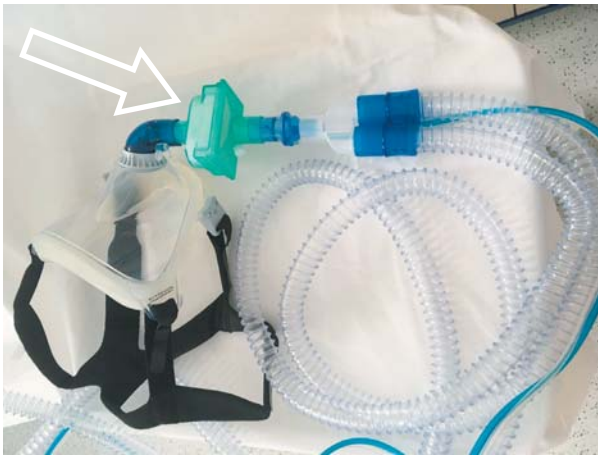


Figure 13. Double limb respiratory circuit for non-invasive ventilation or CPAP consist of inspiratory and expiratory limb. Note the non-vented mask and the antiviral filter (**empty arrow**) between the mask and the circuit

CPAP devices

CPAP therapy may be provided be several various types of devices:

Ventilator. The optimal device for the use of CPAP in a patient with hypoxic respiratory failure is a ventilator, which allows for the titration of FiO_2 up to 100%. It is particularly advantageous to use a ventilator when applying positive pressure with an interface that has a large dead space (especially a helmet) because a large airflow is required, which simpler devices may not be able to generate.

CPAP machine. The most commonly used positive airway pressure generator is a CPAP device dedicated for home use. The problem with these devices lies in generating a gas mixture with FiO_2 greater than 0.4. If a high FiO_2 is needed, the oxygen supply to the respiratory circuit should be increased. To this end, pressure regulators with a flow greater than 15 L/min should be available. A device that generates a constant pressure of no less than 20 cmH_2O is needed to use the helmet, so most home CPAP devices cannot be used with this interface.

CPAP valve mask. The pressure generator can be the flow of blended oxygen and air itself. A device called the Venturi Flow Generator/Driver, guarantees a sufficiently high flow (at least 40 L/min) in order to achieve the correct airway pressure level. The level of FiO_2 is regulated by a Venturi port and properly selected oxygen and airflow. Whereas, the CPAP level is generated by the exhalation valve (Figure 16).

The **Boussignac CPAP valve system** (Vygon, Ecouen, France), used the Bernoulli principle with a virtual valve effect [44], is the only commercially available device that does not incorporate an air-entrainment Venturi system. It is composed of a CPAP mask connected to a cylindrical plastic tube (Figure 17). Gas from an oxygen source flows through the four parallel micro-channels within the tube independently, creating turbulent gas flow and positive pressure within the hollow cylinder. The performance of the Boussignac CPAP system depends only on the delivered oxygen flow [45]. FiO_2 and positive pressure cannot be set by the operator because both are a result of the oxygen flow setting required to power the device and the amount of air the patient inhales above that delivered by the device.

CPAP valve helmet. Bearing in mind a high degree of security of helmet in COVID-19 therapy

Figure 14. Non-invasive ventilation with the use of non-vented full face mask and single limb respiratory circuit with expiratory valve. The expiratory valve (**black arrow**) opens only during expiration. Note the antiviral filter (**empty arrow**) between the mask and the expiratory valve

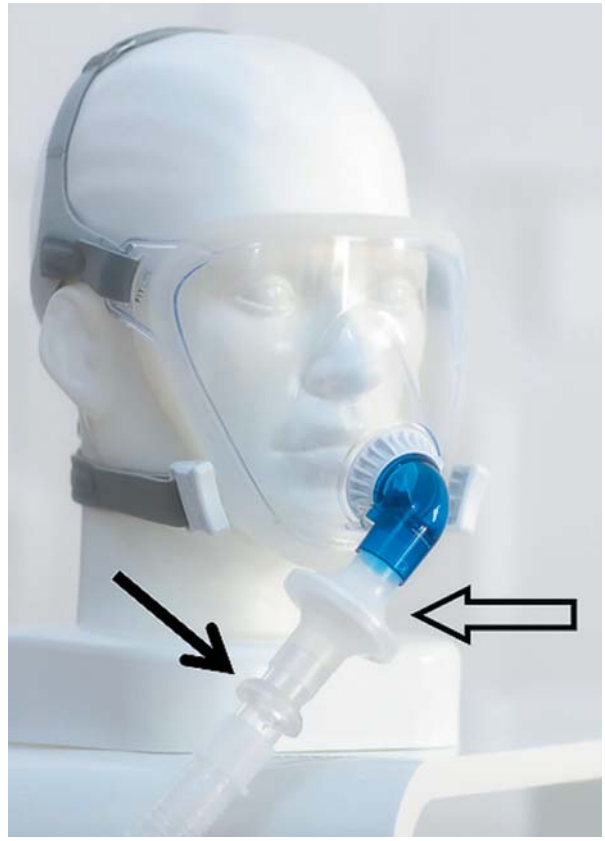


Figure 15. Non-invasive ventilation with the use of non-vented full face mask and single limb respiratory circuit with leak port. Note the leak port (**black arrow**) and antiviral filter (**empty arrow**) between the mask and the leak port

it is practical to consider to use continuous-flow CPAP generator with helmet with exhalatory valve. These are Venturi-effect flow generators, capable of delivering high flows up to 180 L/min and to adjust FiO_2 from 30% to 100%. An easy to use device even outside intensive care (ex. pneumology, internal medicine). For a proper CPAP therapy with the helmet, flows of air/oxygen of at least 40–50 L/min are needed. It can be used with all models of both helmets and masks for CPAP therapy. Continuous-flow CPAP generator with helmet with exhalatory valve is widely used in Italy.

CPAP technical aspects

Pressure titration. The CPAP level determines the effectiveness of improving blood oxygenation. It is recommended to start using CPAP with pressures of 10–12 cmH_2O and gradually increasing them to 20 cmH_2O depending on how the patient tolerates treatment, leaks, and SpO_2. In an Italian study evaluating the treatment of 1,300 patients in the ICU, the average CPAP level was 14 cmH_2O, while the maximum was 22 cmH_2O [10].

Humidification. Humidification of inhaled gases is not recommended because of the increased risk of aerosol spread [46].

Treatment time. The efficacy of CPAP therapy should be strictly monitored so there is no delay in escalating therapy to invasive ventilation if needed. The principles of patient monitoring should be based primarily on the analysis of the oxygenation index (PaO_2/FiO_2 or SpO_2/FiO_2) and evaluation of clinical parameters (i.e. respiratory rate, degree of shortness of breath, and level of consciousness). The assessment of these parameters should be carried out in the initial period of therapy (1–2 hours) constantly. If continuous monitoring of the patient is not possible, satisfactory efficacy and tolerance must be proven 30 minutes after commencement of CPAP therapy, during which time it should be used constantly to achieve clinical improvement.

Conducting CPAP treatment in prone position may have additional benefits in terms of

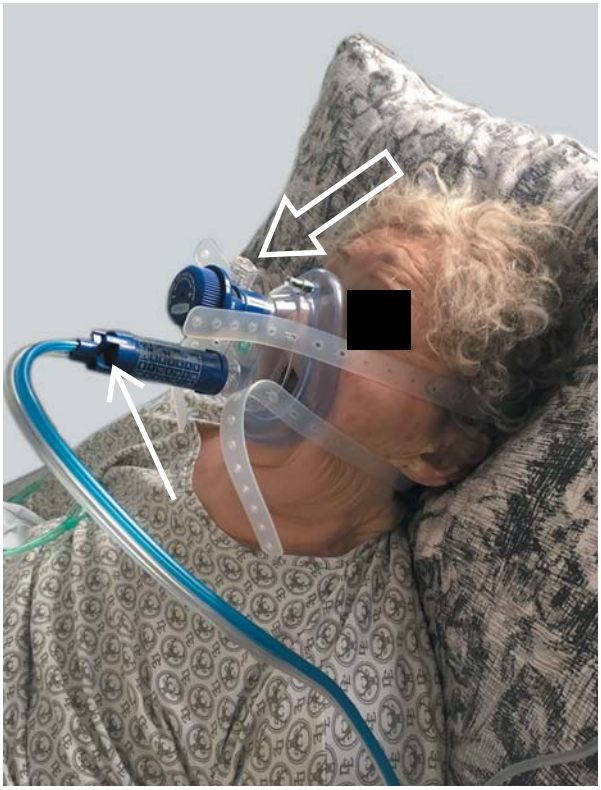


Figure 16. CPAP therapy with the use of Venturi Flow Generator (Easy Flow Venturi). Air and oxygen are delivered via separate cannulas to Venturi adjustable port (**white arrow**). The valve in the mask (**empty arrow**) generates positive pressure under the mask which can be titrated

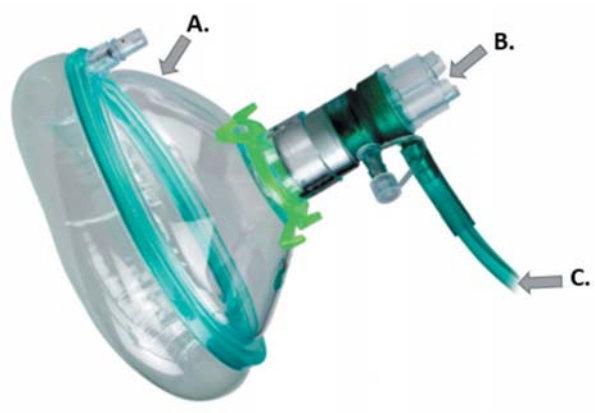


Figure 17. Boussignac CPAP system. The three components of the system includes: **A.** face mask; **B.** the Boussignac CPAP valve; **C.** oxygen tubing [68]

improved oxygenation. The authors found only one prospective study assessing the effectiveness of such therapy in a small group of 20 patients with moderate or severe ARDS in the course of viral pneumonia. Therapy in the prone position was carried out for two hours per day [47]. The results of this innovative study do not provide definitive conclusions about the effectiveness of this positioning, however, there are more and more studies on prone positioning in nonitubated patients with COVID-19 , especially from France [48] and Italy [49], stating that pO_2 is higher in the prone position rather than supine.

B. Non-invasive ventilation (NIV) Treatment of de-novo acute respiratory failure

Non-invasive mechanical ventilation (NIV) is not the treatment of choice for acute (hypoxemic) respiratory failure (ARF, so called de-novo ARF) that occurs in most patients with COVID-19. De-novo ARF is defined as acute respiratory failure in a patient without chronic respiratory diseases characterized by severe hypoxemia (oxygenation index: $PaO_2/FiO_2 \leq 200–300$ mm Hg).

The most common causes of ARF are pneumonia or ARDS. There are a number of exceptional situations in which the use of NIV in ARF has been demonstrated to have a beneficial effect [50]:

1. ARF in an immunocompromised patient;
2. ARF as a post-operative complication;
3. ARF as a consequence of cardiogenic pulmonary edema;
4. ARF due to chest trauma.

The purpose of NIV in ARF is to improve blood oxygenation, facilitate ventilation, reduce respiratory effort, and prevent intubation and complications associated with invasive ventilation. In 2012, a pilot study was published on a small group of 40 patients with moderate hypoxemia (PaO_2/FiO_2 in the 200–300 mm Hg range) who were randomized to NIV or high-flow oxygen therapy via a Venturi mask. A significant reduction in the number of intubations was found (1 patient in the NIV group and 7 patients in the oxygen therapy group, $p = 0.04$) as well as a positive trend towards lower mortality [51]. Unfortunately, this promising study was not repeated in a larger group of patients. Individual observational studies conducted in specialized intensive care centers also pointed to the possibility of beneficial effects of NIV in selected patients. However, the percentage of patients with NIV failure reached 50% in the case of pneumonia and ARDS [52, 53]. The reason for the frequent failure of NIV in the treatment of ARF can be explained by several factors:

1. Difficulty with controlling unintentional leaks;
2. The need to take breaks in conducting NIV due to individual variability in tolerance;
3. The possibility of stomach distension, which can significantly impair ventilation;

4. Difficulty in providing protective ventilation (small tidal volumes of approx. 6 mL/kg of predicted body weight) [54], especially in patients with a higher respiratory drive generating high transpulmonary pressures leading to ventilator-induced lung injury (VILI);
5. The inability to deeply sedate the patient in case of significant patient-ventilator asynchrony;
6. Difficulty in providing NIV in the prone position, which is beneficial in improving oxygenation in patients with ARDS [55], although some attempts have been made [47];
7. An inability to paralyze the patient's muscles, which would be beneficial in not only facilitating protective ventilation, but also improving the redistribution of blood from skeletal muscles to internal organs [56].

The main concern with regards to the treatment of patients with ARF with NIV is the potential delay of intubation and invasive ventilation. NIV failure is a predictive factor of higher mortality and complications associated with invasive ventilation. Risk factors for NIV failure include [53]:

1. Severe state of the patient, expressed by a high SAPS II score (Simplified Acute Physiology Score II) > 35 points;
2. > 40 years old;
3. Severe ARDS, PaO_2/FiO_2 < 100 mm Hg;
4. No improvement during the first hour of NIV, expressed as an oxygenation index of < 146 mm Hg after 1 hour.

NIV was used during the SARS epidemic in 2002 and during the swine flu virus epidemic in 2009. In the first case, the failure rate was about 30% [57], while in the second, it was highly variable and ranged from 13 to 77% [58]. Due to the lack of controlled studies about whether or not the use of NIV reduces the risk of intubation and death due to ARF in the course of viral pneumonia, the European Respiratory Society issued guidelines in 2017 in which they abstained from taking a position on the appropriateness of using NIV in such situations [59]. The use of BPAP should be considered in patients who cannot tolerate the administration of CPAP due to discomfort on expiration. The amount of pressure support should not markedly increase the tidal volume so as not to intensify the potential damaging effect on the lungs. It is believed that an inspiratory pressure 4–10 cmH_2O higher than the expiratory pressure should effectively compensate for the effect of expiratory resistance while not generating large pressure differences during the breathing cycle. In summary, NIV can be conducted in the case of ARF when it presents with a mild or moderate hypoxemia, preferably in a center with experience in conducting this form of ventilatory support. This center should also be able to ensure constant monitoring of the patient with urgent access to intubation and invasive ventilation

Treatment of an acute-on-chronic respiratory failure

In the case of a patient with COVID-19 also suffering from an acute exacerbation of chronic respiratory failure associated with hypercapnia (i.e. an exacerbation of COPD), the indications for the use of NIV are the same as for an acute exacerbation of COPD caused by any other different etiology. In such a clinical situation, the benefits of non-invasive ventilatory support are well documented and proven to reduce the risk of intubation, death, and complications associated with invasive ventilation [50]. Respiratory acidosis (pH < 7.35) is an indication for starting NIV. However, patients with chronic respiratory failure and COVID-19 may develop more severe hypoxemia, which could significantly reduce the efficacy of NIV.

Monitoring of patients in non-ICU setting

The monitoring of every patient with COVID-19 is necessary for their proper management due to the potential risk of acute respiratory failure. In 2017 the British authors created the 'National Early Warning Score 2' (NEWS2) which can be helpful in monitoring patients at risk of respiratory failure [60]. It is simple to fill out and can be completed by lower qualified medical personnel (i.e. medical or nursing student). NEWS2 consists of information about vital signs, state of consciousness, and facts about their use of oxygen therapy. Each measurement value is converted into points, the sum of which indicates the type of intervention to be undertaken. The greater the sum of points, the more severe the patient's condition and the more frequent subsequent assessments that a patient requires.

In patients with severe respiratory failure requiring oxygen therapy with a high FiO_2 > 0.4, or treated with HFNOT or NIV, continuous monitoring of vital signs, especially SpO_2 and respiratory rate, should be required. This is because the patient's potential sudden deterioration will be an indication for intensified treatment (intubation and invasive ventilation), as long as there is no Do Not Resuscitate (DNR) order.

In 2016, Roca *et al*. created an index with the acronym ROX to predict the success of HFNOT in patients with acute respiratory failure due to pneumonia [61]. The ROX index combines three common measurements: FiO_2, SpO_2, and respiratory rate.

It is calculated according to the following formula:

$$ROX = \frac{SpO_2/FiO_2}{\text{breaths/min}}$$

For example, in a patient with a respiratory rate of 30/min and SpO_2 of 90%, with FiO_2 set at 0.50, the ROX index is 1.5. This index is based on the assessment of two elements in the functioning of the respiratory system which, on one hand, are simple to measure, and on the other, reflect its functioning very well. These are respiratory rate, which reflects respiratory effort and the SpO_2/FiO_2 ratio, which highlights the degree of impairment of gas exchange. Higher oxygen concentrations necessary to maintain an adequate SpO_2 and a higher respiratory rate are evidence of a greater impairment of respiratory function and thus a higher risk of failure of HFNOT. Among the components of this index, SpO_2/FiO_2 had a greater value than the respiratory rate. These observations confirm the importance of using the right amount of FiO_2 in increasing the chance of success with HFNOT [62]. The prognostic value of the ROX index was verified during a multicentre, prospective study involving 191 patients with pneumonia [63]. This study showed that ROX ≥ 4.88 after 2, 6, or 12 hours of HFNOT indicated success. While values ≤ 2.85 after 2 hours, ≤ 3.47 after 6 hours, and ≤ 3.85 after 12 hours of using HFNOT testified to its inefficacy. It should be remembered that the reliability of the ROX index has not yet been assessed in patients with COVID-19. In 2019, the monitoring and management algorithm for using HFNOT for acute hypoxemic respiratory failure was updated [31] and took into account the ROX index and the latest reports on prognostic index values [33].

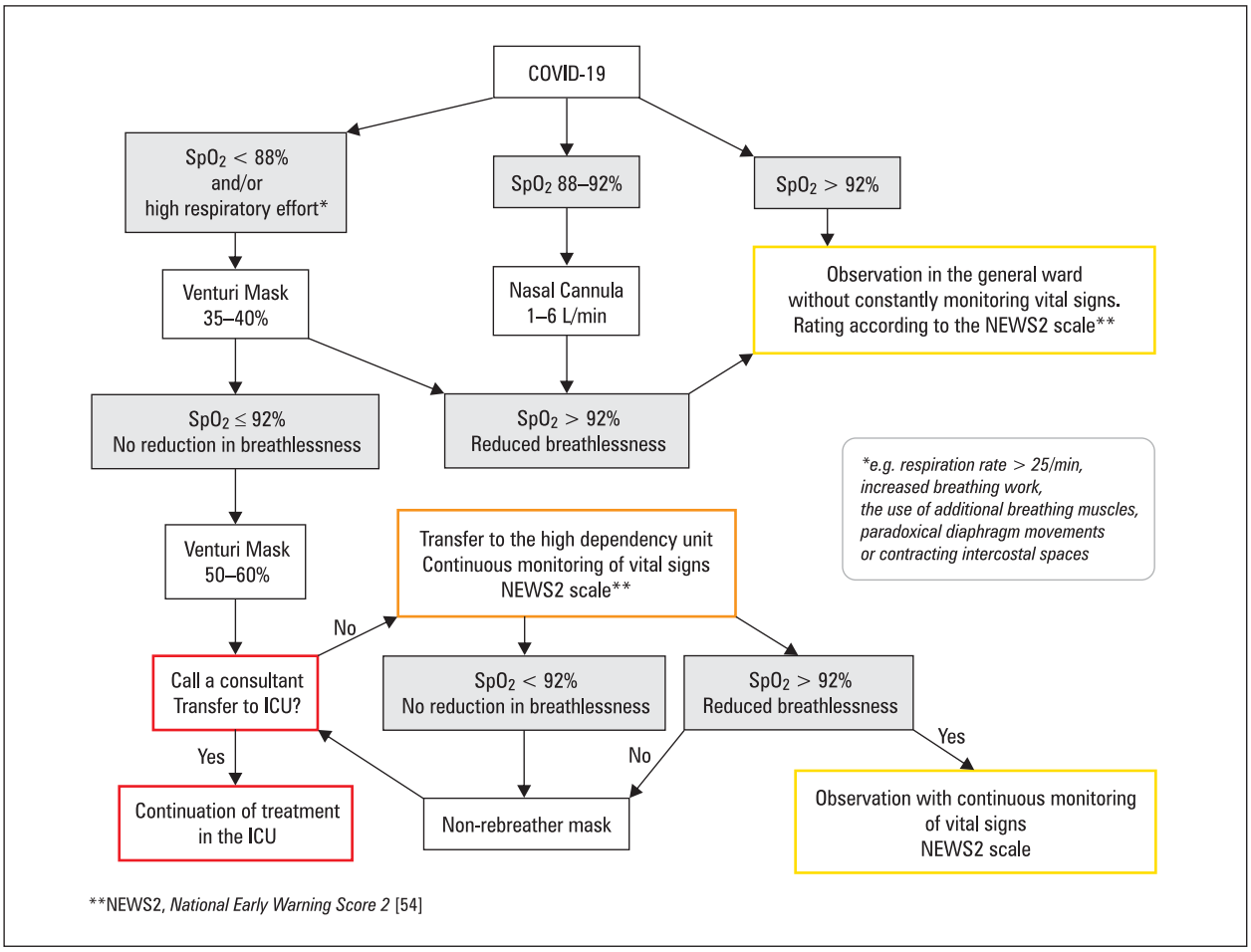


Figure 18. Algorithms for the treatment of respiratory failure in COVID-19 in general ward with the use of conventional of oxygen therapy

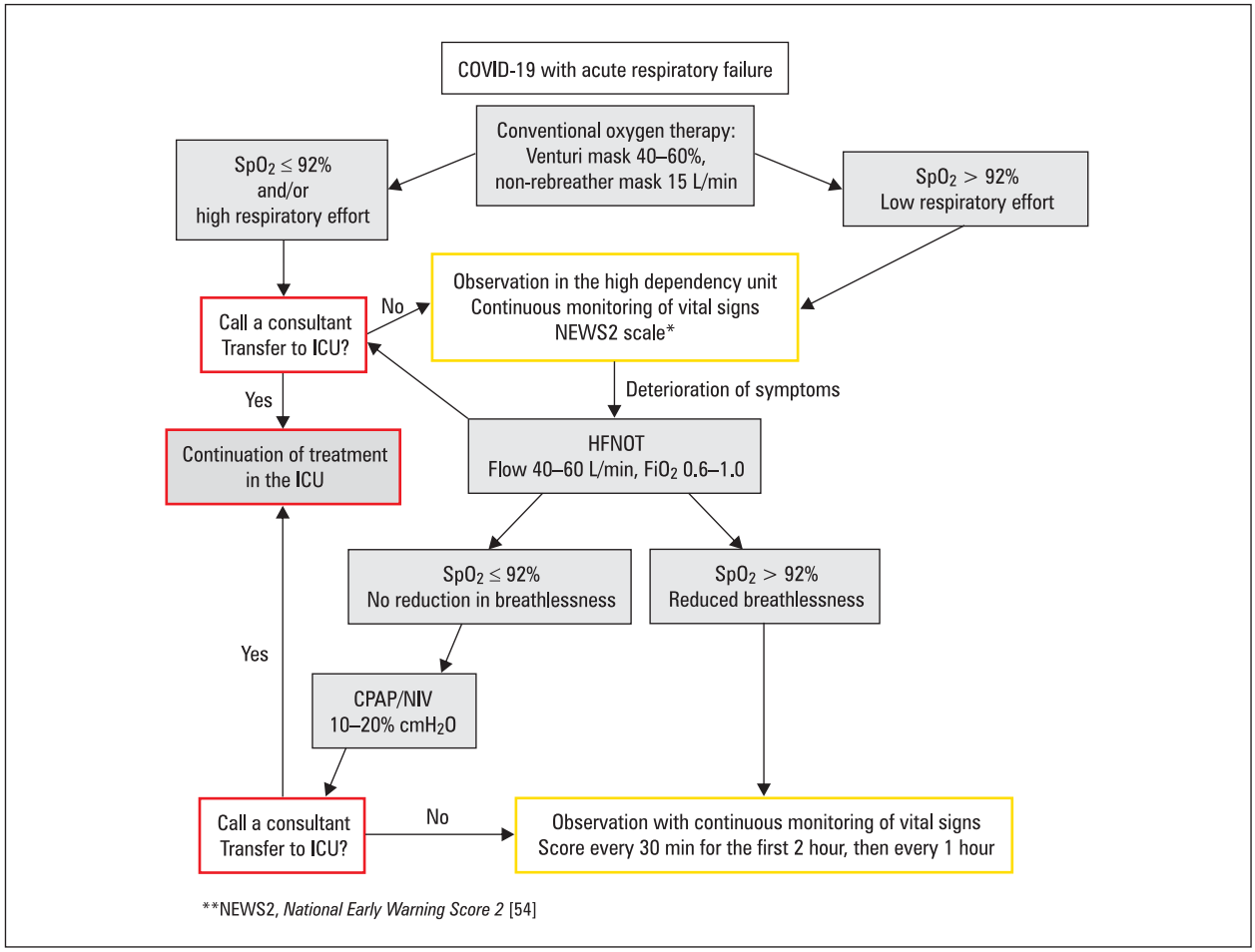


Figure 19. Algorithms for the treatment of respiratory failure in COVID-19 with the use of conventional and advanced technics of oxygen therapy (HFNOT, CPAP, NIV)

Algorithms for the treatment of respiratory failure in COVID-19 outside of the ICU are shown in Figures 18 and 19.

Invasive ventilation

In situations where the above-mentioned methods of treatment of respiratory failure prove to be ineffective, indications for invasive ventilation should be established after anesthesia consultation. These indications include:

1. From a clinical point of view: significant respiratory effort with signs of inspiratory muscle fatigue and failure of other organs and systems — cardiologic, hemodynamic, and disorders of consciousness;
2. From a pathophysiological point of view: severe hypoxemia and/or severe hypercapnia with or without respiratory acidosis that is not improving or is worsening despite intensive treatment.

In the course of the SARS-CoV-2 infection, ARDS may develop. It is not a primary lung disease but a type of extensive inflammatory process in the lungs stemming from various etiologies. ARDS in the course of COVID-19 often develops rapidly and unpredictably. From a practical point of view, it is important to know the criteria for the diagnosis and classification of ARDS, as well as the general principles of ARDS treatment associated with the use of invasive ventilation.

In 2012, an international group of experts established a new definition called the "Berlin definition" [64]. This re-organized definition was made in order to facilitate a more accurate diagnosis of ARDS and to allow for a better adaptation of therapeutic management linked to the severity of this syndrome, both in clinical trials and in everyday practice. It was agreed that ARDS is a type of sudden injury due to inflammatory factors acting on the lungs, which leads

to increased pulmonary vascular permeability, and loss of lung parenchyma. Markers of this clinical syndrome are severe hypoxemia, bilateral parenchymal lung lesions corresponding to non-cardiogenic pulmonary edema (in standard chest radiography or computed tomography), and pathophysiological disorders such as right-to-left shunt, increased dead space, and decreased lung compliance. There are four criteria necessary for the diagnosis of ARDS:

1. Time criteria: the appearance of new or worsening existing respiratory symptoms within 1 week;
2. Radiological criteria: bilateral parenchymal infiltrates that are not caused by exudate, atelectasis, or tumor;
3. Causal criteria: respiratory failure not due to heart failure or fluid overload; an objective assessment (i.e. echocardiography) is required in order to exclude hydrostatic edema if ARDS risk factors are not present;
4. Gasometric criteria: forms the basis for classifying severity of ARDS.

The basis for this classification is based on the oxygenation index (i.e. the ratio of PaO_2 to FiO_2). In this regard, there is:

- mild ARDS: 200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP/CPAP ≥ 5 cmH_2O;
- moderate ARDS: 100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cmH_2O;
- severe ARDS: PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cmH_2O.

The three above-mentioned categories of mild, moderate, and severe ARDS were created to ensure risk stratification and improve the choice of treatment method and setting. At the same time, the widely used term "acute lung injury" (ALI) has been removed from the definition of ARDS. In the new classification, each ARDS category (mild, moderate, severe) is defined by mutually exclusive ranges of PaO_2/FiO_2 values. The creation of a mild category of ARDS formalizes what was previously seen as a less severe form of the syndrome. Finally, by introducing the term mild ARDS, the severity of the disease (27% mortality) and response to protective lung ventilation were recognized.

Over the past 20 years, many clinical studies have been conducted with the goal of developing an optimal treatment for ARDS [65]. Most of them were performed by a group of researchers associated with the ARDS-Network. The ARDS-Network protocol, referred to as the Lung Protective Strategy, should be implemented into standardized practice for the treatment of ARDS in intensive care units. Of the several test modes of rescue ventilation in ARDS [high PEEP ventilation, recruitment maneuvers, prone position, inverse ratio ventilation (IRV), airway pressure release ventilation (APRV), and high frequency oscillation (HFO)], only prone position proved to be a method that improved ventilation with scientifically documented significance. The use of neuromuscular blockade has also been shown to be an important aspect of improving the effectiveness of ventilation in severe ARDS, but remains controversial [56]. From the evaluated rescue therapies in ARDS (surfactant, NO inhalation, extracorporeal CO_2 removal, and extracorporeal oxygenation), only extracorporeal membrane oxygenation (ECMO) proved to be therapeutically valuable in the treatment of ARDS, although the effectiveness of most these techniques were not evaluated in controlled studies in acute respiratory failure in COVID-19.

Extracorporeal gas exchange support

Extracorporeal gas exchange support is the most advanced alternative method to mechanical ventilation in terms of respiratory support. Its task is to replace gas exchange in the lungs while they recover. It consists of two techniques: extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$). The $ECCO_2R$ device is a variant of ECMO characterized by low blood flow and reduced blood oxygenation with a less invasive technique that uses much smaller vascular cannulas. Extracorporeal oxygenation of blood involves the use of a modified extracorporeal circulation apparatus, which is intended for long-term use. There are two types of ECMO:

1. Veno-arterial ECMO: replaces the work of the heart and lungs and is used in the most severe circulatory-respiratory distress syndromes because, apart from blood oxygenation, it generates mechanical circulatory support;
2. Veno-venous ECMO: supports the work of the lungs and is used in respiratory failure.

Currently, the role of this method in supporting respiration was established after the publication of the results of the CESAR study in 2009 and EOLIA study in 2017, which state that ECMO can be considered an effective rescue method for patients who did not benefit from the use of optimal invasive ventilation (prone position, neuromuscular blockade, and use of high PEEP).

In Poland, the detailed recommendations and guidelines of the ECMO Venous Therapy Team were developed in the form of a protocol

and published in its original form in 2009 and then updated in 2016 [66]. These indications apply in full to the use of ECMO in the SARS-CoV-2 pandemic. In practice, a pneumonologist should generally consider the possibility of using veno-venous ECMO in two clinical situations:

1. A severe form of acute respiratory failure when gas exchange cannot be provided by conventional mechanical ventilation and respiratory failure is potentially reversible;
2. Theoretically, as a bridge for lung transplantation patients with end-stage respiratory failure [67].

According to Polish guidelines, the most important contraindication to ECMO therapy is the irreversibility of the disease. In addition, other contraindications for this method of treatment include: severe systemic disease, immunosuppression, intracranial hemorrhage, contraindications to anticoagulation therapy, invasive ventilation for over 7–10 days, lack of treatment with a respirator according to the Lung Protective Strategy, lack of consent of the patient, and over 65 years of age. ECMO therapy should be discontinued when there is extensive ischemia of the brain, massive intracranial bleeding, a diagnosis of another incurable disease, and in the absence of improvement of respiratory function despite therapy [66].

Summary

The COVID-19 disease is mild in approx. 80% of cases, but other patients require hospitalization and a large proportion of them develop viral pneumonia. The consequence of this is acute hypoxic respiratory failure. In the SARS-CoV-2 pandemic era, knowledge of how to treat respiratory failure is important. All physicians should have this knowledge because treating patients with COVID-19 may be the responsibility of not only specialists in respiratory or intensive care medicine, but also the responsibility of doctors who do not deal with the treatment of respiratory failure in their daily practice. Therefore, the main target audience of this review are not so much pulmonologists who have extensive experience in applying the techniques discussed here, but rather doctors of other specialties, who in the age of pandemics must master new skills.

In the absence of specific and causal treatments for COVID-19, the primary therapeutic task is symptomatic management, which consists of ensuring adequate oxygenation of the blood. The optimal SpO_2 value that should be maintained is considered to be between 92–96%. The first step in the treatment of hypoxic respiratory failure is oxygen therapy. It can be guided by the following methods: nasal cannula, simple oxygen mask, Venturi mask, or a non-rebreather mask. Choosing the right technique depends primarily on the effectiveness of obtaining adequate oxygenation, and secondly, on the patient's tolerance of the treatment. If treatment with oxygen therapy is ineffective, high-flow nasal oxygen therapy can be used. This is a relatively new treatment method, which due to its simple technique and high efficiency, is increasingly used in clinical practice. It is more effective than conventional oxygen therapy because it improves SpO_2 and reduces respiratory effort. Its advantage over passive oxygen therapy is that, apart from the supply of a gas mixture with a high (up to 100%) oxygen content, it also generates a low positive airway pressure. Thanks to this, it is considered a method that is in-between passive and active oxygen therapy. Active oxygen therapy refers to administration of inspiratory gases with positive airway pressure. This results in improved gas exchange in the alveolar recruitment mechanism. Oxygen therapy methods using positive airway pressure include CPAP and non-invasive mechanical ventilation (BiPAP). Considering the risk of personnel being infected by aerosol droplets from the patient's exhaled air, the best interface for using CPAP/BiPAP is a helmet or face mask. Since these interfaces are unvented, they do not allow the exhaled air to spread directly into the room without passing through the filter.

Patients with mild respiratory failure can be hospitalized without constant monitoring. The NEWS2 scale is recommended to assess their condition. In the event of moderate or severe hypoxemia, vital signs, including primarily SpO_2 and respiratory rate, must be monitored continuously. These patients should be placed in a high dependency unit. The main purpose of monitoring is to control the effectiveness of treatment by maintaining adequate SpO_2, reducing shortness of breath and breathing effort. In the absence of improvement during the first two hours of treatment, consideration should be given to admit the patient to the ICU because of the high risk of intubation and invasive mechanical ventilation. Delaying this form of treatment can be associated with a higher mortality. In selected patients who do not improve despite the properly conducted invasive ventilation, the use of extracorporeal membrane oxygenation may be considered.

The authors of this article intended to present the most current knowledge about the epidemi-

ology and pathophysiology of respiratory failure in the course of COVID-19, as well as the methods of its treatment. Given the dynamics of the development of a pandemic, this is not an easy task as new scientific data is reported almost every day. However, we believe that the knowledge contained in this review will help doctors in the care of patients with respiratory failure due to COVID-19.

Conflict of interest

None declared.

References:

1. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Available at: www.who.int/csr/sars/country/table2004_04_21/en/. [Last accessed at: 30.04.2020].
2. Mackay IM, Arden KE. MERS coronavirus: diagnostics, epidemiology and transmission. Virol J. 2015; 12: 222, doi: 10.1186/s12985-015-0439-5, indexed in Pubmed: 26695637.
3. Plipat T, Buathong R, Wacharapluesadee S, et al. Imported case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection from Oman to Thailand, June 2015. Euro Surveill. 2017; 22(33), doi: 10.2807/1560-7917.ES.2017.22.33.30598, indexed in Pubmed: 28840828.
4. Zhang H, Penninger JM, Li Y, et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020; 46(4): 586–590, doi: 10.1007/s00134-020-05985-9, indexed in Pubmed: 32125455.
5. Worldmeters. Coronavirus Cases. Available at: www.worldometers. [Last accessed at: 30.04.2020].. info/coronavirus/ 30.; 04: 2020.
6. Guan WJ, Ni ZY, Hu Yu, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18): 1708–1720, doi: 10.1056/NEJMoa2002032, indexed in Pubmed: 32109013.
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054–1062, doi: 10.1016/S0140-6736(20)30566-3, indexed in Pubmed: 32171076.
8. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 [Epub ahead of print], doi: 10.1001/jamainternmed.2020.0994, indexed in Pubmed: 32167524.
9. Omer SB, Malani P, Del Rio C. The COVID-19 pandemic in the US: A clinical update. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.5788, indexed in Pubmed: 32250388.
10. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to icus of the Lombardy Region, Italy. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.5394, indexed in Pubmed: 32250385.
11. Lippi G, Henry BM. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). Respir Med. 2020; 167: 105941, doi: 10.1016/j.rmed.2020.105941, indexed in Pubmed: 32421537.
12. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.4326, indexed in Pubmed: 32191259.
13. Wang D, Hu Bo, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.1585, indexed in Pubmed: 32031570.
14. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5): 475–481, doi: 10.1016/S2213-2600(20)30079-5, indexed in Pubmed: 32105632.
15. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020; 46(6): 1099–1102, doi: 10.1007/s00134-020-06033-2, indexed in Pubmed: 32291463.
16. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation. 2020 [Epub ahead of print], doi: 10.1161/CIRCULATIONAHA.120.047430, indexed in Pubmed: 32330083.
17. O'Driscoll BR, Howard LS, Earis J, et al. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax. 2017; 72(Suppl 1): ii1–ii90, doi: 10.1136/thoraxjnl-2016-209729, indexed in Pubmed: 28507176.
18. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance V 1. 2020.
19. Siemieniuk RAC, Chu DK, Kim LHY, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018; 363: k4169, doi: 10.1136/bmj.k4169, indexed in Pubmed: 30355567.
20. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med. 2020; 46(5): 854–887, doi: 10.1007/s00134-020-06022-5, indexed in Pubmed: 32222812.
21. Hui DS, Hall SD, Chan MTV, et al. Exhaled air dispersion during oxygen delivery via a simple oxygen mask. Chest. 2007; 132(2): 540–546, doi: 10.1378/chest.07-0636, indexed in Pubmed: 17573505.
22. Hui DSC, Chan MTV, Chow B. Aerosol dispersion during various respiratory therapies: a risk assessment model of nosocomial infection to health care workers. Hong Kong Med J. 2014; 20 Suppl 4: 9–13, indexed in Pubmed: 25224111.
23. Dysart K, Miller TL, Wolfson MR, et al. Research in high flow therapy: mechanisms of action. Respir Med. 2009; 103(10): 1400–1405, doi: 10.1016/j.rmed.2009.04.007, indexed in Pubmed: 19467849.
24. Nishimura M. High-Flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. Respir Care. 2016; 61(4): 529–541, doi: 10.4187/respcare.04577, indexed in Pubmed: 27016353.
25. Sun Q, Qiu H, Huang M, et al. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. Ann Intensive Care. 2020; 10(1): 33, doi: 10.1186/s13613-020-00650-2, indexed in Pubmed: 32189136.
26. Rello J, Pérez M, Roca O, et al. CRIPS investigators. High-flow nasal therapy in adults with severe acute respiratory infection: a cohort study in patients with 2009 influenza A/H1N1v. J Crit Care. 2012; 27(5): 434–439, doi: 10.1016/j.jcrc.2012.04.006, indexed in Pubmed: 22762937.
27. Coudroy R, Frat JP, Ehrmann S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015; 372(23): 2185–2196, doi: 10.1056/NEJMoa1503326, indexed in Pubmed: 25981908.
28. Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019; 45(5): 563–572, doi: 10.1007/s00134-019-05590-5, indexed in Pubmed: 30888444.
29. Ni YN, Luo J, Yu He, et al. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med. 2018; 36(2): 226–233, doi: 10.1016/j.ajem.2017.07.083, indexed in Pubmed: 28780231.
30. Spoletini G, Alotaibi M, Blasi F, et al. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. Chest. 2015; 148(1): 253–261, doi: 10.1378/chest.14-2871, indexed in Pubmed: 25742321.

31. Ischaki E, Pantazopoulos I, Zakynthinos S. Nasal high flow therapy: a novel treatment rather than a more expensive oxygen device. Eur Respir Rev. 2017; 26(145), doi: 10.1183/16000617.0028-2017, indexed in Pubmed: 28794144.
32. Miguel-Montanes R, Hajage D, Messika J, et al. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. Crit Care Med. 2015; 43(3): 574–583, doi: 10.1097/CCM.0000000000000743, indexed in Pubmed: 25479117.
33. Ischaki E, Pantazopoulos I. "Blow with the high flow" an updated algorithm. Journal of Emergency and Critical Care Medicine. 2019; 3: 61–61, doi: 10.21037/jeccm.2019.10.03.
34. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy CPAP different masks. Eur Respir J. 2019; 53(4), doi: 10.1183/13993003.02339-2018, indexed in Pubmed: 30705129.
35. Raboud J, Shigayeva A, McGeer A, et al. Risk factors for SARS transmission from patients requiring intubation: a multicentre investigation in Toronto, Canada. PLoS One. 2010; 5(5): e10717, doi: 10.1371/journal.pone.0010717, indexed in Pubmed: 20502660.
36. Kluge S, Janssens U, Welte T, et al. German recommendations for critically ill patients with COVID19. Med Klin Intensivmed Notfmed. 2020 [Epub ahead of print], doi: 10.1007/s00063-020-00689-w, indexed in Pubmed: 32291505.
37. Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an american academy of sleep medicine clinical practice guideline. J Clin Sleep Med. 2019; 15(2): 335–343, doi: 10.5664/jcsm.7640, indexed in Pubmed: 30736887.
38. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004; 351(4): 327–336, doi: 10.1056/NEJMoa032193, indexed in Pubmed: 15269312.
39. Lau ACW, Yam LYC, So LKY. Management of critically ill patients with severe acute respiratory syndrome (SARS). Int J Med Sci. 2004; 1(1): 1–10, doi: 10.7150/ijms.1.1, indexed in Pubmed: 15912185.
40. Hick J, Hanfling D, Wynia M, et al. Duty to plan: health care, crisis standards of care, and novel coronavirus SARS-CoV-2. NAM Perspectives. 2020, doi: 10.31478/202003b.
41. McCann UG, Schiller HJ, Carney DE, et al. Visual validation of the mechanical stabilizing effects of positive end-expiratory pressure at the alveolar level. J Surg Res. 2001; 99(2): 335–342, doi: 10.1006/jsre.2001.6179, indexed in Pubmed: 11469907.
42. National Institute for Health and Care Excellence. COVID-19 rapid guideline: critical care in adults. NICE guideline. Available at: https://www.nice.org.uk/guidance/ng159. [Last accessed at: 30.04.2020].
43. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during noninvasive ventilation via helmets and a total facemask. Chest. 2015; 147(5): 1336–1343, doi: 10.1378/chest.14-1934, indexed in Pubmed: 25392954.
44. Wong DT, Tam AD, Van Zundert TC. The usage of the Boussignac continuous positive airway pressure system in acute respiratory failure. Minerva Anestesiol. 2013; 79(5): 564–570, indexed in Pubmed: 23419338.
45. Volsko TA. Devices used for CPAP delivery. Respir Care. 2019; 64(6): 723–734, doi: 10.4187/respcare.06625, indexed in Pubmed: 31110040.
46. Guidance regarding coronavirus (COVID-19) and obstructive sleep apnoea (OSA): for people who routinely use continuous positive airway pressure (CPAP), their families and health care workers. Available at: www.brit-thoracic.org.uk/media/455098/osa-alliance-cpap-covid-19-advice-20-3-20-v10.pdf. [Last accessed at: 30.04.2020].
47. Ding L, Wang Li, Ma W, et al. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care. 2020; 24(1): 28, doi: 10.1186/s13054-020-2738-5, indexed in Pubmed: 32000806.
48. Elharrar X, Trigui Y, Dols AM, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.8255, indexed in Pubmed: 32412581.
49. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.7861, indexed in Pubmed: 32412606.
50. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017; 50(2), doi: 10.1183/13993003.02426-2016, indexed in Pubmed: 28860265.
51. Zhan Q, Sun B, Liang L, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. Crit Care Med. 2012; 40(2): 455–460, doi: 10.1097/CCM.0b013e318232d75e, indexed in Pubmed: 22020236.
52. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med. 2007; 35(1): 18–25, doi: 10.1097/01.CCM.0000251821.44259.F3, indexed in Pubmed: 17133177.
53. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001; 27(11): 1718–1728, doi: 10.1007/s00134-001-1114-4, indexed in Pubmed: 11810114.
54. Chen J, Lin J, Luo H, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000; 342(18): 1301–1308, doi: 10.1056/NEJM200005043421801, indexed in Pubmed: 10793162.
55. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368(23): 2159–2168, doi: 10.1056/NEJMoa1214103, indexed in Pubmed: 23688302.
56. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010; 363(12): 1107–1116, doi: 10.1056/NEJMoa1005372, indexed in Pubmed: 20843245.
57. Cheung TMT, Yam LYC, So LKY, et al. Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. Chest. 2004; 126(3): 845–850, doi: 10.1378/chest.126.3.845, indexed in Pubmed: 15364765.
58. Estenssoro E, Ríos FG, Apezteguía C, et al. Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. Am J Respir Crit Care Med. 2010; 182(1): 41–48, doi: 10.1164/201001-0037OC, indexed in Pubmed: 20203241.
59. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015; 192(2): e3–19, doi: 10.1164/rccm.201506-1063ST, indexed in Pubmed: 26177183.
60. Royal College of Physicians. National Early Warning Score (NEWS): standardising the assessment of acute-illness severity in the NHS. Report of a working party. London: RCP, 2017. Available at: www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2. [Last accessed: 30.05.2020].
61. Roca O, Messika J, Caralt B, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care. 2016; 35: 200–205, doi: 10.1016/j.jcrc.2016.05.022, indexed in Pubmed: 27481760.
62. Tatkov S. Nasal high-flow therapy: role of fi in the ROX index. Am J Respir Crit Care Med. 2019; 200(1): 115–116, doi: 10.1164/rccm.201902-0376LE, indexed in Pubmed: 30896967.
63. Roca O, Caralt B, Messika J, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019; 199(11): 1368–1376, doi: 10.1164/rccm.201803-0589OC, indexed in Pubmed: 30576221.
64. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012; 38(10): 1573–1582, doi: 10.1007/s00134-012-2682-1, indexed in Pubmed: 22926653.
65. Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on the management of acute respiratory distress syndrome. BMJ

Open Respir Res. 2019; 6(1): e000420, doi: 10.1136/bmjresp-2019-000420, indexed in Pubmed: 31258917.
66. Lango R, Szkulmowski Z, Maciejewski D, et al. Revised protocol of extracorporeal membrane oxygenation (ECMO) therapy in severe ARDS. Recommendations of the Veno-venous ECMO Expert Panel appointed in February 2016 by the national consultant on anesthesiology and intensive care. Anaesthesiol Intensive Ther. 2017; 49(2): 88–99, doi: 10.5603/AIT.a2017.0028, indexed in Pubmed: 28643320.
67. Chen JY, Qiao K, Liu F, et al. Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. Chin Med J (Engl). 2020; 133(12): 1390–1396, doi: 10.1097/CM9.0000000000000839, indexed in Pubmed: 32251003.
68. 68. Boussignac CPAP System. Available at: www.yumpu.com/en/document/read/29383460/cpap-system-lma-north-america. [Last accessed: 31.05.2020].

Alessio Campisi[1*], Andrea Dell'Amore[1*], Luca Bertolaccini[1], Costantino Ricci[2], Alessandra Cancellieri[2], Franco Stella[1]

[1]Department of Cardiothoracic Surgery, S. Orsola Malpighi Hospital, Bologna, Italy
[2]Department of Pathology, S. Orsola Malpighi University Hospital, Bologna, Italy
*The Authors equally contributed to the paper

Sialadenoma papilliferum of the bronchus: a rare tumour of salivary gland origin

Abstract

Sialadenoma papilliferum is a benign salivary tumour which rarely occurs in the bronchial tree. Up to now, only four cases of pulmonary papillary sialadenoma have been reported in the literature.

We discuss the case of a male patient with an accidental finding of a middle lobe nodule. The patient underwent a minimally invasive anatomical resection of the lobe to remove the lesion; the postoperative course was regular, and he was healthy at the last follow-up.

Key words: sialadenoma papilliferum, rare lung cancer, VATS, lobectomy

Adv Respir Med. 2020; 88: 267–270

Introduction

Sialadenoma papilliferum (SP) is a rare, benign, papillary salivary gland tumour, usually diagnosed as a white exophytic mass of the oral and maxillofacial region [1]. Since its first description in 1969 [2], less than 100 cases have been reported in the medical literature, and most of them are located in the palate.

This paper aims to report the fifth case, to the best of our knowledge, of an SP involving the bronchial tree.

Case description

A 66-year-old male was referred to our Department for an incidental finding of a solitary pulmonary nodule of the middle lobe. The patient's medical history included renal transplantation two years earlier from a living donor due to renal failure from mesangial IgA deposits. Eight months after the transplantation, the man underwent right nephrectomy of the native kidney due to a clear cell renal carcinoma in stage pT1a N0 M0. During the standard oncological follow-up, a whole-body computed tomography (CT) scan showed a 12 × 13 mm solitary pulmonary nodule of the middle lobe (Figure 1) with fluorodeoxyglucose (18F-FDG) avidity (SUVmax 4.3) at the positron emission tomography (PET) (Figure 2). A transbronchial biopsy was not feasible, and the CT-guided transthoracic biopsy was not diagnostic. Pulmonary function tests were regular. Therefore, we discussed the indication for surgery during the multidisciplinary oncological team meeting. A VATS middle lobectomy with systematic lymphadenectomy through a biportal approach was performed. The postoperative period was uneventful, and the patient was discharged on the third postoperative day. After almost three years from surgery, he is healthy, with no recurrence.

Pathologically, at the gross examination of the resected lobe, a micro-cystic neoplasm of 1.5 cm in diameter, was found close to the lobar bronchus.

Frozen sections showed a papillary and cystic lesion with no sign of malignancy and the diagnosis was deferred.

Address for correspondence: Alessio Campisi, Department of Cardiothoracic Surgery, S. Orsola Malpighi Hospital, Bologna, Italy; e-mail: alessio.campisi@studio.unibo.it
DOI: 10.5603/ARM.2020.0111
Received: 09.11.2019

ISSN 2451–4934

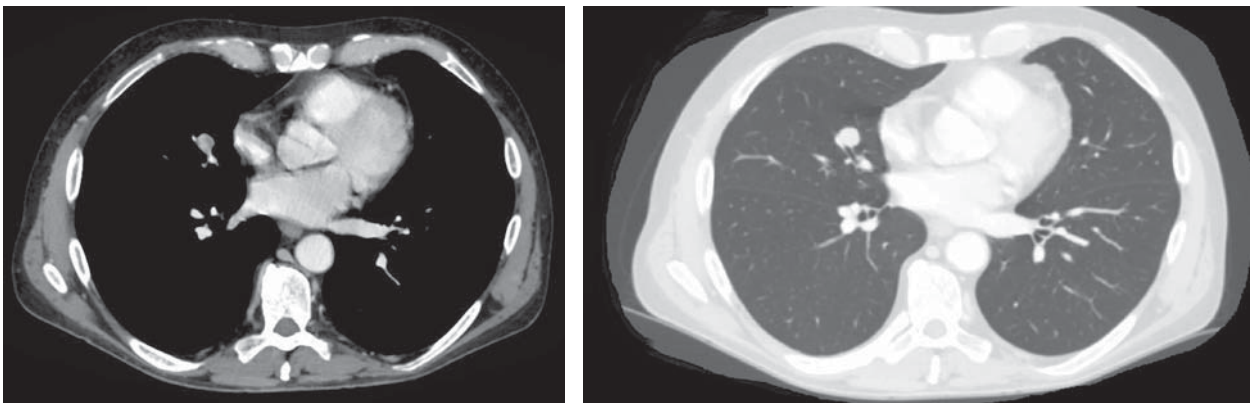


Figure 1. CT scan showing the middle lobe nodule

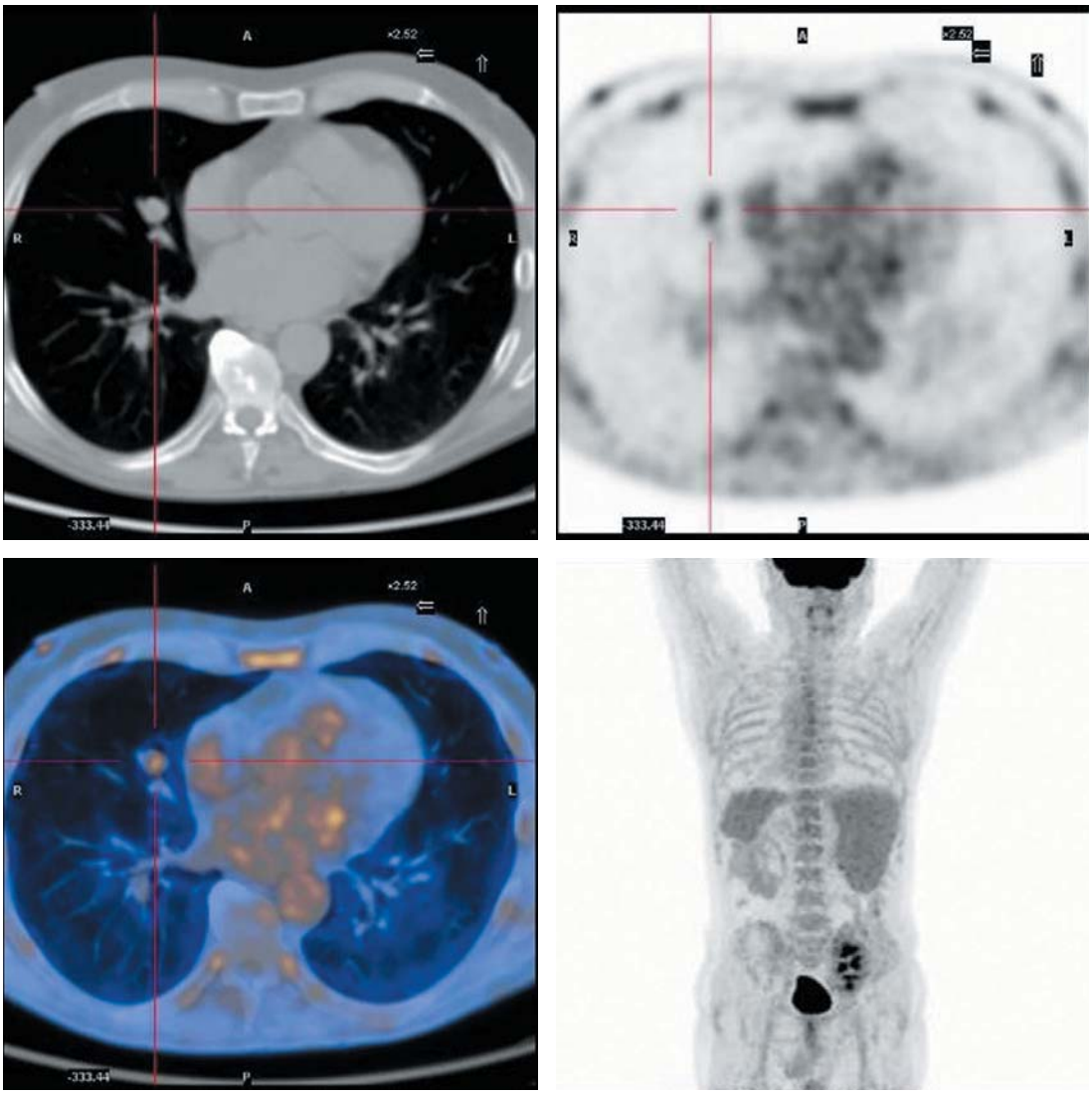


Figure 2. PET 18 F-FDG showing the contrast uptake of the nodule

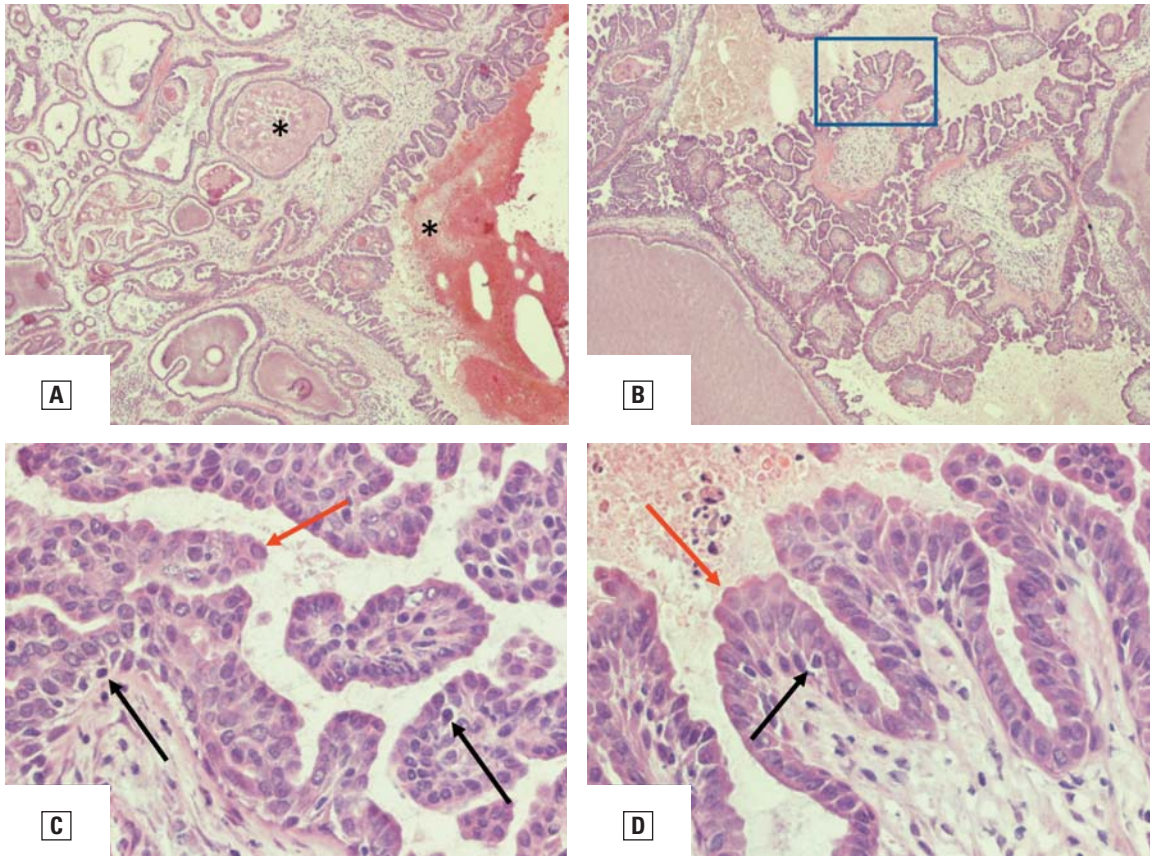


Figure 3. A., B. At low power, both cysts with blood and eosinophilic material (asterisks) and cysts with papillary projections are observed (blue square) (H&E, original magnification 100×); **C., D.** Papillary projections and cysts are lined by a luminal epithelium (luminal cells, red arrows) showing pluristratification, anisonucleosis and nucleoli and a basal monostratified epithelium (basal or aluminal cells, black arrows) with a myoepithelial appearance (H&E, original magnification 400×)

Histologically, the lesion was described as a cystic neoplasm, well-demarcated by a thin fibrous capsule, with cysts containing eosinophilic material or papillary structures lined by at least two layers of the epithelium (Figure 3). At immunohistochemistry, neoplastic cells were negative for TTF1, Napsin A, Thyroglobulin, PAX8, and GATA3. The epithelial cells of the basal layer were positive at immunohistochemistry with p63 and ck14. The suprabasal layer was negative for p63 and only focally positive for ck14; it was often multi-layered, with some micropapillary tufts, and showed mild polymorphic hyperchromatic nuclei and rare prominent nucleoli. Furthermore, the cysts containing eosinophilic material were lined by the same layered epithelium that was negative for TTF1, Napsin A, Thyroglobulin, PAX8, and GATA3 as well. The lesion seems to originate from submucosal bronchial glands.

The described findings are consistent with a cystic papillary neoplasm of undetermined malignant potential (probably, low), most likely originating from bronchial glands. The final diagnosis was sialadenoma papilliferum (SP), a rare subset of ductal papilloma of minor salivary gland origin, also described in the bronchi [3–5]. In our opinion, this tumour could be considered as a "salivary gland type bronchial neoplasm".

Conclusion

Rare primary tumours of the lung account for less than 1% of all primary lung neoplasms and include a wide variety of cancers [6]. They usually present as a non-small cell lung cancer with symptoms related to their size, localisation, and malignancy (cough, dyspnoea, chest pain, haemoptysis, fever, fatigue, etc.). A tissue biopsy is often mandatory to make an accurate diagnosis, and surgery is still the most effective treatment, with chemotherapy and radiotherapy playing a role as adjuvant strategies.

Here, we present the fifth case of SP of the tracheobronchial tree published in the literature. A thorough search was performed in PubMed on December 1st, 2018, using the terms "lung", "bron-

chial" and "sialadenoma/sialadenoma papilliferum" as keywords. Only four studies were found (one was written in German and was excluded). First described in 1969 by Abrams and Finck [2], SP is a benign, neoplasm of salivary gland origin which is named after its histological resemblance to syringocystadenoma papilliferum of cutaneous adnexal origin [7]. In the oral cavity, it appears as a white-coloured, exophytic, papillary lesion of the mucosa [1, 7]. In the three reports analysed, the macroscopic appearance is similar, being described as a well-demarcated, white, papillary or verrucous, sessile to a pedunculated lesion of the trachea or the bronchus [3–5]. It shows a histopathological biphasic growth with an exophytic papillary squamous component and a solid/cystic part. SP is slightly more common among males, with a male-to-female ratio of 1.6:1, mainly affecting individuals > 50 years of age (mean standard ± deviation 56.8 ± 15.5 years) [1]. SP has been reported in a variety of locations characterised by slow growth and a benign course, although few cases of recurrence have been documented [8]. A malignant transformation is still unique, although possible [7].

Besides, the cell of origin of SP is still controversial, but this neoplasm is thought to arise from both the excretory duct cells and bronchial glands in the case of salivary gland tumours and tracheobronchial tree lesions, respectively [3]. According to the literature review [8], the recommended treatment is a conservative surgical approach. In the three reported pulmonary cases, two anatomical resections were performed (a sleeve right upper lobectomy and a lower right lobectomy); in the third one, simple excision of the endotracheal mass was made. In all cases, patients have been free of disease for at least 6 months after surgery.

In our case, we did not have a preoperative diagnosis: therefore, considering the mass as a malignant tumour and evaluating its localisation, we performed a middle lobectomy. Our patient underwent a periodical follow-up CT scan due to the significant risk of recurrence of kidney malignancy under immunosuppression, and he is currently free of tumour.

In conclusion, we report the fifth case of SP occurring in the bronchus. The awareness of the existence of such rare lesions is essential for pathologists, and clinicians should keep in mind the possible occurrence of this intrabronchial exophytic tumoral lesion in the differential diagnosis. It is also mandatory to consider the chance, although improbable, of malignancy for these lesions. Undoubtedly, additional reports with longer follow-up are needed to demonstrate the most appropriate treatment of this very rare lesion.

Conflict of interest

None declared.

References:

1. Kubota Y, Kubo C, Mori Y. Sialadenoma papilliferum of the hard palate: a case report. J Oral Maxillofac Surg. 2012; 70(7): 1609–1612, doi: 10.1016/j.joms.2011.08.012, indexed in Pubmed: 22079070.
2. Abrams AM, Finck FM. Sialadenoma papilliferum. A previously unreported salivary gland tumor. Cancer. 1969; 24(5): 1057–1063, doi: 10.1002/1097-0142(196911)24:5<1057::aid-cncr2820240529>3.0.co;2-l, indexed in Pubmed: 5353939.
3. Honda Y, Shiraishi K, Nomori H, et al. Sialadenoma papilliferum of the bronchus: rare tracheobronchial tumor of salivary gland type. Pathol Int. 2009; 59(8): 572–576, doi: 10.1111/j.1440-1827.2009.02408.x, indexed in Pubmed: 19627541.
4. Grzesik P, Passik C, Mahfoozi A. An unusual cause of dyspnea. Ann Thorac Surg. 2016; 102(4): e333–e334, doi: 10.1016/j.athoracsur.2016.02.051, indexed in Pubmed: 27645975.
5. Bobos M, Hytiroglou P, Karkavelas G, et al. Sialadenoma papilliferum of bronchus. Virchows Arch. 2003; 443(5): 695–699, doi: 10.1007/s00428-003-0879-y, indexed in Pubmed: 12937978.
6. Block MS, Vierkant RA, Rambau PF, et al. Australian Ovarian Cancer Study Group. Rare pulmonary neoplasms. Mayo Clin Proc. 1993; 68(5): 492–498, doi: 10.1016/s0025-6196(12)60199-2, indexed in Pubmed: 8386792.
7. Shimoda M, Kameyama K, Morinaga S, et al. Malignant transformation of sialadenoma papilliferum of the palate: a case report. Virchows Arch. 2004; 445(6): 641–646, doi: 10.1007/s00428-004-1091-4, indexed in Pubmed: 15455228.
8. Fowler CB, Damm DD. Sialadenoma papilliferum: analysis of seven new cases and review of the literature. Head Neck Pathol. 2018; 12(2): 193–201, doi: 10.1007/s12105-017-0852-8, indexed in Pubmed: 28887760.

Hanna Dmeńska[1], Małgorzata Pac[2], Małgorzata Skomska-Pawliszak[2], Barbara Pietrucha[2], Beata Wolska-Kuśnierz[2], Barbara Piątosa[3], Justyna Komarnicka[4], Edyta Heropolitańska-Pliszka[2]

[1]The Pulmonology Outpatients' Clinic, The Children's Memorial Health Institute, Warsaw, Poland
[2]Department of Immunology, The Children's Memorial Health Institute, Warsaw, Poland
[3]Histocompatibility Laboratory, The Children's Memorial Health Institute, Warsaw, Poland
[4]Department of Radiology and Diagnostic Imaging, The Children's Memorial Health Institut, Warsaw, Poland

Progressive bronchiectasis and CMC in a patient with STAT1 GOF — a rare case of primary immunodeficiency

Abstract

Bronchiestasis is a common complication developing in patients with primary immunodeficiency disorders. AD GOF STAT1 deficiency is characterized by CMC, repeated infections, and autoimmunity. It is the most frequently diagnosed entity in a group of PIDs with CMC. Here, we present the first Polish case of a female patient with early-onset bronchiestasis accompanied by CMC and a severe course of infections who was genetically diagnosed with AD GOF1 STAT1 mutation at the age of 15.

Key words: primary immunodeficiency, bronchiectasis, STAT1 GOF, CMC

Adv Respir Med. 2020; 88: 271–277

Introduction

Bronchiectasis is a chronic respiratory disease characterized by an abnormal permanent dilation of the bronchi which are typically described as cylindrical, varicose, or cystic in appearance. The condition is characterized by a vicious cycle of persistent bacterial infections and excessive neutrophilic inflammation leading to the impairment of airway defence mechanisms. Risk factors for bronchiectasis are listed in Table 1 [1]. Appropriate baseline investigations include a chest radiograph, pulmonary function tests (PFT), and sputum bacteriological cultures. However, the gold standard for confirming the diagnosis is high-resolution computed tomography (HRCT) of the chest. The main aims of management are to reduce symptoms and exacerbation frequency and severity, to preserve lung function, and to improve the patient's health-related quality of life [2].

Bronchiectasis is also a well-recognized complication of primary antibody deficiencies (PAD), which are the most frequently diagnosed primary immunodeficiency disorders (PID). PAD patients share a significant susceptibility to respiratory diseases that represent a relevant cause of morbidity and mortality. Pulmonary complications include acute and chronic infection-related diseases such as pneumonia and bronchiectasis, and immune-mediated interstitial lung diseases such as granulomatous-lymphocytic interstitial lung disease (GLILD) and cancer [3]. A recent review of the UK PID Registry data showed that 47% of a cohort of 801 patients with primary hypogammaglobulinemia had bronchiectasis confirmed by HRCT [4]. Unfortunatelly, lung disease can progress in PID patients despite conventional treatment with immunoglobulin G (IgG) replacement therapy and/or antibiotic prophylaxis [4].

High susceptibility to mucosal and skin candidiasis is a hallmark of several PIDs associated with impaired interleukin-17 (IL-17) T cell immunity. Isolated chronic mucocutaneous candidiasis (CMC) was first described in the 1960s, but its genetic causes are still being

Address for correspondence: Edyta Heropolitańska-Pliszka, Department of Immunology, The Children's Memorial Health Institute, Warsaw, Poland; e-mail: ehp@poczta.onet.eu
DOI: 10.5603/ARM.2020.0112
Received: 24.11.2019

ISSN 2451–4934

Table 1. Causes of bronchiectasis with focus on primary immunodeficiencies

Cause	Mean incidence
Primary immunodeficiency disorders — common variable immunodeficiency (CVID) — agamaglobulinaemia (XLA and AR) — hyper-IgM syndromes (HIGM) — autosomal dominant Hyper-IgE Syndrome (AD HIES)	1.1–16.0%
Cystic fibrosis	0.6–2.7%
Alpha-1 antitrypsin deficiency	0.6–11.3%
Primary ciliary dyskinesia	2.0–10.3%
Allergic bronchopulmonary aspergillosis	0.9–7.8%
Autoimmune/connective tissue diseases (typically rheumatoid arthritis, SLE)	1.8–31.1%
Inflammatory bowel diseases	1.0–3.0%
Congenital malformations	0.2–0.6%
Aspiration	0.2–11.3%
Postinfectious	29.0–42.0%
Idiopathic*	26.0–53.0%

*Other causes excluded

investigated. In 2011, a group of scientists from the Laboratory of Human Genetics of Infectious Diseases (Necker Hospital, Paris) reported 47 patients with autosomal dominant (AD) CMC from 20 kindreds with 12 gain-of-function (GOF) mutations in the signal transducer and activator of transcription 1 (STAT1) gene [5].

Case report

Here, we report the first Polish case of a 19-year-old female with a STAT1 GOF pathogenic variant who presented with recurrent respiratory bacterial infections complicated by CMC and severe bronchiectasis. She was born as a second child to young, healthy and unrelated parents after an uneventful pregnancy and delivery, and without a family history of recurrent infections. She received the BCG vaccine during the first days of life. At the 2nd week of age, she was treated with intravenous antibiotics due to multiple abscesses of the scalp. During her first year of life, she was hospitalized for pneumonia twice with accompanied persistent oral thrush (*Candida glabrata*) and severe malnutrition. Infection with typical and atypical bacteria, viruses (CMV), alpha-1 antitrypsin deficiency, cystic fibrosis, and congenital malformations of the respiratory system were excluded. Performed chest computed tomography (CT) revealed inflammatory changes with atelectasis in segment (S) 2 and in the lower lobe of the right lung. Despite the fact that the presence of acid-fast bacilli (AFB) in bronchial lavage was not confirmed, clinical course indicated tuberculosis. During anti-mycobacterial therapy (rifampicin — RMP, isoniazid — INH, streptomycin — SM, pyrazinamide — PZA) lasting for 6 months, systematic clinical improvement was observed with resolution of inflammatory lesions in a second chest CT. At the age of 4, another chest CT was performed due to a chronic cough and periodic bronchopulmonary exacerbations. The results of this CT showed a progression of changes including linear densities in S1 and S2 of the right lung, bilateral striatal-atelectical lesions in S4 and S5, thickening of bronchial walls, and bronchiectasis in S8, S9, and S10 of the left lung. Colonization of airways with *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MSSA) has been observed since then. Since the age of 7, the patient has been suspected of having PID with CMC. Physical examination revealed severe body mass and growth delay (BMI 13 kg/m^2), clubbing, oral thrush, dental caries, splenomegaly, as well as crackling and rhonchi over both lungs. Immunological tests showed IgA, IgG_2, and IgG_4 deficiency, mild CD4+ lymphopenia, reversed CD4/CD8 ratio, and a very low percentage and count of CD19+ cells (Table 2). Initially, common variable immunodeficiency (CVID) was suspected. This was then changed to combined immunodeficiency (CID) and intravenous immunoglobulin supplementation (IVIG), antibiotic and antifungal prophylaxes were recommended. Despite state-of-the-art treatment, the patient still suffered from severe recurrent bacterial and muco-cutaneous fungal (*Candida spp*) infections. Destructive changes in the respiratory tract continued. At the age of 10, she was operated on to treat a severe hiatus hernia. Progressive esophageal obstruction associated with post-inflammatory stenosis of the esophagus (most likely a consequence of chronic candidiasis) required numerous esophageal dilatations. At the age of 13, molecular tests were performed in the Necker Hospital in Paris. Two years later, we were informed about heterozygous missense mutations in STAT1 leading to deleterious amino acid substitutions in the DNA binding domain (P1: c.1154C > T; p.T385M) which provided us with a definitive diagnosis for the patient. The parents of the patient were not genetically evaluated. At the age of 15, she

Table 2. Laboratory tests

Immunoglobulines				
Age [years]	7		16	
BMI [kg/m^2]	13.66		13.2	
	Actual measure [g/L]	**Reference value [g/L]**	**Actual measure [g/L]**	**Reference value [g/L]**
Ig G	15.90	8.53–14.40	12.2	7.06–14.40
Ig A	0.41	0.38–2.35	0.11	0.85–1.94
Ig M	1.80	0.36–1.98	1.65	0.44–1.13
Ig G_1	12.07	6.00–9.61	8.51	5.49–9.80
Ig G_2	0.45	0.98–3.96	1.31	1.68–4.96
Ig G_3	3.36	0.24–0.89	2.34	0.20–0.76
Ig G_4	0.018	0.05–1.58	0.04	0.10–1.64

Flow cytometry analysis — subpopulation of lymphocytes

	No of cells		**Reference value age 5–10 years**		**No of cells**		**Reference value for adults**	
Lymphocytes	**[%]**	**[cell/μl]**	**[%]**	**[cell/μl]**	**[%]**	**[cell/μl]**	**[%]**	**[cell/μl]**
Lymph. T CD3+/CD45+	89.8	2598	55–78	700–4200	98.7	2409	59.7–82.0	900–2600
Lymph. Ts CD3+CD8+/CD45+	63.2	1827	19–34	300–1800	88.9	2168	19.0–38.9	300–1200
Lymph. Th CD3+CD4+/CD45+	20.9	604	27–53	300–2000	7.7	189	30.4–51.2	500–1600
NK cells CD16+56+CD3-/CD45+	2.6	74	4–26	90–900	0.8	20	7.3–24.0	110–540
Lymph. B CD19+/CD45+	89.8	194	10 –31	200–1600	0.30	7	7.2–22.5	100–600

developed a severe invasive skin and pulmonary bacterio-fungal infection which was resistant to fluconazole. Chronic treatment with voriconazole has been implemented since then. At this time, CT scans show a significant degree of cylindrical and cistic bronchiectases in both lungs (Figure 1). Due to hypothyroidism, supplementation of thyroid hormones was incorporated. During the 11-year-follow-up, PFTs were repeatedly performed and an obstructive ventilatory pattern was present increasing airway resistance. Air trapping was gradually worsening. However, difficult cooperation of the patient influcenced PFT quality and brought interpreting difficulties.

At the age of 16, hematopoietic stem cell transplantation (HSCT) was considered due to a progressively deteriorating clinical and immunological condition of the patient (Table 2). However, the unwillingness of patient and her parents towards the procedure together with severe lung disease and the poor worldwide success rates of HSCT discouraged us from this decision. Currently, the patient is treated with subcutaneous immunoglobulins (SCIG), an antifungal agent (voriconazole), and antibacterials (Co-trimoxazole, macrolides, inhaled colistine) for prophylaxis.

Discussion

STAT1 is the target of heritable loss-of-function (LOF) or gain-of-function (GOF) mutations that give rise to distinct clinical phenotypes. STAT1 mediates the actions of many cytokines involved in mounting innate and adaptive immune responses to viruses and intracellular bacteria [5, 6]. Recurrent bacterial infections are common to both types of STAT1 mutations. AR

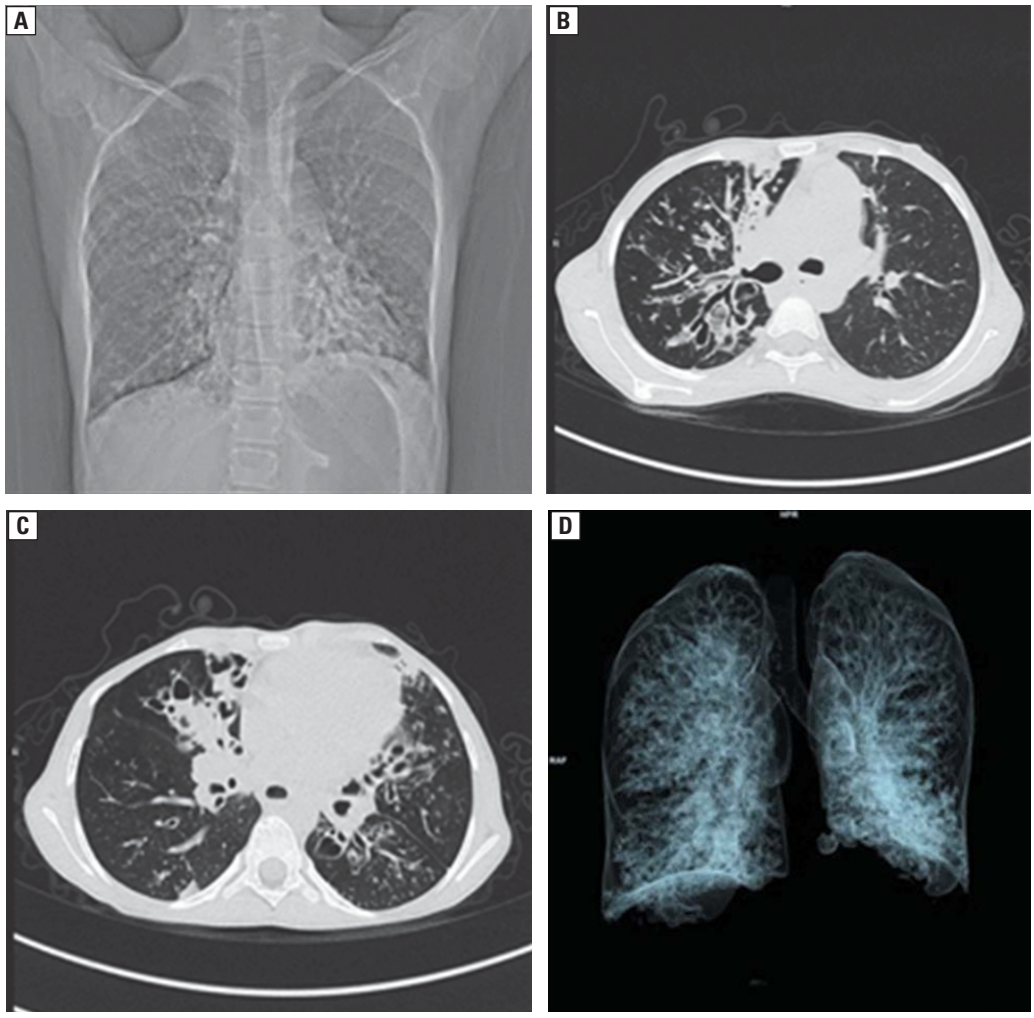


Figure 1. High-resolution computed tomography of the chest. **A.** Frontal plane; **B.** Cystic bronchiectasis with thickening of bronchial walls; **C.** Saccular dilatation of bronchi, partly with mucoid impaction in some places; **D.** three-dimensional imaging — a significant degree of cylindrical and cystic bronchiectasis in both lungs

LOF mutations are additionally defined by invasive mycobacteriosis and viral infections, especially Herpesviridae (HSV, CMV, EBV), whereas AD LOF mutations present with susceptibility to mycobacteria but normal immunity against viruses. AD GOF mutations are distinguished by chronic mucocutaneous candidiasis and autoimmunity [5, 7].

GOF mutations in STAT1 have increasingly been identified as a genetic cause of AD CMC which impaires the development of IL-17-producing T cells [5, 6]. CMC is a heterogeneous disorder with recurrent chronic *Candida spp* infections primarily involving the nails, skin, and oropharynx. CMC can be associated with various pathological conditions listed in Table 3. Recent studies have demonstrated that the clinical spectra of STAT1 GOF mutations continue to expand encompassing bronchiectasis, immune dysregulation, and combined immunodeficiency [8, 9]. Disease manifestations of GOF STAT1 can be mild or severe and life-threatening [9, 10].

Here, we describe a patient with STAT1 GOF mutations who experienced poor weight gain, chronic refractory candidiasis, recurrent pneumonia resulting in bronchiectasis, and severe oral and esophageal candidiases with strictures associated with hypothyroidism. The clinical picture of our patient was consistent with a combined immunodeficiency phenotype resembling a few cases reported in literature [11, 12]. The authors described two patients presenting in early infancy with candidiasis and chronic lung findings including bronchiectasis. One of them also developed a mycobacterial infection.

STAT1 GOF mutations may present early in life with very complex and variable phenotypes. Patients, in most cases, suffer from persistent and recurrent infections of the skin, nails, and mucosa, mainly caused by *C. albicans*, variably associated with bacterial (i.e., respiratory tract and skin), viral (i.e., mostly Herpesviridae), and, less frequently, with mycobacterial infections. They also present with susceptibility to autoimmune diseases (i.e., hypothyroidism, type 1 diabetes, blood cytopenia, systemic lupus erythematosus, vitiligo), enteropathy, cardiac and vascular alterations, bronchiectasis, parodontitis, and failure to thrive [5, 6]. Frequent infectious events increase the risk of chronic lung disease with a severe impact on the quality of life of these patients [7]. Chronic-recurrent infections with different pathogens leading to significant morbidity suggest combined immunodeficiency, CMC, or Mendelian susceptibility to mycobacterial diseases.

Table 3. Primary immunodeficiencies connected with CMC

AD gain-of-function mutation in signal transducer and activator of transcription 1 (GOF STAT1)
Severe combined immunodeficiency (SCID)
Combined immunodeficiencies (CID)
Combined immunodeficiency-like dedicator of cytokinesis 8 deficiency (DOCK8)
AD hyper-IgE syndrome (AD-HIES) - signal transducer and activator of transcription 3 (STAT3) deficiency
Autoimmune polyendocrine syndrome type 1 (APS-1)
IL-12Rβ1 and IL-12p40 deficiencies
IL17F, IL17RA, IL17RC
Tyrosine kinase 2 (TYK2) deficiency
Caspase recruitment domain 9 (CARD9)

In 2016, an international multicenter study examined 274 patients with AD STAT1 GOF mutations. 98% had CMC with a median age at onset of 1 year, 74% had bacterial infections with recurrent lobar pneumonia, bronchitis or interstitial pneumonia (47%), mainly caused by *Streptococcus pneumoniae*, *Pseudomonas aeruginosa, Haemophilus influenzae* and *Staphylococcus aureus,* but only 17 patients (6% of the studied patients) had a mycobacterial infection. Bronchiectasis was reported in 21% of the 274 patients [13]. On one hand, chronic and/or recurrent mucocutaneous fungal infections with predominantly *C. albicans* are the major infectious complications in patients with STAT1 GOF mutations and generally arise in infancy or childhood. On the other hand, the recurrence of pulmonary exacerbations frequently leads to chronic lung disease with an obstructive component as shown by spirometry and progresses to bronchiectasis in childhood. Additionaly colonization with *Pseudomonas aeruginosa* is associated with an increased rate of decline in lung function and a poorer health-related quality of life. That is why careful consideration to the possibility of STAT1 GOF mutations should be given at the time of CMC diagnosis since they are reported to be causative in more than half of CMC patients [13]. Still, we should bear in mind that these patients may exhibit quite different phenotypes, new infections, bronchiectasis, autoimmune diseases, malignancies, and aneurysms that may emerge gradually with age.

Most patients (70–80%) present with normal lymphocyte ratios, immunoglobulin levels, and T-cell function despite the high rate of infections. However, some of the STAT1 GOF mutated patients may develop T (CD3+) and, more frequ-

ently, B (CD19+) cell lymphopenia and hypogammaglobulinemia [7, 13], which was also observed in a described patient above. In STAT1 GOF patients, B cell deficiency has been variably reported with loss of both switched and unswitched memory B cells with age which, together with a low concentration of immunoglobulins, may suggest CVID. This disease-bound progressive loss of immunologic function despite appropriate treatment (antibacterial, antifungal prophylaxis and immunoglobulins substitution) may be another possible reason for newly acquired infections as well as explain the progression of lung disease, which our patient experienced. CVID was also the first provisional diagnosis which was given to the reported patient after a wide range of immunological tests performed for the first time. Recently, a STAT1 GOF mutation has been detected in a patient with a diagnosis of CVID, CMC, and delayed neurocognitive development in association with Th17 deficiency and low Treg counts [14]. That is why most of patients are initially followed with various immunological diagnoses such as CID, IPEX-like syndrome and even undergo HSCT before identification of the molecular defect.

It was reported that phenotypic manifestations of the various STAT1 mutations may differ despite the similar molecular and cellular/immunological features. However, Uzel *et al.* [15], Soltesz *et al.* [16], and Sampaio *et al.* [17] reported patients with the same c.1154C>T (p.Thr385Met) GOF STAT1 mutation as found in our patient. These patients presented with CMC, recurrent lower respiratory tract infections, bronchiectasis, and autoimmunities similar to the case described here. That being said, more clinical information and phenotype–genotype studies are required to define clinical phenotype caused by AD STAT1 GOF.

Management of patients with STAT1 GOF mutations should target prevention and treatment of infections. Prophylactic antimicrobials and IVIG are routinely used for this purpose. JAK (Janus kinase) inhibitors may potentially be useful in some patients as adjunct therapy pending definitive treatment with HSCT [18]. The fact that CMC is heterogeneous, progressive, and unpredictable in its course should alert physicians to recognize early HSCT as a feasible treatment option to avoid severe morbidity and mortality. However, HSCT is variable in success because despite being curative, it brings with it a significant risk of secondary graft failure and death [18]. Thus, the outcome of this procedure has not been well established in patients with GOF-STAT1 mutations yet.

Conclusion

The clinical presentations of our patient with severe, early-onset CID support the notion that STAT1 GOF mutations give rise to a wide range of disease phenotypes including fungal and mycobacterial infections, autoimmunity, and combined immunodeficiency. Regardless, the most commonly seen presenting symptom and clinical presentation is that of progressive bronchiectasis. The proper treatment may not stop progressive and devastating lung disease, which in turn may be a detterent to deciding to use HSCT as a treatment option.

Acknowledgements

The authors are grateful to the patient and her family for their cooperation, and to the scientists from the Laboratory of Human Genetics of Infectious Diseases at the Necker Hospital in Paris for performing molecular tests.

Conflict of interest

The authors declare no conflict of interest.

References:

1. Smith MP. Diagnosis and management of bronchiectasis. CMAJ 2017; 189: E828-E835. doi: 10.1503/cmaj.160830
2. Bush A, Floto RA. Pathophysiology, causes and genetics of paediatric and adult bronchiectasis. Respirology. 2019; 24: 1053-1062. doi: 10.1111/resp.13509
3. Yazdani R, Abolhassani H, Asgardoon MH, et al. Infectious and Noninfectious Pulmonary Complications in Patients with Primary Immunodeficiency Disorders. J Investig Allergol Clin Immunol. 2017; 27(4): 213-224. doi: 10.18176/jiaci.0166.
4. Shillitoe B, Bangs C, Guzman D, et al. The United Kingdom Primary Immune Deficiency (UKPID) registry 2012 to 2017. Clin Exp Immunol. 2018; 192(3): 284-291. doi: 10.1111/cei.13125.
5. Liu L, Okada S, Kong XF, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med. 2011; 208(8): 1635-1648. doi: 10.1084/jem.20110958
6. Frans G., Moens L., Schaballie H., et al. Gain-of-function mutations in signal transducer and activator of transcription 1 (STAT1): chronic mucocutaneous candidiasis accompanied by enamel defects and delayed dental shedding. J Allergy Clin Immunol. 2014; 134(5): 1209-1213.e6. doi: 10.1016/j.jaci.2014.05.044
7. Dotta L, Scomodon O, Padoan R, et al. Clinical and immunological data of nine patients with chronic mucocutaneous candidiasis disease. Data Brief. 2016; 7: 311-315. doi: 10.1016/j.dib.2016.02.040
8. Breuer O, Daum H, Cohen-Cymberknoh M, et al. Autosomal dominant gain of function STAT1 mutation and severe bronchiectasis. Respir Med. 2017; 126: 39-45. doi: 10.1016/j.rmed.2017.03.018.
9. Huh HJ, Jhun BW, Choi SR, et al. Bronchiectasis and Recurrent Respiratory Infections with a De Novo STAT1 Gain-of-Function Variant: First Case in Korea. Yonsei Med J. 2018; 59(8): 1004-1007. doi: 10.3349/ymj.2018.59.8.1004
10. Sharfe N, Nahum A, Newell A, et al. Fatal combined immunodeficiency associated with heterozygous mutation in STAT1. J

Allergy Clin Immunol. 2014; 133(3): 807-817. doi: 10.1016/j.jaci.2013.09.032
11. Baris S, Alroqi F, Kiykim A, et al. Severe Early-Onset Combined Immunodeficiency due to Heterozygous Gain-of-Function Mutations in STAT1. J Clin Immunol. 2016; 36(7): 641-648. doi: 10.1007/s10875-016-0312-3.
12. Eren Akarcan S, Ulusoy Severcan E, Edeer Karaca N, et al. Gain-of-Function Mutations in STAT1: A Recently Defined Cause for Chronic Mucocutaneous Candidiasis Disease Mimicking Combined Immunodeficiencies. Case Reports Immunol. 2017; 2017: 2846928. doi: 10.1155/2017/2846928.
13. Toubiana J, Okada S, Hiller J, et al. International STAT1 Gain-of-Function Study Group. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood. 2016; 127(25): 3154-3164. doi: 10.1182/blood-2015-11-679902.
14. Kobbe R, Kolster M, Fuchs S, et al. Common variable immunodeficiency, impaired neurological development and reduced numbers of T regulatory cells in a 10-year-old boy with a STAT1 gain-of-function mutation. Gene. 2016; 586(2): 234-238. doi: 10.1016/j.gene.2016.04.006
15. Uzel G, Sampaio EP, Lawrence MG, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. J Allergy Clin Immunol. 2013; 131(6): 1611–1623. doi: 10.1016/j.jaci.2012.11.054.
16. Soltész B, Tóth B, Shabashova N, et al. New and recurrent gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis from Eastern and Central Europe. J Med Genet. 2013; 50(9): 567-578. doi: 10.1136/jmedgenet-2013-101570
17. Sampaio EP, Hsu AP, Pechacek J, et al. Signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations and disseminated coccidioidomycosis and histoplasmosis. J Allergy Clin Immunol. 2013; 131(6): 1624-1634. doi: 10.1016/j.jaci.2013.01.052.
18. Leiding JW, Okada S, Hagin D, et al. Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation and the Primary Immune Deficiency Treatment Consortium. Hematopoietic stem cell transplantation in patients with gain-of-function signal transducer and activator of transcription 1 mutations. J Allergy Clin Immunol. 2018; 141(2): 704-717.e5. doi: 10.1016/j.jaci.2017.03.049.

Antidiarrheal pill in the airway

Viswesvaran Balasubramanian[1], Hari Kishan Gonuguntla[2], Nitesh Gupta[3]

[1]Department of Pulmonary Medicine, Yashoda Hospitals, Malakpet, Hyderabad, India
[2]Division of Interventional Pulmonology, Yashoda Hospitals, Secunderabad, Hyderabad, India
[3]Department of Pulmonary, Critical Care & Sleep Medicine, VMMC & Safdarjung Hospital, New Delhi, India

Pill aspiration depicts an unusual type of foreign body aspiration necessitating a discrete diagnostic and therapeutic approach [1]. Some pills may remain intact in the endobronchial tree for many years without causing much harm, whereas others may dissolve [2]. The clinical outcomes vary from an asymptomatic granuloma to severe, life-threatening airway complications, depending upon the chemical properties of the pill. We report a compelling case of pill aspiration in a healthy patient.

A 50-year-old gentleman, non-smoker, presented with respiratory distress after episodes of paroxysmal cough for one day. On clinical examination, palpable crepitus was present in the neck. The chest radiograph revealed a left upper lobe collapse, prompting further assessment. The patient denied history of chest pain, vomiting, weight lifting, rapid ascent, or descent of altitude. Computed tomography (CT) revealed radiopaque foreign body at the bifurcation in the left main bronchus. Also, there were present pneumomediastinum, small apical pneumothorax, and subcutaneous emphysema (Figure 1A). Subsequently, on repeated enquiry, the patient reported paroxysmal coughing episodes while consuming his tablet loperamide.

Endobronchial assessment with flexible bronchoscope through a rigid bronchoscope identified a white powdery foreign body emerging from granulation tissue at the distal opening of the left upper lobe bronchus. Single application of the cryoprobe was unsuccessful in extracting the pill enbloc, so multiple cryoprobe applications were done to remove the disintegrated pill particles (Figure 1B). At the end of the procedure, approximately the 80% patency of the airway was restored. Follow-up bronchoscopy, done 3 weeks later revealed complete patency of the airways without residual scar. On subsequent follow-up, the man remained asymptomatic.

Aspiration of a foreign body into the airways is a potentially fatal situation posing a diagnostic challenge. The symptoms range from asymptomatic to non-resolving pneumonia and respiratory distress of variable degrees, depending on the location of FB. Subcutaneous emphysema is among least common presentations of foreign body bronchus.

The development of subcutaneous emphysema is attributed to a ball-valve mechanism. Alveolar or airway breach allows the escape of air into the perivascular tissue around the pulmonary arteries which communicate with the mediastinum from which air may ascend into the neck and chest wall [3].

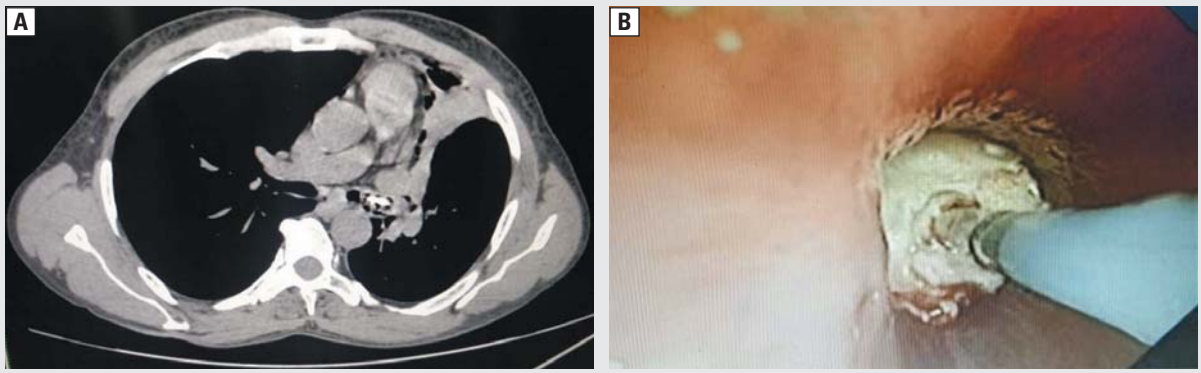


Figure 1. A. CT thorax confirms left upper lobe collapse due to radiopaque foreign body (arrow); **B.** Flexible bronchosopy revealed an airway obstruction in the proximal left upper lobe bronchus. The entire granulation tissue along with the tablet was removed with a cryoprobe

Address for correspondence: Nitesh Gupta, Department of Pulmonary, Critical Care & Sleep Medicine, VMMC & Safdarjung Hospital, New Delhi, India; e-mail: niteshgupta2107@gmail.com
DOI: 10.5603/ARM.2020.0114
Received: 09.01.2020

ISSN 2451–4934
Conflict of interest: None declared

The diagnosis of FB aspiration requires a detailed history of aspiration and clinical symptoms and signs. The radiographic evaluation reveals either radiopaque FB or indirect signs such as lobar collapse, segmental atelectasis, or innocuous infiltrates [4]. The location of FB is more common on the right side than the left one. The direct visualization of the foreign body by a bronchoscope confirms the diagnosis. The features of tissue reactions to FBs include granulation tissue formation, endobronchial stenosis, strictures, edema, and airway distortion.

The availability of flexible catheters allows the use of cryotherapy through flexible bronchoscopes. The cryotherapy probe is traditionally used for the treatment of endobronchial lesions and parenchymal biopsy. It is also an excellent instrument that can be used to remove foreign airway bodies. The mechanism facilitating the use of cryotherapy probes to remove foreign bodies requires a certain amount of water content in the FB, suggesting that most organic material is appropriate for this approach. Fruchter et al., in an ex vivo study involving retrieval of 18 commonly aspirated objects using cryoprobes, demonstrated successful retrieval of inorganic objects (including pill) with low water content [5]. In the present case, a flexible cryoprobe used the slippery properties of the granulation tissue on the foreign body by freezing it onto the probe's tip. To further facilitate removal, one may consider spraying saline over the object and immediate freezing of the foreign body, which then contains water to allow for successful cryoextraction as performed in the current case.

References:

1. Kinsey CM, Folch E, Majid A, et al. Evaluation and management of pill aspiration: case discussion and review of the literature. Chest. 2013; 143(6): 1791–1795, doi: 10.1378/chest.12-1571, indexed in Pubmed: 23732590.
2. Kupeli E, Khemasuwan D, Tunsupon P, et al. "Pills" and the air passages: a continuum. Chest. 2015; 147(1): 242–250, doi: 10.1378/chest.14-0531, indexed in Pubmed: 25560862.
3. Findlay CA, Morrissey S, Paton JY. Subcutaneous emphysema secondary to foreign-body aspiration. Pediatr Pulmonol. 2003; 36(1): 81–82, doi: 10.1002/ppul.10295, indexed in Pubmed: 12772230.
4. Kupeli E, Khemasuwan D, Tunsupon P, et al. "Pills" and the air passages. Chest. 2013; 144(2): 651–660, doi: 10.1378/chest.13-0080, indexed in Pubmed: 23918109.
5. Fruchter O, Kramer MR. Retrieval of various aspirated foreign bodies by flexible cryoprobe: in vitro feasibility study. Clin Respir J. 2015; 9(2): 176–179, doi: 10.1111/crj.12120, indexed in Pubmed: 24521482.

Unusual initial presentation of ABPA as hydropneumothorax

Juvva Kishan Srikanth, Nitesh Gupta, Sumita Agrawal, Shibdas Chakrabarti, Pranav Ish

Department of Pulmonary, Critical Care & Sleep Medicine, VMMC & Safdarjung Hospital, New Delhi, India

A 48-year-old female with bronchial asthma presented with right-sided pleuritic chest pain since 20 days followed by cough with expectoration and shortness of breath since 15 days. She was not compliant with her asthma medications. On examination, the patient was febrile with tachycardia, tachypnea, hypotension and room air saturation of 85%. Respiratory system examination revealed tracheal deviation to the left, reduced chest expansion and decreased breath sounds in the entire right hemithorax and the presence of succussion splash.

Chest X-ray PA view showed right hydropneumothorax. High-resolution computed tomography (HRCT) scan of the thorax demonstrated right-sided loculated hydropneumothorax with collapse of the underlying lung (Figure 1A). Intercostal drainage (ICD) tube insertion was performed and the pleural fluid aspirate showed exudative, lymphocytic fluid with low ADA. The patient was initiated on broad-spectrum antibiotic therapy. Follow-up HRCT scan demonstrated complete resolution of hydropneumothorax, and ICD tube was removed. Also, the presence of underlying bronchiectasis (varicose type) was documented on the right side (Figure 1B). On further evaluation the patient was found to have peripheral eosinophilia (A.E.C. = 3800/μL). The Af-IgE (0.58 kU/L), total IgE (2157 IU/mL) and Af-IgG (141 mgA/L) were positive; thereby confirming allergic bronchopulmonary aspergillosis (ABPA) as per ISHAM criteria [1]. Alternative etiologies of hydropneumothorax were ruled out by negative sputum and pleural fluid analysis for tubercular, bacterial and fungal cultures.

The patient was initiated on inhaled therapy and oral Prednisolone at a dose of 0.5 mg/kg/day for two weeks, then on alternate days for eight weeks [1]. The woman improved symptomatically after 10 weeks and is currently under follow-up.

The literature search yielded 7 case reports of pneumothorax/hydropneumothorax in ABPA [2–5]. Of 7 cases, only 3 had initial presentation as pneumothorax/hydropneumothorax [2–4]; the remaining four had pleural complication on follow-up. The probable etiology of pleural complications in ABPA is either secondary to severe underlying bullous lung disease or impacted mucus acting as a ball valve leading to air trapping and rupture of the bronchus [2–5].

This case highlights the need to suspect ABPA, even if the patient presents with pleural pathology (pneumothorax or hydropneumothorax) in a known case of bronchial asthma and peripheral eosinophilia.

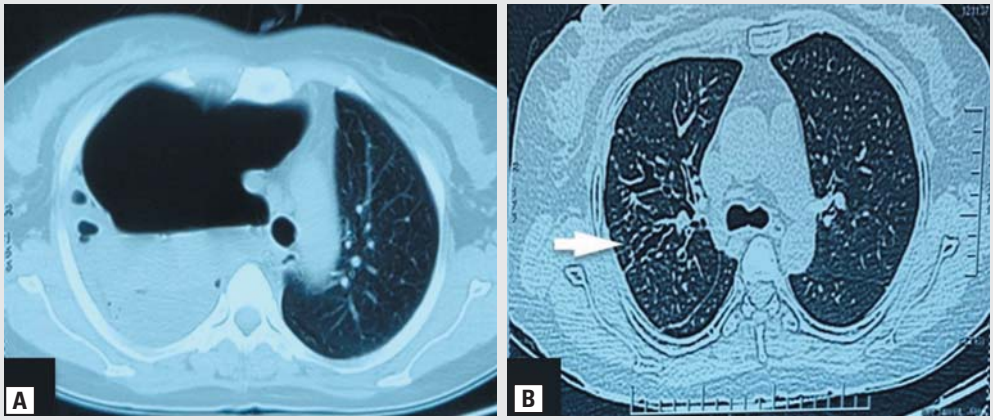


Figure 1. A. High-Resolution Computed Tomography of the chest demonstrating right-sided hydropneumothorax; **B.** complete re-expansion of the right lung with the presence of central bronchiectasis (varicose type; white arrow)

Address for correspondence: Nitesh Gupta, Department of Pulmonary, Critical Care & Sleep Medicine, VMMC & Safdarjung Hospital, New Delhi, India; e-mail: niteshgupta2107@gmail.com
DOI: 10.5603/ARM.2020.0115
Received: 20.01.2020

ISSN 2451–4934
Conflict of interest: None declared

References:

1. Agarwal R, Chakrabarti A, Shah A, et al. For the ABPA complicating asthma ISHAM working group. Clinical & Experimental Allergy. 2013; 43: 850–873.
2. Das A, Das S, Basuthakur S. Right-sided pneumothorax and right upper lobe collapse: Two unusual presentations of allergic bronchopulmonary aspergillosis. The Journal of Association of Chest Physicians. 2014; 2(2): 71, doi: 10.4103/2320-8775.135116.
3. Vishnukanth G, Dwivedi DP, Joseph J, et al. Secondary spontaneous pneumothorax. An unusual clinical presentation of allergic bronchopulmonary aspergillosis. Indian Journal of Immunology and Respiratory Medicine. 2017; 2(3): 93–95.
4. Suri T, Makkar N, Ray A, et al. A unique case of hydropneumothorax in allergic bronchopulmonary aspergillosis. Med Mycol Case Rep. 2019; 25: 29–31, doi: 10.1016/j.mmcr.2019.07.003, indexed in Pubmed: 31338287.
5. Isaac BT, Samuel JT, Mukherjee DK, et al. Loculated pneumothorax due to a rare combination resulting in an interesting chest radiograph. Clin Respir J. 2017; 11(6): 1074–1078, doi: 10.1111/crj.12457, indexed in Pubmed: 26789278.

An uncommon presentation of osteosarcoma

Mantha Satya Padmaja[1], Sourin Bhuniya[2], Suprava Naik[3], Mukund Sable[4], Sudip Ghosh[2], Prasanta Raghab Mohapatra[2]

[1]Pulmonary Medicine and Critical Care, All India Institute of Medical sciences, Bhubaneswar, India
[2]Department of Pulmonary Medicine and Critical Care, All India Institute of Medical Sciences, Bhubaneswar, India
[3]Department of Radiodiagnosis, All India Institute of Medical sciences, Bhubaneswar, India
[4]Department of Pathology, All India Institute of Medical Sciences, Bhubaneswar, India

A 20-year old female presented to our department with complaints of sudden-onset dyspnea and right-sided chest pain for the last month. The patient was started on empirical anti-tuberculosis therapy by a local physician, but there was no respite from the symptoms and she deteriorated clinically. A detailed patient history revealed that she had pain and swelling over the right knee, left arm, as well as vague complaints of generalized body aches for the last 5 months. On clinical examination, she had tachycardia and tachypnoea with an oxygen saturation of 90% at room air. There were enlarged, hard, and non-tender lymph nodes over the right axilla (2 × 2 cm) and bilateral inguinal regions (2 × 1 cm). Lung auscultation revealed dull notes and decreased breath sounds over the left hemithorax. Examination of the lower limbs revealed a diffuse, tender swelling over the right distal thigh. Pleural fluid analysis was exudative with ab ADA of 24 IU/L, and without evidence of any abnormal cells. Radiographic imaging of the right knee was suggestive of an osteogenic malignancy (Figure 1). Serum alkaline phosphatase level was also elevated. Contrast-enhanced computed tomography (CECT) of the thorax and abdomen (Figure 1) revealed extensive calcification of bilateral pleurae, mediastinum, hila and pulmonary vessels. There were multiple enlarged and calcified mediastinal and abdominal lymph nodes along with a calcified left adrenal mass. Excision biopsy of the right axillary lymph node showed sheets of malignant cells surrounding the malignant osteoid with brisk mitotic activity. Immunohistochemical studies showed that the tumour cells were diffusely and strongly immunopositive for Vimentin, while immunonegative for CK, LCA, SALL4, Desmin, Myogenin, S100 and HMB45 (Figure 2). Thus, a diagnosis of metastatic osteosarcoma was made. The patient was critically ill, rapidly progressed to respiratory failure and finally died in the intensive care unit.

The most common primary bone malignancy is osteosarcoma, with the peak incidence in the second decade of life. Around 10% of patients present with distant metastases. The most common sites of metastasis are the lungs and bone, while the unusual sites of metastasis include the brain, abdominal viscera, lymph nodes, pleura, pericardium and the oral cavity [1]. Analysis of an autopsy database in Japan showed 12.1% involvement of pleura in patients who died of metastatic osteosarcoma. However, extensive involvement of pleura in primary osteosarcoma during life is very rare. Extensive involvement of pleura may occur either from hematogenous or direct spread from the underlying lung. In our case, bilateral extensive calcification of the pleura was probably due to hematogenous spread from the primary lesion in the right leg.

Regional lymph node involvement in osteosarcoma is rare with reported incidence rates ranging from < 1% to 10%. The incidence of lymph node metastasis as reported by the Co-operative Osteosarcoma Study Group (COSS) is 0.8%, whereas other series reported clinically detectable lymph node metastasis to be less than 4% at initial presentation [2, 3]. Patients diagnosed with osteosarcoma who have regional lymph node metastasis have a poor overall survival when compared to those without regional node involvement [4]. In one series, the median survival rate reported in this group was 8.5 months after diagnosis, which was similar to those with distant metastasis. Our patient had predominantly metastasis to the pleura and lymph nodes, which is usually rare. Regional lymph node involvement can serve as an adverse prognostic indicator independent of other known prognostic factors in osteosarcoma.

A high index of suspicion and meticulous clinical examination is essential for early diagnosis in cases of undiagnosed pleural effusion and peripheral lymphadenopathy.

Address for correspondence: Sourin Bhuniya, Department of Pulmonary Medicine And Critical Care, All India Institute of Medical Sciences, Bhubaneswar, India; e-mail: sbhuniya@hotmail.com
DOI: 10.5603/ARM.2020.0121
Received: 26.01.2020

ISSN 2451–4934
Conflict of interest: None declared

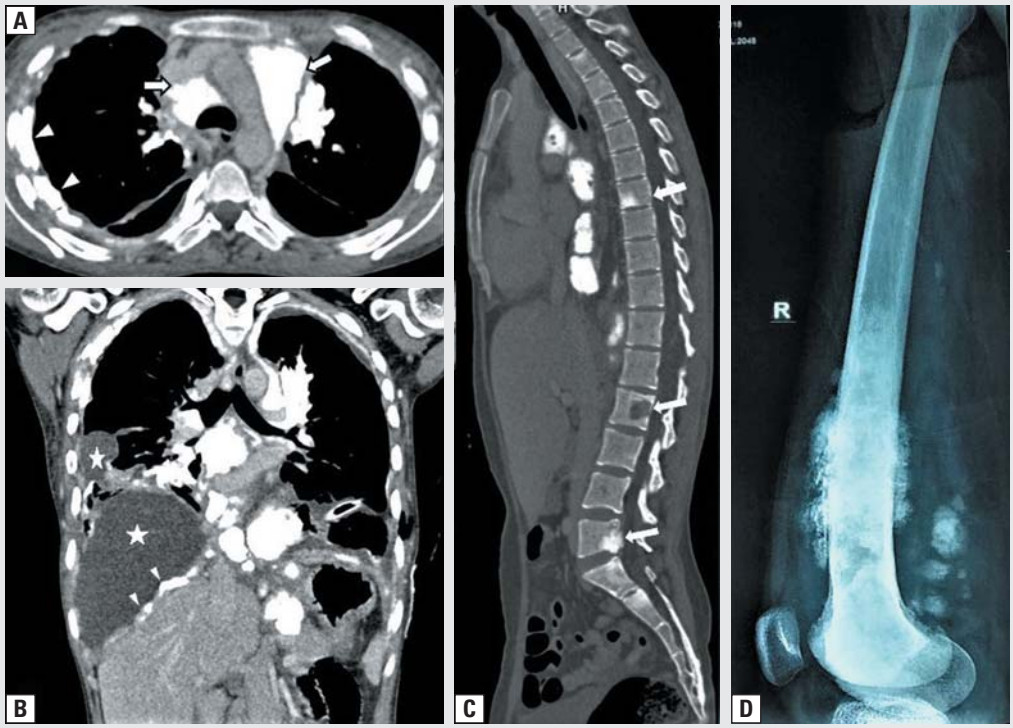


Figure 1. Axial CECT at the level of aortic arch (**A.**) shows multiple large calcified paraaortic and pre-tracheal lymph nodes (arrows), irregular right sided pleural thickening and calcification (arrowheads). Coronal (**B.**) and sagittal bone window (**C.**) reformatted images show extensive mediastinal, perivascular, gastrohepatic metastatic calcified lymphadenopathy, extensive pleural calcification including bilateral diaphragmatic pleura (narrow arrowheads in **B.**), multiple bilateral loculated pleural effusion (stars in **B.**), lytic and sclerotic metastasis in vertebrae (arrows in **C.**). In the same patient, x-ray of right thigh lateral view (**D.**) shows bone tumour with aggressive periosteal reaction at distal femoral metaphysis

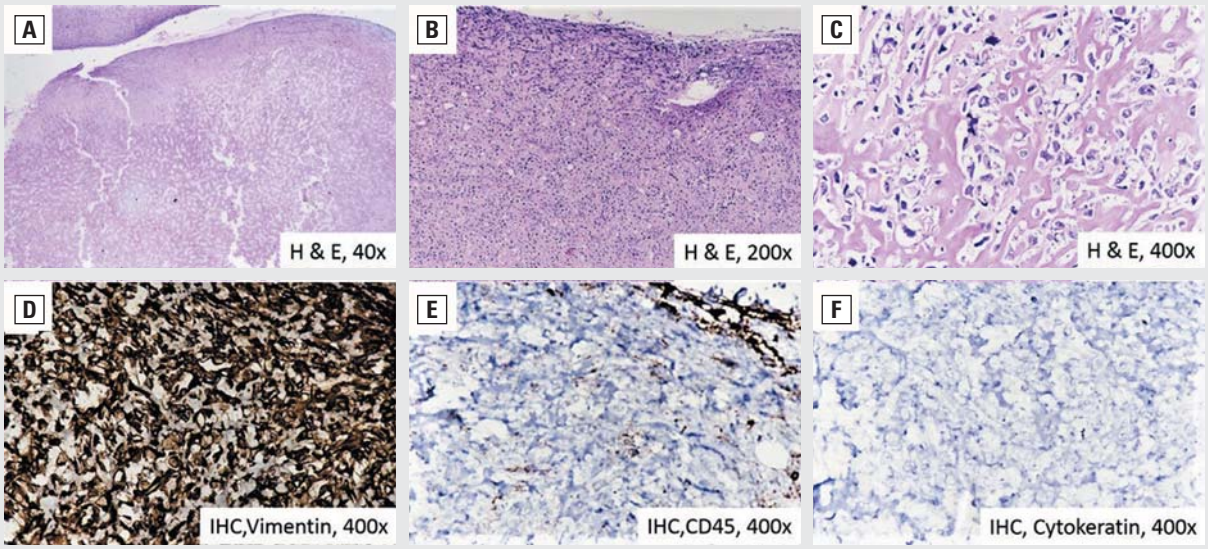


Figure 2. Histopathological examination of lymph node shows complete replacement of lymph node by a tumour tissue, with peripheral rim of lymphoid cells (**A.**, **B.**). The tumour shows atypical cells with extensive osteoid formation (**C.**). The tumour was immunopositive for vimentin (**D.**), while negative for CD45 (**E.**) and cytokeratin (**F.**)

References:

1. Nouyrigat P, Berdah JF, Roullet B, et al. Osteosarcoma with calcified regional lymph nodes. Pediatr Radiol. 1993; 23(1): 74–75, doi: 10.1007/BF02020235, indexed in Pubmed: 8469605.
2. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol. 2002; 20(3): 776–790, doi: 10.1200/JCO.2002.20.3.776, indexed in Pubmed: 11821461.
3. Meyers PA, Heller G, Healey JH, et al. Osteogenic sarcoma with clinically detectable metastasis at initial presentation. J Clin Oncol. 1993; 11(3): 449–453, doi: 10.1200/JCO.1993.11.3.449, indexed in Pubmed: 8445419.
4. Thampi S, Matthay KK, Goldsby R, et al. Adverse impact of regional lymph node involvement in osteosarcoma. Eur J Cancer. 2013; 49(16): 3471–3476, doi: 10.1016/j.ejca.2013.06.023, indexed in Pubmed: 23867123.

Nipun Malhotra[1], Shekhar Kunal[2]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India
[2]Department of Cardiology, SMS Medical College, Jaipur, India

The catch-22 of the COVID-19 "lockdown"

To the Editor

The turn of the year marked the ominous birth of what later developed into a pandemic. The Chinese city of Wuhan reported a cluster of 44 cases of pneumonia which had an unknown etiology [1]. The offending agent was later found to be a novel coronavirus, the third of its type to cause a major outbreak in humans over the past two decades following SARS and MERS. The resulting disease was later named COVID-19 [2]. The virus' high rate of infectivity in a city of almost 10 million people led to a rapid and exponential growth of cases. The healthcare system quickly became overwhelmed and the Chinese government responded by imposing a lockdown. The aim was straight-forward: to stagger the exponential growth of new cases and thus "flatten the curve" [3]. This allowed the healthcare system to have some more flexibility in order to respond to the huge number of patients.

India identified its first case on 30th January 2020 [4]. The patient was a student returning from the city of Wuhan. With an ever-increasing number of cases being diagnosed over the coming weeks, countries further imposed travel restrictions and closed international borders to prevent the spread of the disease. This initial measure only delayed the unavoidable and many countries began to see a rapid increase in cases. Local transmission played a significant role in this increase. Consequently, on March 11th, 2020, the World Health Organization declared that COVID-19 was a "pandemic" [2]. Over the next 10 days, India noticed the beginning of an exponential upstroke in cases. The goal of the Government of India was to "stagger the cases" and "flatten the curve". Therefore, they responded by initiating an unprecedented nationwide lockdown which brought all non-essential services to a halt.

The flip side of the coin

In absence of a definitive treatment or an effective vaccine, lockdown and social distancing are the two weapons to combat this pandemic. The aim behind the lockdown was to contain the spread and to upscale healthcare facilities in order to better manage the potential "flood" of cases. Another merit of this plan was that it would theoretically allow for healthcare research teams to come up with an effective curative and/or prophylactic treatment plan. The strategy has arguably worked, with the number of new cases outside of "hotspot areas" not showing a disastrous increment. There are, however, unsolicited effects that bear considerable relevance in a country with limited resources.

A double-edged sword

State governments throughout India have designated major tertiary care hospitals to specifically manage COVID-19. Medical subspecialty services in the Indian public health setup are extremely scarce outside of tertiary care centers. A vast majority of super specialty and subspecialty services in India are limited to tertiary care centers. In most of these hospitals, routine out-patient services have been halted with only emergency services being delivered. In addition, resident doctors of these specialties have been

Address for correspondence: Shekhar Kunal, Department of Cardiology, SMS Medical College, Jaipur, Rajasthan, India; e-mail: shekhar.kunal09@gmail.com
DOI: 10.5603/ARM.a2020.0097
Received: 22.04.2020

ISSN 2451–4934

diverted to perform COVID-19 duties in order to form a large pool of health care professionals (HCP) that are focused on this specific medical issue. This was largely done to maximize the treatment of the huge number of COVID-19 patients as well as to have adequate backup in the unfortunate event that frontline HCPs were to get infected. Further, planned medical procedures and surgeries have been postponed for the foreseeable future. Hospitals have been advised to discharge all patients who are not very ill in order to create space for COVID-19 patients. These steps also contribute towards decreasing potential cross-infection.

A majority of India's 1.3 billion population belong to low/middle-income groups which mainly utilize public health services for their health needs. These people also depend on government provisions for disease-related follow-up and pharmacological re-fills. This fact is further compounded by the country's high prevalence of diseases such as hypertension, coronary artery disease, diabetes mellitus, cataract, chronic obstructive pulmonary disease, tuberculosis, and various malignancies [5]. Considering the above-mentioned information, it is important to note that long duration lockdowns carry a risk of aggravating and losing control of the treatment of chronic illnesses. Financial constraints also inhibit the use of home-based monitoring devices which further heightens the risk.

Logic and logistics

The interconnected digital world has spread awareness about preventative measures against an infective pandemic disease more effectively and quickly than at any time in the past. To HCP's, avoiding hospital contact during this trying time has become fundamentally and logically pertinent. The 'nation' may be under lockdown, but the "disease" isn't. Even when people fall ill from diseases other than COVID-19, they will tend to avoid hospital contact. This has mostly been seen in patients experiencing acute coronary syndromes and cerebrovascular incidents. They may either ignore symptoms, consult local health services for symptomatic treatment, or even self-medicate. In doing so, an essential evaluation of symptoms that may require special tests is not completed. In addition, the majority of low/middle-income households primarily use affordable public transport systems. For people seeking care in public hospitals, the curbs on transport create a hurdle in their ability to physically be able to get to well-equipped centers culminating in treatment delay.

A receding ocean before the tsunami

During the periods of lockdown, stable patients with chronic diseases have been advised to stay at home and avoid going to hospitals for routine follow up. Patients requiring non-urgent care have been asked to wait and routine procedures/surgeries have also been put on hold. In addition to this, patients are avoiding hospital visits with a fear of contracting COVID-19. As a result, the number of these patients is accumulating. Once the lockdown restrictions are taken down, the flood of patients will undoubtedly put the health care system, which may already be depleted, in further distress. In addition, the lockdown hampers the economy of the country as a whole which can lead to an economic crisis. This will further impair our spending on strengthening healthcare services, purchasing testing kits, and funding the purchase of equipment and drugs.

The benefit of a nationwide "lockdown" has its positives and negatives. It has dampened the potential explosion of COVID-19 cases in countries such as India and Singapore. However, its doubtless effect on patients with non-COVID-19 illnesses is worrisome. A prolonged lockdown which will seemingly benefit COVID-19 containment will also impair patients with other diseases. As such, this period cannot be indefinite. India has slowly but progressively managed to reduce the morbidity and mortality resulting from "disease" in general. It is prudent to address this catch-22 situation extensively and promptly or else the good work that has been accomplished up to this point may be tarnished.

Conflict of interest

Authors have no conflict of interest to declare.

References:

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579: 270–273.
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020; 91: 157–160.
3. Lau H, Khosrawipour V, Kocbach P, et al. The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China. J Travel Med. 2020; 27(3), doi: 10.1093/jtm/taaa037.
4. Ministry of Health and Family Welfare. Update on Novel Coronavirus: one positive case reported in Kerala. Available at: https://pib.gov.in/PressReleaseIframePage.aspx?PRID=1601095. [Last accessed on: 15th April 2020].
5. Arokiasamy P. India's escalating burden of non-communicable diseases. Lancet Glob Health. 2018; 6(12): e1262–e1263, doi: 10.1016/s2214-109x(18)30448-0.

Pranav Ish[1], Nipun Malhotra[1], Sumita Agrawal[2], Nitesh Gupta[1]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India
[2]Department of Pulmonary, Critical Care and Sleep Medicine, Medipulse Hospital, Jodhpur, Rajasthan, India

Relative lymphocytosis in COVID-19 — a ray of hope

Dear Editor

A recent article on 150 COVID-19 patients from Wuhan, China, was a comprehensive analysis of clinical predictors of mortality [1]. Age, cardiovascular comorbidities, total leucocyte counts, lymphocyte count, platelet count, liver and kidney functions, IL-6, C-reactive peptide (CRP) and cardiac biomarkers were significantly associated with increased mortality. Fulminant myocarditis was stressed as a poor prognostic marker. However, an equally important parameter is the percentage of lymphocytes. In the same trial , total leucocyte count was 10.62×10^9 cells/litre vs 6.76×10^9 cells/litre in the dead *vs* survival group, respectively. On the other hand, lymphocytopenia was more profound; 0.662×10^9 cells/litre in the dead group *vs* 1.4262×10^9 cells/litre in the survival group. Both these values were statistically significant (p value < 0.05) [1].

Similarly, in an initial compilation of data of 51 COVID-19 patients at the authors' current centre from India, a trend supporting all the above observations is becoming increasingly noticeable. The **mean leucocyte count was 5.7×10^9 cells/ /litre with a mean lymphocyte percent of 40.6%** (Figure 1, 2). As the mean leucocyte count falls in the normal range, this is a relative lymphocytosis, defined as increased lymphocyte percent to 40% or more [2]. The mean haemoglobin was 16 g/dL and platelet count was 260×10^9 per litre. All the patients had stable vitals, preserved organ functions and required only symptomatic treatment for fever with or without cough; thereby being classified as having mild upper respiratory tract infection [3].

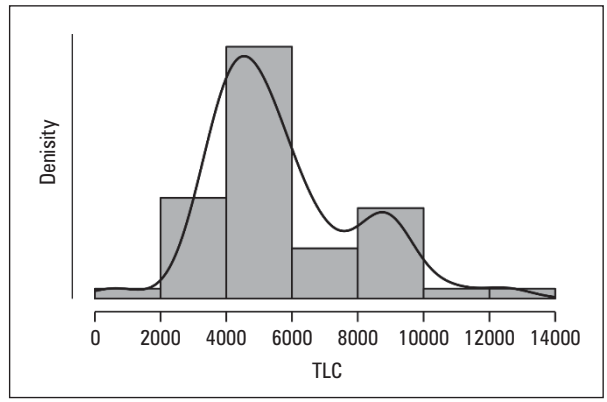


Figure 1. The distribution of total leucocyte count with a mean of 5.7 $\times 10^9$ cells/litre

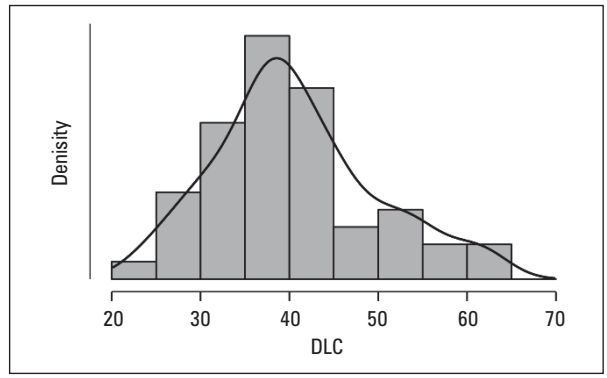


Figure 2. The lymphocyte percent is normally distributed with mean of 40.6% and a standard deviation of 9.0%

Lymphopenia has been found to be very common (85%) in critically ill COVID-19 patients [4]. Another study tried to develop predictive models,

Address for correspondence: Nitesh Gupta, Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India; e-mail: niteshgupta2017@gmail.com
DOI: 10.5603/ARM.a2020.0098
Received: 11.04.2020

ISSN 2451–4934

where lymphocyte count > 20% at day 10 of illness has been found to be characteristic of the moderate group with favourable prognosis [5]. In concordance with that, as our mean lymphocyte count was 40.6%, all patients were predicted to have a recovery.

Multiple mechanisms have been proposed for lymphopenia in severe COVID-19. Direct lymphocyte inhibition, lymph node destruction, inflammatory cytokines, lactic acidosis supressing lymphocytes and coronavirus attaching to the angiotensin-converting enzyme 2 (ACE2) receptor on lymphocyte are few plausible explanations [4]. However, relative lymphocytosis defies all these pathophysiologies and hence may be an indication of a favourable prognosis. Acute viral illnesses like varicella, influenza, infectious mononucleosis are also associated with relative lymphocytosis; most of these eventually develop a spontaneous recovery [6]. The mechanism as to why some people respond favourably needs further research.

This is a very significant observation as a leucocyte count with differential count is done in all patients at admission. This, along with other predictors like age and comorbidities, can be used to make a quick, early decision on the further priority and triage, thereby assisting in efficient resource allocation.

Conflict of interest

None declared.

References

1. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020; 46(5): 846–848, doi: 10.1007/s00134-020-05991-x.
2. Hamad H, Mangla A. Lymphocytosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.
3. Revised Guidelines on Clinical Management of COVID-19. Downloaded from: https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf. [Last accessed on 9 April 2020].
4. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. . 2020; 8(5): 475–481, doi: 10.1016/s2213-2600(20)30079-5.
5. Tan Li, Wang Qi, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020; 5(1), doi: 10.1038/s41392-020-0148-4.

Andreas Afthinos[1], Aggeliki Pandi[1], Maria Horti[2], Ilias C Papanikolaou[1]

[1]Pulmonary Department, Corfu General Hospital, Greece
[2]Pathology Unit, Sismanoglio General Hospital, Greece

Infliximab-induced erythema multiforme in a patient with chronic sarcoidosis

Dear Editor

Tumor Necrosis Factor-α (TNF-α) inhibitors, in particular infliximab, have shown effectiveness as a third-line treatment option in relapsing, refractory sarcoidosis that requires an increased dose of corticosteroids plus one or more anti-sarcoidosis disease modifying drugs [1]. Infliximab has demonstrated effectiveness in severe pulmonary sarcoidosis and in extra-pulmonary sarcoidosis with multi-organ involvement. Bone involvement is reported to occur in 5-13% of patients at some point during their chronic disease course. Recently, in a study of 64 sarcoidosis patients, Zhou et al. found that bone disease occurs mainly in white females with chronic multi-organ disease. This bone involvement most commonly affects the spine (68.8%), pelvis (35.9%), and hands (15.6%). These patients are chronically treated with corticosteroids and almost a quarter of them (23.5%) received infliximab, which appears to be beneficial in chronic bone sarcoidosis [2].

In this article, we report on a case of a 68-year-old Caucasian female with chronic active sarcoidosis which had pulmonary, cutaneous, and joint involvement. The patient also had an unbalanced calcium metabolism. Physical examination of the hands exhibited severe dactylitis (purple-violet discoloration, swelling, distortion, pain, numbness, and nail dystrophy). Due to the relapsing nature of her disease, significant arthralgia after the tapering of pharmacological therapy (prednisone below 15mg in combination with leflunomide 20mg/d), and significant side-effects (osteoporosis), she was started on infliximab 5mg/kg. She received 6 doses of infliximab during a 6 month period (at 0, 2, 6, 12, 18, and 24 weeks, respectively). At the end of the 6 months of treatment, the patient showed significant clinical improvement with complete resolution of her arthritis. Angiotensin-converting enzyme levels fell from 110 U/l to 58 U/l. However, shortly before the last infliximab infusion, she developed an erythematous, patchy, and painful cutaneous lesion located unilaterally and affecting the dorsal, lateral, and phalangeal skin surface of the right lower foot (Figure 1A). The lesion was biopsied and a histopathological examination revealed erythema multiforme (EM) (Figure 1B). Since the patient had not received any other medications which had been known to cause EM, and all cultures and tests for viruses, fungi, and microbes were negative, this was considered to be an infliximab-related infusion reaction resulting in erythema multiforme. After the 6th infusion, infliximab was withdrawn (as initially planned) and EM gradually subsided without any other intervention.

In two recently published studies focusing on refractory sarcoidosis patients with cutaneous symptoms, French investigators treating these patients with anti-TNF-α agents reported discontinuation rates due to adverse effects of 24% and 23%, respectively [3, 4]. Notable side effects that necessitated withdrawing treatment with anti-TNF-α agents included infections and serious immunological reactions. On the other hand, cutaneous reactions stemming from the use of these agents are described to occur commonly (up to

Address for correspondence: Ilias Papanikolaou, Corfu General Hospital, Pulmonary Department, Corfu, Greece; e-mail: icpapanikolaou@hotmail.com
DOI: 10.5603/ARM.2020.0131
Received: 16.04.2020

ISSN 2451–4934

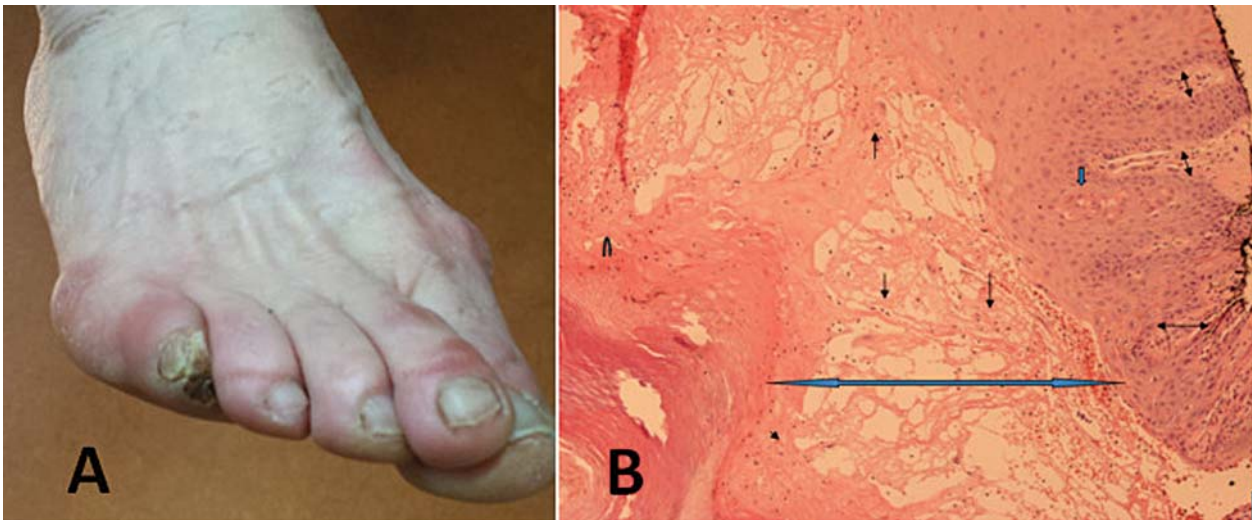


Figure 1. A. Patchy erythematous lesions of the right lower foot at the resolution phase after infliximab discontinuation. **B.** Erythema multiforme: Intraepidermal edema with liquefactive necrosis (double thick arrow), lymphocytic exocytosis (simple arrows), spongiosis (simple thick arrow), dyskeratotic cells, and dermal inflammatory infiltrate including lymphocytes and histiocytes (double thin arrow) (Hematoxylin-Eosin stain X100)

25%) in patients treated for rheumatologic conditions and inflammatory bowel diseases. Such reactions include psoriasis, xerosis, eczema, skin infections, skin cancer, palmoplantar pustulosis, alopecia areata, bullous pemphigoid, drug-induced lupus, and urticaria [5, 6]. However, EM due to infliximab is rare. Although a 2009 Food and Drug Administration (FDA) report included infliximab cutaneous adverse events, only 21 such cases have been reported and all were related to rheumatologic conditions [7, 8]. This case is the first to our knowledge to describe EM after therapy with infliximab in a patient with sarcoidosis.

Cutaneous involvement in sarcoidosis is frequent, affecting up to 25% of patients at some point in their disease course. In our patient, the differential diagnosis included specific or non-specific cutaneous sarcoidosis involvement, skin infections, drug-related reactions, and paradoxical sarcoid-like reactions (reported mainly with use of etanercept in rheumatoid arthritis and inflammatory bowel diseases) [9]. The updated ACCESS organ assessment tool classified our patient`s skin lesions as possibly being due to sarcoidosis because of their atypical nature, therefore, histologic confirmation was mandatory [10]. Since no granulomas were discovered and a temporal association with infliximab administration existed, we considered this EM to be infliximab-related.

Infliximab-induced EM may warrant drug interruption or discontinuation. Therefore, it is important to consider infliximab-induced EM in the differential diagnosis. This would have significant implications for the patient because it could lead to avoiding unnecessary treatment escalation for presumed treatment failure and allowing for appropriate local or systemic EM therapy as well as, if necessary, changing the treatment. In our case, tapering infliximab resulted in EM resolution. Corticosteroids (prednisone) were successfully tapered to a dose of 7.5 mg. The patient also received leflunomide. The patient has remained stable for 18 months without the need to introduce another mode of pharmacological treatment.

References:

1. Baughman RP, Drent M, Kavuru M, et al. Sarcoidosis Investigators. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006; 174(7): 795–802, doi: 10.1164/rccm.200603-402OC, indexed in Pubmed: 16840744.
2. Zhou Y, Lower EE, Li H, et al. Clinical characteristics of patients with bone sarcoidosis. Semin Arthritis Rheum. 2017; 47(1): 143–148, doi: 10.1016/j.semarthrit.2017.02.004, indexed in Pubmed: 28274482.
3. Heidelberger V, Ingen-Housz-Oro S, Marquet A, et al. Efficacy and tolerance of anti-tumor necrosis factor α agents in cutaneous sarcoidosis: a french study of 46 cases. JAMA Dermatol. 2017; 153(7): 681–685, doi: 10.1001/jamadermatol.2017.1162, indexed in Pubmed: 28564695.
4. Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, et al. Groupe Sarcoïdose Francophone. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. Semin Arthritis Rheum. 2017; 47(2): 288–294, doi: 10.1016/j.semarthrit.2017.03.005, indexed in Pubmed: 28392046.
5. Havmose M, Thomsen SF. Development of paradoxical inflammatory disorders during treatment of psoriasis with TNF inhibitors: a review of published cases. Int J Dermatol. 2017; 56(11): 1087–1102, doi: 10.1111/ijd.13691, indexed in Pubmed: 28737221.

6. Segaert S, Hermans C. Clinical signs, pathophysiology and management of cutaneous side effects of anti-tumor necrosis factor agents. Am J Clin Dermatol. 2017; 18(6): 771–787, doi: 10.1007/s40257-017-0296-7, indexed in Pubmed: 28597181.
7. STN: BL 103772/5258. Food and Drug Administration report. 0ctober. ; 29: 2009.
8. Edwards D, Boritz E, Cowen EW, et al. Erythema multiforme major following treatment with infliximab. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013; 115(2): e36–e40, doi: 10.1016/j.oooo.2012.08.001, indexed in Pubmed: 23036796.
9. Decock A, Van Assche G, Vermeire S, et al. Sarcoidosis-Like lesions: another paradoxical reaction to anti-tnf therapy? J Crohns Colitis. 2017; 11(3): 378–383, doi: 10.1093/ecco-jcc/jjw155, indexed in Pubmed: 27591675.
10. Judson MA, Costabel U, Drent M, et al. The WASOG Sarcoidosis Organ Assessment Instrument: An update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis. 2014; 31(1): 19–27, indexed in Pubmed: 24751450.