TURKISH JOURNAL OF EMERGENCY MEDICINE

Clinical Guideline

Access this article online
Quick Response Code:

Website: www.turkjemergmed.org

DOI: 10.4103/2452-2473.329630

2021 Guideline for the Management of COPD Exacerbations: Emergency Medicine Association of Turkey (EMAT) / Turkish Thoracic Society (TTS) Clinical Practice Guideline Task Force

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Submitted: 30-09-2021
Revised: 08-10-2021
Accepted: 09-10-2021
Published: 29-10-2021

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Abstract:

Chronic obstructive pulmonary disease (COPD) is an important public health problem that manifests with exacerbations and causes serious mortality and morbidity in both developed and developing countries. COPD exacerbations usually present to emergency departments, where these patients are diagnosed and treated. Therefore, the Emergency Medicine Association of Turkey and the Turkish Thoracic Society jointly wanted to implement a guideline that evaluates the management of COPD exacerbations according to the current literature and provides evidence-based recommendations. In the management of COPD exacerbations, we aim to support the decision-making process of clinicians dealing with these patients in the emergency setting.

Keywords:

Chronic obstructive pulmonary disease, dyspnea, emergency medicine, practice guideline (MeSH database)

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an important public health issue in both developed and developing countries. It is an important preventable and treatable disease and poses a heavy socioeconomic burden due to its high morbidity and mortality.[1] COPD is the third most common cause of death in the world, according to the World Health Organization (WHO).[2] As per WHO's

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How to cite this article: Doğan NÖ, Varol Y, Köktürk N, Aksay E, Alpaydın AÖ, Çorbacıoğlu ŞK, *et al*. 2021 Guideline for the Management of COPD Exacerbations: Emergency Medicine Association of Turkey (EMAT) / Turkish Thoracic Society (TTS) Clinical Practice Guideline Task Force. Turk J Emerg Med 2021;21:137-76.

projections for 2030 and 2045, COPD will continue to be the third most common cause of mortality after ischemic heart disease and stroke.[3] According to Turkey's data, COPD is the fourth most common cause of mortality,[4,5] and according to the 2019 Health Statistics Yearbook published by the Turkish Ministry of Health, COPD affects 7.1% of individuals aged >15. Furthermore, it was seen that years of life lost due to COPD increased by 53.8% in 2019 compared to that in 2002.[6]

COPD is a disease that progresses with exacerbations, and exacerbations not only worsen the course of the disease but also increase rates of hospitalizations and readmission, thus posing a burden on the health-care system and the economy.[1] A substantial portion of COPD exacerbations observed in Turkey is managed in emergency departments where human resources and logistics facilities are relatively limited. Moreover, scientific data available for the management of patients with COPD exacerbation in the emergency departments are unfortunately limited. For all these reasons, there is a need for developing scientific guidelines based on the available evidence that will guide physicians in the diagnosis, treatment, and referral of patients with COPD exacerbation presenting to a hospital.

As a result, the Emergency Medicine Association of Turkey (EMAT) and Turkish Thoracic Society (TTS) intended to actualize, through a joint effort, an evidence-based guideline developed in consideration of scientific data, which includes the aspects such as diagnosis, treatment, and referral of patients with COPD exacerbations, especially in the emergency healthcare system. The main purpose of the guideline is to assist clinicians in managing emergency cases of COPD exacerbations, which currently occupy a significant share in the health-care system and are expected to continue doing so in the coming years.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2021 Report. Available from: http://goldcopd.org. [Last accessed on 2021 May 25].
2. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. [Last accessed on 2021 May 25].
3. World Health Organization. Projections of Mortality and Causes of Death, 2016-2060. Available from: https://www.who.int/healthinfo/global_burden_disease/projections/en/. [Last accessed on 2021 May 25].
4. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the global burden of disease study 2019. Lancet 2020;396:1204-22.
5. Halpin DM, Celli BR, Criner GJ, Frith P, Varela MV, Salvi S, *et al*. The GOLD summit on chronic obstructive pulmonary disease in low-and middle-income countries. Int J Tuberc Lung Dis 2019;23:1131-41.
6. TR Ministry of Health, 2019 Health Statistics Yearbook. Available from: https://dosyasb.saglik.gov.tr/Eklenti/40564,saglik-istatistikleri-yilligi-2019pdf.pdf?0. [Last accessed on 2021 May 25].

2. Methods

2.1. Establishment of the study group and meetings

The plan to implement a joint practice guide on the exacerbations of COPD through a collaboration of the EMAT and the TTS was initiated after the proposal submitted by EMAT on October 17, 2019, was accepted by TTS. Accordingly, the first framework development meeting between the associations was held on December 21, 2019, with the participation of representatives from EMAT and TTS. Written and signed conflict of interest declaration form was obtained from all the participants. Conflict of interest statements of panel members is presented in Appendix 1.

Decisions were made on the following in the first and the following meeting (dated February 2020): The guideline will be prepared as clinical policy guidelines based on patient/population, intervention, comparison, and outcome (PICO) formulation; responses to PICO questions will be collected from end-users using e-mail groups and social media; the Grading of recommendations assessment, development, and evaluation system will be used; principles of literature review and sponsor support will not be received for any stage of the study. However, due to the COVID-19 pandemic, which also affected Turkey as of March 2020, the meetings were interrupted until June 2020. Since then, the meetings were held online through the Zoom platform.

2.2. Preparation of clinical questions

Before the clinical questions regarding COPD exacerbation were prepared, it was announced (between January 1, 2020 and January 15, 2020) that a joint guideline would be created, and the questions prepared by the physicians regarding the subject would be considered. The announcement was made on the e-mail groups and social media tools of EMAT and TTS. The questions were forwarded to both the associations as structured PICO formulations or in the free-text format. Responses to seven questions regarding the diagnosis of COPD exacerbation, 31 questions regarding treatment, and 14 questions regarding prognosis were submitted by participants. Next, the questions were discussed by three groups of panel members from both the associations at the meeting held on February 2020 with the contribution of research methodology experts; attempts were made to express the questions in the form of PICO formulations. Questions that could not be expressed as PICO questions were archived for consideration in the narrative review section.

Of the questions expressed as PICO questions, 4 regarding diagnostic value and 20 regarding treatment were voted on by the panel members. Accordingly, it was decided to continue with the first ten clinical questions that achieved highest scores in the scoring process.

2.3. Preparation of outcomes

In June 2020, a literature review regarding the prepared PICO questions was conducted, and the questions were finalized by including the outcomes that were regarded as knowledge gaps in the literature. In October 2020, all outcomes were voted on by the panel members. Voting was conducted online using Google Sheets in a blinded fashion. The panel members scored the outcomes out of 9 points; outcomes were scored as follows: 7–9 points (critical outcome should be included in the guideline), 4–6 points (significant outcome should be included in the guideline), or 1–3 points (nonsignificant outcome). Accordingly, it was decided to include 15 outcomes derived from the six questions that were decided to be reviewed in the literature. The questions that were decided to be reviewed in the literature during the panel voting were as follows:

1. Is there a difference between the mortality when procalcitonin-guided antibiotics are used and that when standard care is provided to patients presenting to the hospital with symptoms of COPD exacerbation?
2. In patients presenting to the hospital with symptoms of COPD exacerbation and receiving antibiotic treatment is there a difference between β-lactams and fluoroquinolones, between β-lactams and macrolides, or between fluoroquinolones and macrolides in terms of mortality, hospital readmission, and admission to the intensive care unit?
3. In patients presenting to the hospital with symptoms of COPD exacerbation, is there a difference between systemic and inhaled corticosteroids in terms of mortality, hospital readmission, and admission to the intensive care unit?
4. In patients presenting to the hospital with symptoms of COPD exacerbation, is there a difference between high-flow nasal oxygen therapy (HFNOT) and noninvasive mechanical ventilation (NIMV) and between HFNO and standard oxygen therapy in terms of mortality, hospital readmission, and admission to the intensive care unit?
5. In patients with suspected COPD exacerbation before presenting to the hospital, is there a difference between titrated and standard oxygen therapies in terms of mortality and admission to the intensive care unit?
6. In patients presenting to the hospital with symptoms of COPD exacerbation and receiving antibiotic treatment, is there a difference between short-term antibiotic therapy (5–7 days) and long-term antibiotic therapy (14 days) in terms of mortality, hospital re-admission, and admission to the intensive care unit?

2.4. Literature review

The literature review was conducted in English and Turkish through PubMed and Web of Science without publication date limitation and using keywords and advanced search methods. MeSH terms and natural language terminology were used during PubMed and Web of Science reviews, and the review was conducted by three separate panel subgroups. All article types except for case reports and case series were planned to be included; the references of narrative reviews, systematic reviews, and meta-analyses included were also evaluated for the possible inclusion of a suitable study.

The abstracts of the included articles were transferred to the *Rayyan QCRI*[1] program. With respect to article evaluation, the articles assigned to each clinical question were evaluated by two different investigators blinded to each other. The articles which were found suitable by both the investigators were transferred to the *Zotero* software for full-text evaluation. In cases where two investigators disagreed, the decision was made by a third investigator. Consequently, all full-text articles on relevant clinical questions were archived on the *Zotero* software.

2.5. Evaluation of the results and the risk of bias

Two or three panelists were assigned to each clinical trial question. Full-text articles related to the PICO questions were reviewed by the appointed panelists. The effect sizes as well as continuous and categorical variables in the articles were recorded by the panel members. The revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) was used for the assessment of risk of bias in the randomized clinical studies included,[2] and Risk Of Bias in Nonrandomized Studies-of Interventions (ROBINS-I) was used for the assessment of risk of bias in observational studies.[3] The risk of bias was assessed under different subheadings for each study planned to be included; the studies to be included in the meta-analysis were selected by a methodologist (S. K.).

2.6. Synthesis of evidence and preparation of recommendations

In the guideline, seven domains were evaluated using ROBINS-I, and five domains were evaluated using ROB-2 during evidence evaluation. Studies confirmed as critical and at high risk of bias as a result of the assessment by at least two panel members were not included in the meta-analysis. In case of differences of opinion among the panel members, the opinion of a third panel member or research methodologist was sought. The results of ROB-2 and ROBINS-I evaluations of the studies are presented in Tables 2.1 and 2.2.

The recommendations in the guideline were expressed in two different sections. Sections related to diagnostic and prognostic approaches and treatment interventions, which were developed through clinical questions and

Table 2.1: Evaluation of the risk of bias in randomized clinical trials according to the "Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2)"

Question	Outcome	Article	D1	D2	D3	D4	D5	Result
1	Mortality	Verduri, 2015	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
1	Mortality	Corti, 2016	High risk	High risk	High risk	Low risk	Low risk	High risk
1	Mortality	Zou, 2018	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
1	Mortality	Stolz, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Mortality	vanVelzen, 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Mortality	Elmes, 1965	High risk	High risk	Low risk	Some concerns	Some concerns	High risk
2	Mortality	Nouira, 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Not suitable for PICO	Pines, 1968	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Mortality	Ruiz-Gonzales, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Mortality	Wilson, 2004 (MOSAIC)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Mortality	Allegra, 1996	High risk	High risk	High risk	High risk	High risk	High risk
2	Revisit	Wilson, 2012 (MAESTRAL)	Low risk	Low risk	Low risk	High risk	Low risk	High risk
2	Revisit	Vermeersch, 2019	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
2	Revisit	Vermeersch, 2019	Some concerns	Low risk	Low risk	Low risk	High risk	High risk
3	Not suitable for PICO	Maltais, 2002	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
3	Not suitable for PICO	Maltais, 2002	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
3	Not suitable for PICO	Maltais, 2002	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
3	Not suitable for PICO	Maltais, 2002	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
3	Revisit	Maltais, 2002	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
3	Not suitable for PICO	Maltais, 2002	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
3	Not suitable for PICO	Gunen, 2007	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
3	Revisit	Gunen, 2007	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
3	Revisit	Gunen, 2007	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
3	Revisit	Uçar, 2014	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
3	Revisit	Uçar, 2014	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
3	Revisit	Ding, 2016	Some concerns	High risk	High risk	Low risk	Low risk	High risk
3	Revisit	Stallberg, 2009	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
4	Not suitable for PICO	Doshi, 2020	Some concerns	Low risk	Low risk	Low risk	High risk	High risk
4	Mortality	Austin, 2010	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
6	Not suitable for PICO	Gotfried, 2005	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
6	Not suitable for PICO	Lorenz, 1998	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
6	Not suitable for PICO	Gotfried, 2001	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
6	Adverse effect	Debate,1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
6	Not suitable for PICO	Debate,1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
6	Not suitable for PICO	Debate,1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
6	Revisit	Debate,1999	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
6	Not suitable for PICO	Sethi, 2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Not suitable for PICO	Sethi, 2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Not suitable for PICO	McCarty, 2001	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
6	Adverse effect	McCarty, 2001	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
6	Not suitable for PICO	Wasilewski,1999	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
6	Not suitable for PICO	Wasilewski,1999	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
6	Adverse effect	Wasilewski,1999	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
6	Not suitable for PICO	Masterton, 2001	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
6	Not suitable for PICO	Masterton, 2001	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
6	Not suitable for PICO	Masterton, 2001	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
6	Adverse effect	Masterton, 2001	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
6	Not suitable for PICO	Chodosh, 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Not suitable for PICO	Chodosh, 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Adverse effect	Chodosh, 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Not suitable for PICO	Roede, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Not suitable for PICO	Roede, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Revisit	Roede, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Adverse effect	Roede, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 2.2: Evaluation of the risk of bias in observational studies according to the "Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I)"

Question	Outcome	Article	D1	D2	D3	D4	D5	D6	D7	Result
1	Mortality	Ulrich, 2019	Critical risk	Critical risk	Serious risk	Low risk	Critical risk	Low risk	Moderate risk	Critical risk
2	Mortality	Kiser, 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Mortality	Rothberg, 2010	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
2	Mortality	Stefan, 2013	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
2	Revisit	Bremmer, 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
2	Revisit	Ernst, 2019	Serious risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Low risk	Serious risk
2	Revisit	Kiser, 2019	Moderate risk	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
2	Revisit	Joyner, 2020	Low risk	Low risk	Low risk	Serious risk	Low risk	Low risk	Low risk	Serious risk
4	Mortality	Lee, 2018	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	Moderate risk
5	Mortality	Sun, 2019	Serious risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Serious risk
5	Mortality	Ringbaek, 2015	Serious risk	Serious risk	Moderate risk	Serious risk	Low risk	Moderate risk	Moderate risk	Serious risk

finalized according to the results of the relevant literature review, named as. "Evidence-Based Recommendations for Clinical Questions," which also assesses the relevant risk of objective bias. Recommendations that were included in the narrative review section of the guideline and had a relatively low level of evidence were given as a "Panel Recommendation" throughout the text.

2.7. Statistical analysis

Statistical analyses were performed using the *MedCalc* software (Version 20-Trial Version, MedCalc Ltd., Belgium). Heterogeneity between the studies included in the meta-analysis was tested using the Cochrane Q statistic and I^2 value. If I^2 was >50%, the random-effects model was used, and if it was <50%, the fixed effects model was used. Relative risk (RR) was used for calculating the effect size. Effect sizes were shown with forest graphs. Statistical significance level was set at $P < 0.05$.

2.8. Preparation of the narrative review section

The narrative review section of the guideline was prepared under the supervision of two-panel members (E. A., A. Ö. A.). This section was planned to consist of sections that were planned to be included in the meta-analysis performed using the questions collected at the beginning but could not be included due to the risk of bias and insufficiency of available publications on the subject that meet the appropriate criteria, although they could guide physicians in clinical practice. The literature review and writing of these sections were carried out with the contributions of other panel members. Two panelists from EMAT and TTS were appointed as authors for each chapter, and the chapters and recommendations written were evaluated and approved by all the panel members.

2.9. Preparing and publishing the draft and guideline

The first draft of the guide was created by two-panel members appointed by both the associations (N. Ö. D, Y. V.). All statements, statistical analyses, evidence, and recommendation levels of the draft text were evaluated and approved by both the project methodologist and other panel members. Subsequently, the final version of the guideline was evaluated and approved by the board of directors of both the associations. The guideline text was kept as a draft on the websites of both associations for criticism for 1 month. Then, the final version of the text was published as a guideline.

References

1. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
2. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
3. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.

3. Chronic Obstructive Pulmonary Disease and Chronic Obstructive Pulmonary Disease Exacerbations

Definitions and impact of chronic obstructive pulmonary disease exacerbations

Exacerbations of COPD are acute clinical conditions that occur relatively often in the natural course of the disease and are associated with considerable consequences occurring both during and after an exacerbation. Exacerbations have adverse effects on the quality of life; they are associated with work loss, temporary or permanent reductions in respiratory functions and exercise capacity, increased use of healthcare resources, frequent hospitalizations, and death.[1]

Because one of the main goals of COPD management is to reduce and prevent exacerbations, they have been selected as the end point in many studies. Therefore, there is a need for a precise and monitorable definition of a "COPD exacerbation." The most important problem in this regard is that exacerbations are heterogeneous and patient-reported clinical events, and a specific biomarker describing COPD

exacerbation and/or COPD exacerbation phenotype has not been discovered. The main symptoms of exacerbation are not specific, and differential diagnosis must necessarily be made in patients presenting to the emergency department with symptoms of COPD exacerbation.[2]

Definitions

Since the 1980s, numerous definitions for COPD exacerbations have been developed. These have been used in clinical studies either as symptom-based (dyspnea, cough, sputum volume, and purulence) or event-based (antibiotic or corticosteroid requirement, need for hospitalization, etc.) definitions. However, these definitions have not yet been adequately evaluated in terms of validity, reliability, and sensitivity.[3]

The first definition of exacerbations was the empirical definition and classification suggested by Anthonisen *et al*. in 1987, which is still used in clinical practice for antibiotic use.[4] Anthonisen classified exacerbations into three groups according to symptoms:

- Type 1: Dyspnea and increase in the amount and purulence of the sputum
- Type 2: The coexistence of both of these symptoms
- Type 3: Presence of any of these symptoms accompanied by any of the following: upper respiratory tract infection, fever with no other cause, increased wheezing, increased cough, and 20% increase in the respiratory rate or heart rate from the baseline in the past 5 days.

Exacerbations have been defined as an acute event requiring additional treatment for respiratory symptoms and analyzed in three parts in the *"Global Initiative for Chronic Obstructive Lung Disease"* (GOLD) reports since 2018. The GOLD definition of exacerbation combines both symptom-and event-based definitions and also rates the severity of exacerbations:[5]

- Mild exacerbation: Only short-acting β-agonists are sufficient
- Moderate exacerbation: Short-acting β-agonist and antibiotic and/or oral corticosteroid requirement
- Severe exacerbation: Emergency department presentation and hospitalization requirement.

Table 3.1: Definition of chronic obstructive pulmonary disease exacerbation

An increase in dyspnea is ≥5 (on a visual analog scale ranging from 0-10) and
A decrease in oxygen saturation of at least 4% during the stable period, or an O_2 saturation below 90% if there is no baseline value, and
CRP ≥3 mg/dl and
Peripheral blood neutrophil count ≥9000/mm^3 or peripheral blood eosinophil count >2% and
Absence of heart failure, pneumothorax, pleural effusion, pneumonia on lung imaging
Exclusion of pulmonary thromboembolism by applying clinical risk tools (with d-dimer and CT angiography if necessary); exclusion of heart failure by ECG, proBNP, and/or echocardiography

ECG=Electrocardiography, CT=Computed tomography, proBNP=Prohormone B-type natriuretic peptide, CRP=C-reactive protein

Taking into account the principles of personalized treatment for exacerbations,[6] clinical presentation of COPD,[7] and exacerbation phenotypes,[8] a new definition for exacerbations has been proposed [Table 3.1].[9] However, this definition has not been validated yet.

Individuals who have not been diagnosed with COPD before and who are at risk for COPD but do not have airflow limitation may also experience events resembling exacerbations. For this reason, it should be noted that individuals with risk factors for COPD and a history of chronic bronchitis symptoms may present with clinical manifestations similar to exacerbations and a patient with undiagnosed COPD may initially present with an exacerbation. In these patients, a differential diagnosis should be conducted for exacerbation, and then they should be referred for a detailed evaluation while they are stable.

Etiology

Infections, especially viral infections, are responsible for most exacerbations; however, environmental factors such as air pollution and ambient temperature may also initiate and/or increase the severity of exacerbations.[10] Nonetheless, the necessity of determining the etiology of exacerbations remains to be controversial; causative organisms of exacerbations have not yet been fully identified, and current definitions do not reflect the different types of exacerbations and complexity of the disease. Although four different exacerbation phenotypes (bacterial, viral, eosinophilic, and pauci-inflammatory) have been defined in studies, the corresponding clinical manifestations of these phenotypes remain to be clearly defined.[11] Sputum purulence is considered as an indicator of exacerbations caused by infection.[1,12] In the GOLD 2021 report, according to Anthonisen's criteria, antibiotic use is recommended for type 1 and type 2 exacerbations with sputum purulence and in patients with respiratory failure.[4] However, methods other than sputum purulence are needed to distinguish infectious exacerbations from noninfectious causes.

The incidence of exacerbations is higher in some patients with COPD. The definition of "frequent exacerbation phenotype" is used for this group of patients, and this phenotype is defined as ≥2 exacerbations per year in GOLD reports.[5]

PANEL RECOMMENDATION-1

A COPD exacerbation is characterized by patients feeling a noticeable, persistent worsening of their respiratory symptoms (shortness of breath, cough, and/or sputum) beyond daily variations. It is important that exacerbations are standardized by a common tool. The panel recommends using the symptom-based definition in the diagnosis of exacerbations.

References

1. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, *et al.* Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017;49:1600791.
2. Wedzicha JA, Martinez FJ, editors Chronic Obstructive Pulmonary Disease Exacerbations Lung Biology in Health and Disease. Claude Lenfant, executive editor: ISBN: 9781138372450, CRC Press, 2018.
3. Pauwels R, Calverley P, Buist AS, Rennard S, Fukuchi Y, Stahl E, *et al.* COPD exacerbations: The importance of a standard definition. Respir Med 2004;98:99-107.
4. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of COPD. Updated 2021. Available from: http://goldcopd.org/. [Last accessed on 2021 Feb 01].
6. Agusti A, Faner R, Celli B, Rodriguez-Roisin R. Precision medicine in COPD exacerbations. Lancet Respir Med 2018;6:657-9.
7. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. Eur Respir J 2007;29:1224-38.
8. Noell G, Cosío BG, Faner R, Monsó E, Peces-Barba G, de Diego A, *et al.* Multi-level differential network analysis of COPD exacerbations. Eur Respir J 2017;50:1700075.
9. Kim V, Aaron SD. What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement. Eur Respir J 2018;52:1801261.
10. Turkish Thoracic Society's Perspective on the GOLD 2021 Chronic Obstructive Pulmonary Disease (COPD) Report, 2021. Available from: https://toraks.org.tr/site/community/news/10329. [Last accessed on 2021 May 26].
11. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: Identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662-71.
12. Chronic Obstructive Pulmonary Disease (Acute Exacerbation): Antimicrobial Prescribing. NICE Guideline. December 05, 2018. Available from: https://www.nice.org.uk/guidance/ng114. [Last accessed on 2021 May 26].

4. Prehospital Medical Care for Chronic Obstructive Pulmonary Disease Exacerbations

4.1. Recognition and initial stabilization

In the prehospital setting, dyspnea of unknown cause is an independent risk factor for mortality, and its 30-day mortality rate is higher than that of patients with chest pain (*risk ratio* [RR]: 2.55, 95% confidence interval [CI]: 2.09–3.10).[1] In the USA, 1.9% of the patients who received treatment before hospitalization received it due to respiratory distress; the most common final diagnoses of these patients were reported to be congestive heart failure (CHF) (16%), pneumonia (15%), and COPD exacerbation (13%).[2]

Since incorrect treatment can lead to undesirable consequences, accurate diagnosis is the key for treating patients with dyspnea in the prehospital setting. However, in the prehospital setting, where focused examinations such as imaging and laboratory tests other than physical examination and medical history evaluation are not possible, it may not be possible for the health-care professional to achieve accurate diagnosis. In Denmark, where anesthetists are employed in the prehospital setting, it was reported that 92.9% of the patients diagnosed with COPD exacerbation had the same diagnosis at discharge.[3] In Australia, it has been reported that the prehospital staff accurately diagnosed 57% of patients with exacerbations and 41% of patients with asthma.[4] It is believed that accurate diagnosis in patients with COPD exacerbation is extremely important for providing optimal treatment, but diagnosis may be more difficult, especially in patients with advanced disease, because they may have comorbidities and multiple problems at the same time.[5]

Shortness of breath is one of the five major causes of ambulance calls and the second most frequent complaint leading to death in adult patients after cardiac arrest.[6] Final diagnoses of patients evaluated for dyspnea in the emergency health-care system are known to have a broad spectrum, and the most common diagnosis in the adult population is COPD exacerbation (20.4%). Other common diagnoses are lung infections and heart failures.[7,8] Respiratory diseases evaluated in the emergency department are more common in young and elderly patients, with asthma[9] being more common in young patients and exacerbations of COPD being more common in elderly patients.[10] The presence of a large number of comorbidities in elderly patients is a factor that affects prognosis and also leads to difficulties in diagnosis. Age, medical history, abnormal vital signs, electrocardiography (ECG) findings, pain symptoms, and the delay between symptom onset and call time are important factors for early risk assessment during the prehospital evaluation of a patient whose main complaint is dyspnea.[8] It is difficult to determine prognostic markers for mortality in patients with suspected COPD exacerbation in the prehospital setting. It has been reported that on-site treatment may be sufficient in 10% of patients with exacerbation and 30% of the patients brought to the hospital are discharged within 24 h, but mechanical ventilation is required in 6% of the patients, and the 30-day mortality is 30%. For this reason, in patients with suspected exacerbation, it is not recommended to administer only on-site treatment before the hospital without transferring the patient.[11]

As noted above, although there exist challenges in differentiating between exacerbations and other causes of shortness of breath, patients should be managed according to the basic principles of prehospital care, and the diagnoses most likely to be confused with a COPD exacerbation should also be considered. Increased

shortness of breath, increased cough and sputum, and/or a change in the characteristics of cough and sputum are the three cardinal signs of a COPD exacerbation. Accompanying unconsciousness is an important finding indicating the severity of respiratory failure. Furthermore, wheezing is one of the common symptoms, and therefore it may be difficult to differentiate it from asthma. The prehospital differential diagnosis of asthma and COPD exacerbation is difficult. Since the management of both the clinical conditions is similar, it is recommended to develop a common clinical practice guideline for the prehospital setting.[3] Respiratory distress and wheezing should not merely suggest asthma or COPD exacerbation. Moreover, cardiac asthma is an important clinical condition that is confused with these two diagnoses. Cardiac asthma occurs due to heart failure and is often misdiagnosed. Unlike asthma, it occurs mostly in elderly patients, and unlike COPD exacerbation, it does not present with progressive worsening over hours or days but presents with sudden and severe shortness of breath that usually awakens the patient.[12] Pulmonary thromboembolism (PTE), spontaneous pneumothorax, and pneumonia should also be considered in the differential diagnosis of COPD exacerbations.[13] In addition to the physical examination findings, a detailed medical history guides the differential diagnosis after the first stabilization. The diagnoses of cardiac dysrhythmia and myocardial infarction should be excluded by prehospital ECG evaluation in patients with acute dyspnea and/or chest pain.[14]

Prehospital management of patients with COPD exacerbation includes ensuring adequate oxygenation and ventilation, the initiation of NIMV or invasive mechanical ventilation if necessary, and the use of short-acting bronchodilators. The presence of unconsciousness and respiratory distress together indicates the need for NIMV or invasive mechanical ventilation. Being in a forced position (e.g., being in a tripod position is indicative of the severity of respiratory distress), using the accessory respiratory muscles, having a high respiratory rate ($\geq$30 breaths/min), inability to form complete sentences, and/or low oxygen saturation suggest that respiratory and/or oxygen support should be initiated. For a patient with severe respiratory distress whose airway is at risk and/or has impaired consciousness, the back should be elevated, the mandible should be pulled forward if necessary, and high-flow oxygen should be initiated. Furthermore, the patient is placed in a sitting position, the soft palate is separated from the posterior pharynx, and the airway is passively opened. The diaphragm moves down, and the lung expands.[15] The prehospital monitoring of patients' end-tidal carbon dioxide ($ETCO_2$) levels may be useful in elucidating the obstructive or cardiac etiology. Lower $ETCO_2$ levels suggest heart failure.[16,17]

PANEL RECOMMENDATIONS-2

All patients who are thought to have a COPD exacerbation in the prehospital stage should first be assessed according to the principle of stabilizing the airway, breathing, and circulation. Airway safety of patients should be ensured, and the severity of respiratory distress should be evaluated

In the initial evaluation of patients with acute respiratory distress before the hospital, intravenous vascular access should be established; continuous cardiac monitoring and a 12-lead ECG should be provided

Stabilization of patients with acute respiratory distress before the hospital and focusing on the possible diagnoses among many differential diagnoses is the recommended approach

Patients with suspected COPD exacerbation should be transferred to the hospital for definitive treatment.

4.2. Oxygenation

Adequate oxygen administration is vital for patients presenting with a COPD exacerbation. However, not titrating the inhaled oxygen can lead to carbon dioxide retention, which may be detrimental to the patient's prognosis. As a matter of fact, hypercapnia, respiratory acidosis, and death have been shown to be more common in patients with COPD who receive high amounts of oxygen compared to those who receive enough oxygen to maintain its saturation between 88% and 92% before the hospital.[18] The routine administration of high-flow oxygen therapy should be avoided in patients with COPD exacerbations, and treatment should be individualized.[19] Initially, low-flow oxygen therapy should be administered through a Venturi mask or nasal cannula (1–2 L/min), and the oxygen therapy should be titrated to a target saturation level of 88%–92%.[20,21] A PICO question on this topic is discussed in Section 4.3.

Prehospital NIMV treatment may be considered for patients whose target oxygen saturation cannot be achieved with conventional oxygen therapy or whose respiratory distress continues. Boussignac-type continuous positive airway pressure (CPAP) devices are available in the ambulances in Turkey, and these devices can be easily used during transport. In addition, it is possible to apply CPAP or bi-level positive airway pressure (BiPAP) using mechanical ventilators in ambulances. In some studies, favorable results of prehospital CPAP application in patients with COPD exacerbation have been reported by clinicians.[22-25] However, existing studies are not consistent enough to draw a firm conclusion about prehospital NIMV, and randomized controlled trials are needed for clearer results.[26] In contrast, national and local guidelines in the USA recommend CPAP or BiPAP for patients with severe respiratory distress and bronchospasm.[27,28]

4.3. Prehospital titrated oxygen therapy for patients with suspected chronic obstructive pulmonary disease exacerbation

Clinical question:

- P: Patients admitted to the hospital after an exacerbation of COPD
- I: Application of titrated oxygen therapy (adjusting oxygen saturation such that it is in the range of 88%–92%)
- C: Standard O_2 therapy (without titration, free, or high dose)
- O: Composite outcome (mortality, number of readmission, and need for intensive care unit admission) was determined, and a literature review was conducted using appropriate keywords.

In the literature review, a randomized clinical trial and a retrospective cohort study comparing titrated oxygen therapy with the standard oxygen therapy were found.[18,29] Based on the RoB2 and ROBINS-I evaluations, the articles were found to have moderate and high risks of bias, respectively.

A randomized controlled study by Austin *et al*. conducted in the prehospital setting included 405 patients with COPD exacerbation and compared the efficacy of titrated oxygen therapy with that of standard oxygen therapy. The diagnosis of COPD was confirmed by pulmonary function tests performed in the past 5 years in 214 patients, and the others were reported to be unconfirmed but possible COPD cases. In the first group, oxygen was administered to the patients through a mask, and the amount of oxygen administered was adjusted such that the oxygen saturation was between 88% and 92%. In the other group, oxygen therapy was given at a dose of 6–8 L/min without observing any oxygen saturation target. In this study, in which prehospital mortality and in-hospital mortality were evaluated as the primary end points, the mortality rate was 4% in the titrated oxygen therapy group and 9% in the high-dose oxygen therapy group; the prehospital and in-hospital rates were found to be 2% and 9%, respectively, in the confirmed COPD subgroup. The study found that the administration of titrated oxygen reduced overall mortality by approximately 58% in all patient groups (RR: 0.42, 95% CI: 0.20–0.89; $P = 0.02$), and the mortality reduction rate was 78% in patients with confirmed COPD (RR: 0.22, 95% CI: 0.05–0.91; $P = 0.04$). However, these results were obtained according to the intention-to-treat analysis results; no statistically significant difference in mortality was detected between the groups in the per-protocol analysis results ($P = 0.23$ for the comparison of mortality in all patients; $P = 0.14$ for the comparison among patients with confirmed COPD). It was also reported in the study that respiratory acidosis was less common in the patient group that received titrated oxygen therapy (mean pH difference: 0.12 [standard error = 0.05, $P = 0.01$, $n = 28$]); (mean pCO_2 difference: −33 mmHg [standard error = 16.3, $P = 0.02$, $n = 29$]). In conclusion, in the randomized controlled study, it was concluded that the administration of titrated oxygen therapy reduced mortality, respiratory acidosis, and hypercapnia compared to the administration of high-dose oxygen therapy in patients presenting with COPD exacerbation. In the comparison of respiratory acidosis and hypercapnia, a statistically significant difference was found between the groups in favor of the group, in which titrated oxygen was used in both intention-to-treat and per-protocol analyses.[18]

Data from 397 patients with COPD exacerbation brought to the hospital by an ambulance consecutively were analyzed in a retrospective analysis.[29] In that study, which partially answered the clinical question, the two treatment groups were not actually compared, but the frequency of inappropriate oxygen therapy (oxygen given such that SpO_2 >92%) and its consequences were analyzed. The presence of respiratory acidosis, need for ventilation support, length of hospital stay, and in-hospital mortality were determined as the measured outcomes in the study. It was reported that most of the patients (88.7%) received inappropriate high-dose oxygen therapy in the ambulance before reaching the hospital, and only a few patients were provided with appropriate oxygen therapy. Although mortality was found to be higher in the group of patients with SpO_2 values <92% compared to patients with SpO_2 values >92% (50% vs. 33.3%), it cannot be inferred that the reason for hypoxemia was the administration of titrated oxygen therapy in patients with hypoxemia. The reason for this may be that the patients were more critically ill rather than the method of oxygen therapy administered. Accordingly, in that retrospective analysis, it seems more appropriate to rely on the conclusion that appropriate oxygen therapy was administered in a very small number of patients rather than on the group comparison.

EVIDENCE-BASED RECOMMENDATIONS FOR CLINICAL QUESTIONS-1

Uncontrolled oxygen therapy should not be started during the transport of patients who were evaluated in the prehospital period with COPD exacerbation. Free and high amount of oxygen should be avoided as it may cause or increase hypercapnia

Oxygen saturation of the patients should be monitored continuously, and oxygen therapy should be applied to keep SpO_2 at the level of 88%-92%

Nasal cannula or Venturi mask should be used for oxygen therapy

Prehospital NIMV (CPAP or BiPAP) treatment may be considered for patients whose target SpO_2 cannot be reached with conventional oxygen or whose respiratory distress continues.

4.4. Other treatments

Short-acting β-2 agonists and/or short-acting anticholinergic drugs are recommended to be used in bronchodilator therapies although there is no high-quality evidence in the prehospital management of COPD exacerbations.[30] Short-acting bronchodilator drugs can be administered using metered-dose inhalers

(MDIs) or nebulizers. Although there are studies on the use of levalbuterol and terbutaline, which are short-acting β-2 agonists, in the prehospital setting,[31-33] salbutamol is a cheaper and more accessible drug that is used more commonly in clinical practice. In a Cochrane review evaluating the efficacy of administrations using air-chamber MDIs or nebulizers in these patients in terms of improvement in the first forced expiratory volume (FEV1) value and safety, no difference was found between the two methods of administration.[34] Inhaled salbutamol treatment should be initiated in the prehospital setting for COPD exacerbation patients with bronchospasm. Although there are limited data on the prehospital settings, the administration of ipratropium bromide may be considered for patients with suspected bronchospasm.[28] Salbutamol is administered with a 5 mg nebulizer (or six puffs of MDI) and can be repeated without interruption if the patient's respiratory distress persists. Ipratropium should be administered along with salbutamol for up to three doses.[27]

Systemic corticosteroids are effective in shortening the length of hospital stay and improving oxygenation and lung functions in cases of COPD exacerbations.[30] There was no difference between oral and parenteral treatments in terms of treatment failure, relapse, or mortality.[35] There are no studies on the use of systemic corticosteroids in the prehospital setting.[30] However, several guidelines recommend the use of systemic corticosteroid therapy for COPD exacerbations cases in the prehospital setting.[27,28]

PANEL RECOMMENDATIONS-3

Short-acting bronchodilator treatment can be started in the prehospital setting in patients with suspected COPD exacerbation before their transfer to a hospital

Due to the risk of hypercapnia, it is not recommended to apply the nebulizer mask by connecting it to the oxygen source.

References

1. Bøtker MT, Kirkegaard H, Christensen EF, Terkelsen CJ. Dyspnea is a dangerous symptom in the pre-hospital setting. Scand J Trauma Resusc Emerg Med 2015;23:O7.
2. Prekker ME, Feemster LC, Hough CL, Carlbom D, Crothers K, Au DH, *et al*. The epidemiology and outcome of prehospital respiratory distress. Acad Emerg Med 2014;21:543-50.
3. Williams TA, Finn J, Fatovich D, Perkins GD, Summers Q, Jacobs I. Paramedic Differentiation of asthma and COPD in the prehospital setting ıs difficult. Prehosp Emerg Care 2015;19:535-43.
4. Pittet V, Burnand B, Yersin B, Carron PN. Trends of pre-hospital emergency medical services activity over 10 years: A population-based registry analysis. BMC Health Serv Res 2014;14:380.
5. Sneath E, Bunting D, Hazell W, Tippett V, Yang IA. Pre-hospital and emergency department pathways of care for exacerbations of chronic obstructive pulmonary disease (COPD). J Thorac Dis 2019;11 Suppl 17:S2221-9.
6. Ibsen S, Lindskou TA, Nickel CH, Kløjgård T, Christensen EF, Søvsø MB. Which symptoms pose the highest risk in patients calling for an ambulance? A population-based cohort study from Denmark. Scand J Trauma Resusc Emerg Med 2021;29:59.
7. Lindskou TA, Pilgaard L, Søvsø MB, Kløjgård TA, Larsen TM, Jensen FB, *et al*. Symptom, diagnosis and mortality among respiratory emergency medical service patients. PLoS One 2019;14:e0213145.
8. Kauppi W, Herlitz J, Magnusson C, Palmér L, Axelsson C. Characteristics and outcomes of patients with dyspnoea as the main symptom, suffered by prehospital emergency nurses – A retrospective observational study. BMC Emerg Med 2020;20:67.
9. Søvsø MB, Hermansen SB, Færk E, Lindskou TA, Ludwig M, Møller JM, *et al*. Diagnosis and mortality of emergency department patients in the North Denmark region. BMC Health Serv Res 2018;18:548.
10. Kelly AM, Keijzers G, Klim S, Graham CA, Craig S, Kuan WS, *et al*. An observational study of dyspnea in emergency departments: The Asia, Australia, and New Zealand Dyspnea in emergency departments study (AANZDEM). Acad Emerg Med 2017;24:328-36.
11. Lindvig KP, Brøchner AC, Lassen AT, Mikkelsen S. Prehospital prognosis is difficult in patients with acute exacerbation of chronic obstructive pulmonary disease. Scand J Trauma Resusc Emerg Med 2017;25:106.
12. Tully B. Prehospital Care for Dyspnea. EMS World Issue; April 2020. Available from: https://www.emsworld.com/article/1224040/prehospital-care-dyspnea. [Last accessed on 2021 Apr 28].
13. Snyder SR, Kivlehan SM, Collopy KT. COPD exacerbation. What are the keys to treating it in the prehospital setting? EMS World 2015;44:54-60.
14. Beygui F, Castren M, Brunetti ND, Rosell-Ortiz F, Christ M, Zeymer U, *et al*. ACCA study group on pre-hospital care. Pre-hospital management of patients with chest pain and/or dyspnoea of cardiac origin. A position paper of the Acute Cardiovascular Care Association (ACCA) of the ESC. Eur Heart J Acute Cardiovasc Care 2020;9 Suppl 1:59-81.
15. Merelman A, Levitan R. A modern approach to basic airway management. J Emerg Med Serv 2018;43:4.
16. Hunter CL, Silvestri S, Ralls G, Papa L. Prehospital end-tidal carbon dioxide differentiates between cardiac and obstructive causes of dyspnoea. Emerg Med J 2015;32:453-6.
17. Klemen P, Golub M, Grmec S. Combination of quantitative capnometry, N-terminal pro-brain natriuretic peptide, and clinical assessment in differentiating acute heart failure from pulmonary

Table 5.1.1: History characteristics to be questioned in patients with chronic obstructive pulmonary disease exacerbation

Evaluation of dyspnea severity with the mMRC dyspnea scale
Increase in the amount and purulence of sputum
Fever and upper respiratory tract infection symptoms
Symptoms related to systems other than respiratory system
History of non-COPD lung disease
Evaluation of systemic comorbidities, drug use, and drug use compliance
Increased need for bronchodilator therapy
Recent use of antibiotics/oral corticosteroids
Oxygen use at home
Use of NIMV at home
History of hospitalization for COPD exacerbation in the last 1 year
History of previous intensive care unit admission
The need for mechanical ventilation before
The need for social support
History of psychiatric illness

COPD=Chronic obstructive pulmonary disease, NIMV=Noninvasive mechanical ventilation, mMRC=Modified medical research council

disease as cause of acute dyspnea in prehospital emergency setting: Study of diagnostic accuracy. Croat Med J 2009;50:133-42.
18. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: Randomized controlled trial. BMJ 2010;341:c5462.
19. Kopsaftis Z, Carson-Chahhoud KV, Austin MA, Wood-Baker R. Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2020;1:CD005534.
20. Yang IA, Brown JL, George J, Jenkins S, McDonald CF, McDonald VM, *et al*. COPD-X Australian and New Zealand guidelines for the diagnosis and management of chronic obstructive pulmonary disease: 2017 update. Med J Aust 2017;207:436-42.
21. O'Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society guideline for oxygen use in adults in healthcare and emergency settings. BMJ Open Respir Res 2017;4:e000170.
22. Luiz T, Kumpch M, Grüttner J, Madler C, Viergutz T. Prehospital CPAP therapy by emergency physicians in patients with acute respiratory failure due to acute cardiogenic pulmonary edema or acutely exacerbated COPD. *In Vivo* 2016;30:133-9.
23. Hensel M, Strunden MS, Tank S, Gagelmann N, Wirtz S, Kerner T. Prehospital non-invasive ventilation in acute respiratory failure is justified even if the distance to hospital is short. Am J Emerg Med 2019;37:651-6.
24. Thompson J, Petrie DA, Ackroyd-Stolarz S, Bardua DJ. Out-of-hospital continuous positive airway pressure ventilation versus usual care in acute respiratory failure: A randomized controlled trial. Ann Emerg Med 2008;52:232-41, 241.e1.
25. Schmidbauer W, Ahlers O, Spies C, Dreyer A, Mager G, Kerner T. Early prehospital use of non-invasive ventilation improves acute respiratory failure in acute exacerbation of chronic obstructive pulmonary disease. Emerg Med J 2011;28:626-7.

Table 5.1.2: Evaluation steps of patients with a prediagnosis of chronic obstructive pulmonary disease exacerbation in the emergency department

Taking the patient to the monitored bed with a high triage score
Establishing the vascular access and taking blood samples
Evaluation of vital signs and the degree of respiratory failure
Oxygen administration by titration to keep the oxygen saturation between 88% and 92%
Evaluation of the need for arterial blood gas analysis
Evaluation of the need for noninvasive mechanical ventilation or invasive mechanical ventilation
Starting short-acting bronchodilator therapy and repeating it at frequent intervals
Evaluation of the 12-lead ECG
Evaluation of other laboratory tests
Evaluation of chest X-ray
Deciding on the need for computed tomography of the thorax
Evaluation of differential diagnoses, planning of additional tests, and treatments as needed
Evaluation of antibiotic need
Determining the need for systemic corticosteroid therapy
Monitoring the response to treatment
Correction of metabolic disorders (such as volume status, electrolytes, kidney functions, and acid-base balance disorders)
Evaluation of the need for hospitalization/ICU admission (if the patient is in the 2nd level hospital, evaluation of the need for referral to the 3rd level hospital)
Initiation of deep vein thrombosis prophylaxis in patients requiring hospitalization
Discharge from the emergency department to home and planning the treatment regimen for patients who have an adequate treatment response and do not need hospitalization

ECG=Electrocardiography, ICU=Intensive care unit

Table 5.1.3: Differential diagnosis in patients prediagnosed with chronic obstructive pulmonary disease exacerbation

Heart failure
Symptoms/signs: New onset or increased dyspnea compared to stable condition, tachycardia, tachypnea, orthopnea, pretibial edema, and pleural effusion
Further examination: BNP/NT-proBNP level measurement, echocardiography, and cardiology consultation
Pulmonary thromboembolism
Symptoms/findings: Deep hypoxemia inconsistent with the severity of COPD, hypotension, examination findings suggestive of deep vein thrombosis, new-onset atrial fibrillation on ECG, right bundle branch block, T-wave inversion in V1-3 leads/ST-segment depressions, elevated cardiac biomarkers, increased BNP/NT-proBNP levels, ans presence of increased risk factors for pulmonary thromboembolism
Further examination: Pretest probability assessment should be done. It is recommended to use risk scores such as wells or Geneva. Thoracic computed tomographic angiography should be requested for "possible pulmonary thromboembolism" cases. D-dimer should be requested for cases with "low probability of pulmonary thromboembolism", and thoracic computed tomographic angiography should be requested if the test score is high. Pulmonary thromboembolism can be excluded in cases with normal D-dimer results. Combinations of ventilation-perfusion scintigraphy, lower extremity Doppler ultrasonography, and echocardiography can be used in patients who cannot be given contrast material. However, it has been reported that d-dimer elevation can occur without thromboembolism during COPD exacerbations, and pulmonary thromboembolism is detected in only 30% of these patients[4]
Pneumothorax
Symptoms/signs: Decreased breath sounds, unilateral stabbing flank pain, unresponsiveness to COPD exacerbation therapies, sudden worsening under NIMV/IMV, and previous history of pneumothorax
Further examination: Small and loculated pneumothorax may be missed on chest X-ray. Bedside lung ultrasonography and noncontrast chest computed tomography may be considered for these patients
Pneumonia
Symptoms/signs: Fever, rales or bronchial breathing on auscultation, suspicious infiltrates on chest X-ray, leukocytosis, high CRP, and procalcitonin levels
Further examination: If a specific diagnosis cannot be made on chest X-ray, noncontrast thorax computed tomography can be considered
Dysrhythmias
Symptoms/signs: New-onset palpitations and shortness of breath
Further examination: ECG, continuous cardiac monitoring, cardiology consultation
Acute coronary syndrome
Symptoms/signs: Increased dyspnea, chest pain, new-onset heart failure signs, increased cardiac biomarkers
Further examination: ECG, cardiac biomarker monitoring, cardiology consultation

NT-proBNP=N-terminal prohormone B-type natriuretic peptide, BNP=B-type natriuretic peptide, ECG=Electrocardiography, COPD=Chronic obstructive pulmonary disease, NIMV=Noninvasive mechanical ventilation, CRP=C-reactive protein, IMV=Invasive mechanical ventilation, ST segment

Table 5.1.4: The assessment of severity of chronic obstructive pulmonary disease exacerbation

Mild COPD exacerbation (no respiratory failure)
PaO_2 >60 mmHg, $PaCO_2$ <45 mmHg, pH >7.30 in room air
Respiratory rate <30/min at the time of admission
Absence of cor pulmonale
No need for NIMV
Reduction in the patient's shortness of breath after treatment
Absence of moderate to severe COPD exacerbation criteria (shown below)
Moderate COPD exacerbation (mild respiratory failure)
Respiratory rate above 30/min during emergency department admission
Use of accessory respiratory muscles
Presence of cor pulmonale
PaO_2 <60 mmHg, $PaCO_2$ >45 mmHg, pH: 7.25-7.35 in room air
Oxygen requirement FiO_2 <40%
Short-term/intermittent need for NIMV (<6 h)
Presence of acute or new onset disorders requiring hospitalization: new onset
dysrhythmias, heart failure, acute coronary syndrome, acute renal failure
Uncontrolled diabetes mellitus, severe pneumonia
Absence of severe COPD exacerbation criteria (shown below)
Severe COPD exacerbation (severe respiratory failure)
In addition to moderate COPD exacerbations
Impaired consciousness due to hypercapnia
Hemodynamic instability
pH level below 7.25
Oxygen demand, FiO_2 ≥40%
Long-term/intermittent need for NIMV (≥6 h)
IMV need

COPD=Chronic obstructive pulmonary disease, NIMV=Noninvasive mechanical ventilation, IMV=Invasive mechanical ventilation

PANEL RECOMMENDATIONS-4

Patients with a prediagnosis of COPD exacerbation should be included in the high-priority triage category in the emergency department and followed up in a monitored bed

Patients should be questioned for high-risk history features for COPD exacerbations [Table 5.1.1]

Attention should be paid to the evaluation steps of patients with a prediagnosis of COPD exacerbation in the emergency department [Table 5.1.2]

In patients with prediagnosis of COPD exacerbation, differential diagnoses such as heart failure, pneumonia, pulmonary thromboembolism, dysrhythmias, and acute coronary syndrome should be considered [Table 5.1.3]

Factors associated with increased mortality in patients with a prediagnosis of COPD exacerbation should be questioned

In patients with COPD exacerbation, "exacerbation severity" should be evaluated and taken into account in decisions about treatment, transfer between hospitals, discharge, and hospitalization [Table 5.1.4].

26. Bakke SA, Botker MT, Riddervold IS, Kirkegaard H, Christensen EF. Continuous positive airway pressure and noninvasive ventilation in prehospital treatment of patients with acute respiratory failure: A systematic review of controlled studies. Scand J Trauma Resusc Emerg Med 2014;22:69.
27. National Association of State EMS Officials. (). National model EMS clinical guidelines. Version 2.0; 2017. Available from: https://nasemso.org/wp-content/uploads/National-Model-EMS-Clinical-Guidelines-2017-PDF-Version-2.2.pdf. [Last accessed on 2021 Apr 28].
28. Hodroge SS, Glenn M, Breyre A, Lee B, Aldridge NR, Sporer KA, *et al.* Adult patients with respiratory distress: Current evidence-based recommendations for prehospital care. West J Emerg Med 2020;21:849-57.
29. Ringbaek TJ, Terkelsen J, Lange P. Outcomes of acute exacerbations in COPD in relation to pre-hospital oxygen therapy. Eur Clin Respir J. 2015 May 11;2.
30. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2021 Report. Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. [Last accessed on 2021 Apr 28].
31. van Geffen WH, Douma WR, Slebos DJ, Kerstjens HA. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD. Cochrane Database Syst Rev. 2016 Aug 29;2016(8):CD011826.
32. Thompson M, Wise S, Rodenberg H. A preliminary comparison of levalbuterol and albuterol in prehospital care. J Emerg Med 2004;26:271-7.
33. Sagarin MJ. A preliminary comparison of levalbuterol and albuterol in prehospital care. J Emerg Med 2005;28:349.
34. Zehner WJ Jr., Scott JM, Iannolo PM, Ungaro A, Terndrup TE. Terbutaline vs. albuterol for out-of-hospital respiratory distress: Randomized, double-blind trial. Acad Emerg Med 1995;2:686-91.
35. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014 Sep 1;(9):CD001288.

5. Evaluation and Stabilization of Chronic Obstructive Pulmonary Disease Exacerbation in the Emergency Department

5.1. Initial approach, history, and differential diagnosis

COPD exacerbation is one of the common causes of presentations to the emergency department due to shortness of breath. Patients with COPD exacerbation apply to the health-care system mostly through emergency departments. The main presenting symptom of the patients is usually an increase in shortness of breath. Patients with dyspnea should be included in the high-priority triage category in the emergency department and evaluated in monitored beds.

First, the vital signs of the patient (blood pressure, heart rate, peripheral oxygen saturation, respiratory rate, and body temperature) should be measured, and the patient should be kept under continuous cardiac monitoring. A brief history of the patient should be obtained, at least two vascular accesses (with 14–18 F branulas) should be established in critical cases, and blood samples should be collected for conducting laboratory examinations. Next, it should be evaluated whether patients show any signs of severe respiratory failure that require emergency airway management. In patients with findings of severe respiratory failure, priority should be given to

the provision of hemodynamic stability, oxygenation, and avoiding possible hypercapnia without wasting time after obtaining a detailed medical history and conducting a systemic inquiry and detailed physical examination. For patients who can provide a medical history, characteristics of the patient's dyspnea (onset of dyspnea, severity, etc.), systemic diseases, drug use, and details that suggest high risk for COPD exacerbations should be questioned [Table 5.1.1].

The most common symptoms observed in patients with COPD exacerbation are increased dyspnea, increased amount and purulence of sputum, drowsiness, and symptoms associated with upper respiratory tract infection. Vital signs vary according to the severity of disease in the stable period and whether or not the patient has an accompanying disease; however, tachycardia, low oxygen saturation, and tachypnea are usually observed. In the physical examination, lung and heart sounds should be monitored; accessory respiratory muscle use, consciousness status, cyanosis, intercostal muscle retraction, heart sounds, jugular venous engorgement, pretibial edema, and changes in the diameter and color of the legs should be evaluated. Decreased respiratory sounds, rhonchi, and wheezing are common abnormal findings of respiratory system auscultation. Patients may be prone to sleep due to hypercapnia and hypoventilation in critical cases (prearrest state).

Oxygen therapy should be initiated quickly for hypoxic patients with respiratory distress. Suspected hypercapnia should not preclude the use of oxygen in patients with hypoxic respiratory failure. The maintenance of oxygen saturation in the range of 88%–92% is sufficient for most cases.[1,2] Target values for oxygen saturation can be achieved by maintaining a sufficient amount of oxygen flow using a nasal cannula, simple mask, or nonrebreather mask. Furthermore, it should be kept in mind that the use of high-flow oxygen in hypercapnic patients may trigger hypoventilation by developing respiratory center depression, and excessive oxygen therapy should not be administered for a prolonged period of time. Arterial blood gas (ABG) analysis may be necessary at this stage to reveal the metabolic status and detect oxygenation level and hypercapnia (for the indications of ABG analysis, Section 5.2). Along with oxygenation, inhaled bronchodilators (see Sections 6.1 and 6.2) and NIMV, if required (see Section 6.7), should be initiated without delay. Subsequently, it is important to perform lung imaging and differential diagnosis as well as evaluate treatment response and hospitalization requirement. The steps for the evaluation of patients with a prediagnosis of COPD exacerbation in the emergency department are shown in Table 5.1.2.

Table 5.2.1: Expected bicarbonate levels in acute and chronic respiratory failure

Expected bicarbonate level in patients with acute respiratory failure
$\Delta HCO_3=0.1\times\Delta PaCO_2$
In a patient with a $PaCO_2$ value of 65 mmHg, the $PaCO_2$ increased by 20 mmHg compared to the normal value. In this case, the patient's HCO_3 increase should be 2 mEq/l, and the expected HCO_3 level should be between 24 and 26 mEq/L. If you see a lower HCO_3 value in ABG, it should be considered that the patient's renal compensation mechanism is not working adequately
Expected bicarbonate level in patients with chronic respiratory failure
$\Delta HCO_3=0.4\times\Delta PaCO_2$
In a patient with a $PaCO_2$ value of 85 mmHg, the $PaCO_2$ increased by 40 mmHg compared to the normal value. In this case, the patient's HCO_3 increase should be 16 mEq/l, and the expected HCO_3 level should be between 38 and 40 mEq/L. If you see a lower HCO_3 value in ABG, it should be considered that the patient's renal compensation mechanism is not working adequately

ABG=Arterial blood gas

PANEL RECOMMENDATIONS-5

Arterial blood gas analysis is recommended for the following patients:

- Patients with SpO_2 <92% at emergency department admission
- Patients with altered mental status
- Patients with signs of hemodynamic deterioration (such as hypotension and peripheral hypoperfusion findings)
- Patients presenting with moderate-to-severe COPD exacerbations [Table 5.1.4].
- Arterial blood gas should be obtained after initial stabilization of the patient in the emergency department
- Venous blood gas analysis and $ETCO_2$ measurement are not reliable alternative methods for predicting hypercarbia and metabolic status
- Patients who do not have hypercarbia and respiratory acidosis at the time of admission, who have mild COPD exacerbation features, who do not worsen during follow-up, and who do not show metabolic deterioration can be followed up with peripheral oxygen saturation and respiratory rate monitoring.

Differential diagnosis

The most common causes of COPD exacerbations are bacterial and viral lower respiratory tract infections. In particular, concomitant pneumonia should be recognized in patients with the abovementioned infections. Decompensated heart failure, dysrhythmias, pneumothorax, pneumonia, and PTE are important differential diagnoses in patients with COPD. In patients with COPD exacerbation, the incidence of concurrent PTE is around 16%.[3] The differential diagnoses of patients with a prediagnosis of COPD exacerbation in the emergency department and necessary diagnostic tests are summarized in Table 5.1.3.

Factors associated with increased mortality in patients with chronic obstructive pulmonary disease exacerbation

There are various risk scores such as the dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation (DECAF) and Ottawa COPD scores, which determine in-hospital mortality in patients with COPD exacerbation.[4-6]

Severity of chronic obstructive pulmonary disease exacerbation

The severity of COPD exacerbation in patients should be determined by considering the findings at presentation to the emergency department, blood gas analysis results, and treatment response [Table 5.1.4].[7] "COPD exacerbation severity" should be taken into account in addition to "factors associated with in-hospital mortality" while making decisions regarding hospitalization in wards and intensive care units, transfer between hospitals, and discharge of the patients.[7]

References

1. Turkish Thoracic Society's Perspective on the GOLD 2017 Chronic Obstructive Pulmonary Disease (COPD) Report. Available from: https://toraks.org.tr/site/community/downloads/2211. [Last accessed on 2021 May 04].
2. Wijesinghe M, Perrin K, Healy B, Hart K, Clay J, Weatherall M, *et al*. Pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. Intern Med J 2011;41:618-22.
3. Aleva FE, Voets LW, Simons SO, de Mast Q, van der Ven AJ, Heijdra YF. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: A systematic review and meta-analysis. Chest 2017;151:544-54.
4. Shapira-Rootman M, Beckerman M, Soimu U, Nachtigal A, Zeina AR. The prevalence of pulmonary embolism among patients suffering from acute exacerbations of chronic obstructive pulmonary disease. Emerg Radiol 2015;22:257-60.
5. Stiell IG, Perry JJ, Clement CM, Brison RJ, Rowe BH, Aaron SD, *et al*. Clinical validation of a risk scale for serious outcomes among patients with chronic obstructive pulmonary disease managed in the emergency department. CMAJ 2018;190:E1406-13.
6. Steer J, Gibson J, Bourke SC. The DECAF Score: Predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax 2012;67:970-6.
7. Global Strategy for Diagnosis, Management and Prevention of COPD. The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 2021 Report. Available from: https://goldcopd.org/2021-gold-reports/ [Last accessed on 2021 May 04].

5.2. Arterial blood gas evaluation

ABG analysis is a test that provides important information regarding arterial blood oxygenation, alveolar ventilation, pulmonary gas exchange, and acid-base balance.[1] ABG analysis should be used to detect respiratory failure in patients with COPD exacerbation, determine the indication for oxygen therapy, measure treatment response, and in the differential diagnosis of metabolic disturbances accompanying COPD exacerbations.[2]

The first step in evaluating the functional status of patients with COPD exacerbation presenting to the emergency department is measuring peripheral oxygen saturation and vital signs. ABG analysis should be performed for the following indications in patients presenting with the clinical presentation of a COPD exacerbation:[3,4]

- Cases with SpO_2 < 92% on room air
- Patients with acute altered consciousness
- Patients with signs of hemodynamic deterioration (with findings of hypotension and peripheral hypoperfusion)
- Patients with moderate/severe exacerbation (see Section 5.1).

In patients with obvious signs of severe respiratory failure, necessary oxygen and respiratory supports should be administered immediately without wasting any time, and ABG should be performed after the patient is stabilized.

ABG analysis is useful for determining exacerbation severity and therapeutic requirements. During patient follow-up, the use of ABG and the number of repeated measurements may vary according to the degree of respiratory failure or metabolic status of the patient. It is necessary to monitor ABG and evaluate the effectiveness of the respiratory support devices used as the clinical condition of a patient with hypercapnia and related respiratory acidosis changes. Hypercapnia and hypoxemia, which can be detected through blood gas analysis, can objectively reveal the need for oxygen therapy and positive pressure ventilation (see Section 6.7). ABG levels obtained during monitoring at the emergency department are also used for making decisions regarding discharge, transfer between hospitals, or the need for hospitalization in the ward or intensive care unit.

Patients who fall under mild COPD exacerbation criteria, those who do not have hypercapnia and respiratory acidosis according to the results of the initial ABG analysis, who do not show metabolic deterioration, and who do not worsen during the follow-up can be followed up by peripheral oxygen saturation and respiratory rate monitoring without the need for performing repeated ABG analyses.

Blood gas analysis performed using a venous blood sample is sufficient to assess tissue pH and electrolyte and lactate levels but cannot accurately detect partial carbon dioxide pressure ($PaCO_2$).[5-12] $PaCO_2$ in venous blood measures tissue carbon dioxide and does not reflect the arterial $PaCO_2$ value. Since the bicarbonate level is calculated by an indirect method using pH and pCO_2 and the Henderson–Hasselbach equation in blood gas analyses, the blood gas analysis of venous samples does not show the bicarbonate level accurately. Therefore, blood gas analysis should be performed with arterial samples to accurately determine hypercapnia and the metabolic status.[13] In COPD exacerbations, capnograph-measured end-tidal carbon dioxide ($ETCO_2$) shows moderate correlation to indicate arterial $PaCO_2$; therefore, it is not a reliable method for estimating $PaCO_2$.[14]

It should also be investigated whether the renal compensation mechanisms are functioning properly and whether there is a metabolic component accompanying the clinical presentation in patients with respiratory acidosis. Considering the acute or chronic course of the patient's respiratory failure, it should be examined whether the patient has reached the expected bicarbonate value.[15] It should be noted that metabolic acidosis that may accompany respiratory acidosis may aggravate the patient's clinical condition. In addition to pH and $PaCO_2$ values, base excess (BE; base deficit), bicarbonate, and lactate levels should also be taken into consideration [Table 5.2.1].

References

1. Sevinç C, Uzun O, editor. Respiratory emergencies. In: Thorax Books. In: www.toraks.org.tr.
2. Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, Siegel MD, eds. Fishman Pulmonary Diseases and Disorders. 4th Ed., Vol.1, p.741, McGraw-Hill Education.
3. Turkish Thoracic Society, COPD Prevention, Diagnosis and Treatment Report; 2014. p. 60. www.toraks.org.tr.
4. Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease. Available from: https://copdx.org.au/copd-x-plan/x-manage-exacerbations/x2-copd-acute-exacerbation-plan/. [Last accessed on 2021 May 05].
5. Kelly AM, Klim S. Agreement between arterial and venous pH and pCO2 in patients undergoing non-invasive ventilation in the emergency department. Emerg Med Australas 2013;25:203-6.
6. Woods M, Hodgson D. Towards evidence-based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 2: In patients presenting with an exacerbation of COPD can a normal venous blood gas pCO2 rule out arterial hypercarbia? Emerg Med J 2015;32:251-3.
7. Lim BL, Kelly AM. A meta-analysis on the utility of peripheral venous blood gas analyzes in exacerbations of chronic obstructive pulmonary disease in the emergency department. Eur J Emerg Med 2010;17:246-8.
8. Emerman CL, Connors AF, Lukens TW, Effron D, May ME. Relationship between arterial blood gases and spirometry in acute exacerbations of chronic obstructive pulmonary disease. Ann Emerg Med 1989;18:523-7.
9. Wong EK, Lee PC, Ansary S, Asha S, Wong KK, Yee BJ, *et al.* Role of venous blood gases in hypercapnic respiratory failure chronic obstructive pulmonary disease patients presenting to the emergency department. Intern Med J 2019;49:834-7.
10. Byrne AL, Bennett M, Chatterji R, Symons R, Pace NL, Thomas PS. Peripheral venous and arterial blood gas analysis in adults: Are they comparable? A systematic review and meta-analysis. Respirology 2014;19:168-75.
11. Byrne AL, Bennett MH, Pace NL, Thomas P. Peripheral venous blood gas analysis versus arterial blood gas analysis for the diagnosis of respiratory failure and metabolic disturbance in adults. Cochrane Database Syst Rev 2013;2013:CD010841.
12. Domaradzki L, Gosala S, Iskandarani K, Van de Louw A. Is venous blood gas performed in the emergency department predictive of outcome during acute on chronic hypercarbic respiratory failure? Clin Respir J 2018;12:1849-57.
13. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, *et al.* BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax 2016;71 Suppl 2:i1-35.
14. Tyagi D, Govindagoudar MB, Jakka S, Chandra S, Chaudhry D. Correlation of $PaCO_2$ and $ETCO_2$ in COPD patients with exacerbation on mechanical ventilation. Indian J Crit Care Med 2021;25:305-9.
15. Roberts JR. Roberts and Hedges' Clinical Procedures in Emergency Medicine and Acute Care. 7th ed. Philadelphia, USA: Elsevier; 2019. p. 1534.

5.3. Laboratory tests

5.3.1. Complete blood count

The definition of COPD exacerbation is an event-based definition. Since there is no gold-standard diagnostic method, it is difficult to standardize the management of exacerbations based on this definition in practice. The results of laboratory tests and biomarker studies, which are often used to standardize diagnosis and management, are controversial. There is limited evidence regarding which tests should be performed during a COPD exacerbation. Routine hematological and biochemical tests are usually used for differential diagnosis, appropriate treatment selection, and prognosis estimation rather than exacerbation diagnosis.

COPD exacerbations are associated with increased airway resistance and systemic inflammation. Increased leukocyte count, C-reactive protein (CRP), and fibrinogen values in the peripheral blood have been reported in patients with COPD and frequent exacerbations.[1,2] However, systemic inflammation is also observed in other diseases, and this can often be due to comorbidities. An elevated leukocyte count alone is not specific and should not be interpreted as a marker of infection, and a normal leukocyte count should not be considered as an evidence of absence of infection. Therefore, results obtained for inflammatory markers should be evaluated along with the clinical findings of the patient. In the diagnosis of an exacerbation, a combination of elevated CRP and leukocyte levels along with increased symptoms may be useful to distinguish between exacerbation and stable state.[3] In addition, patients with COPD and elevated leukocyte counts and other inflammatory markers experience more exacerbations and have a higher mortality rate than patients without elevated inflammatory markers.[4,5] Therefore, a complete blood count should be requested from patients with COPD presenting to the emergency department with suspected exacerbation. Furthermore, there is no relationship between peripheral leukocyte count and lung function worsening, and leukocyte count should not be used as an indicator of disease severity or an exacerbation.[6,7]

Complete blood count results, such as hemoglobin, eosinophil, and leukocyte values, can provide information regarding the management and prognosis of the patient.

Hemoglobin is an easily and inexpensively measured marker having a prognostic value.[8] Both low and high values may be observed in COPD, but the distribution

varies greatly according to the population studied. Historically, secondary polycythemia appeared to be a striking feature of COPD, especially before the introduction of oxygen use at home, but its current prevalence seems to be low.[9] When evaluating data on the prevalence and prognostic significance of anemia, it should be remembered that most patients from the COPD population may have multiple chronic diseases. However, the prevalence of anemia is also high in patients with COPD presenting with exacerbation, and low hemoglobin values are associated with increased mortality.[10]

In some patients with COPD exacerbation, eosinophil counts increase along with an increase in other inflammatory cells. The blood eosinophil count correlates quite well with sputum and airway eosinophil levels and can be used as a measure of airway eosinophilia in COPD cases.[11] In COPD exacerbations, eosinophilia is a predictive biomarker for eosinophilic airway inflammation and the effectiveness of inhaled corticosteroid therapy.[12,13] In COPD, patients with eosinophilia (≥300 cells/L or ≥2%) have a higher incidence of exacerbations compared to patients without eosinophilia.[14,15]

COPD exacerbations that are characterized by increased eosinophilic inflammation of the airway are usually milder since they are associated with lower mortality and shorter hospital stays. The presence of viral infection in exacerbations characterized by airway eosinophilia remains controversial, and bacterial infections are rarely present.[16,17]

PANEL RECOMMENDATIONS-6

Complete blood count should be requested in patients presenting to the emergency department with a COPD exacerbation

The leukocyte count should not be used as an indicator of disease or severity of exacerbation.

5.3.2. C-reactive protein

Tests for evaluating serum CRP levels should be requested from patients who present to the emergency department and are suspected to have COPD exacerbation. CRP is a well-known inflammatory biomarker that can be used along with sputum purulence for identifying bacterial COPD exacerbation phenotypes and predicts prognosis and adverse outcomes.[1,18,19]

A total of 36 plasma biomarkers were evaluated in 90 patients with COPD during stable and exacerbation periods to determine the phenotype of COPD exacerbation. Although CRP was found to be the most selective biomarker in this study, it was reported to be insufficient by itself to confirm the diagnosis of exacerbation. Serum CRP values of ≥8 mg/ml are 95% selective and 57% sensitive for the diagnosis of exacerbation when combined with a major symptom (increased dyspnea, sputum volume, or purulence). However, none of the other systemic biomarkers examined in this study were found useful for predicting the severity of exacerbation.[19]

Widespread application of the GOLD strategy with the use of self-reported sputum purulence may result in the overuse of antibiotics in COPD exacerbation cases. It is clear that prescribing unnecessary antibiotics for respiratory diseases results in higher medical costs, side effects, and antibiotic resistance. The use of CRP may reduce unnecessary antibiotic use in patients with COPD exacerbations without harming them. In a study conducted in a primary care center where patients were randomized to either the group for which the decision of antibiotic use was made using CRP or the group for which the decision of antibiotic use was made using usual care, fewer patients reported antibiotic use in the CRP-guided group than in the usual care group (57.0% vs. 77.4%).[20] Another study in which patients hospitalized due to COPD exacerbations were randomized to receive antibiotics according to either the GOLD or CRP strategy (CRP ≥50 mg/ml) found that fewer patients in the CRP group were treated with antibiotics compared to those in the GOLD group (31.7% vs. 46.2%).[21] According to that study, it was also found that the 30-day treatment failure rate was almost equal (44.5% in the CRP group vs. 45.5% in the GOLD group).

In conclusion, in case of severe exacerbations of COPD, the use of CRP as a biomarker along with clinical findings to guide antibiotic treatment for primary care outpatients may lead to a significant reduction in the prescription of antibiotics in emergency departments.

In a previous report based on studies investigating the effect of CRP on biomarkers that guide the decision of antibiotic use in exacerbation cases, its use was not recommended since it was reported to be elevated in both bacterial and viral infections.[22] However, according to the results of two studies conducted in the United Kingdom and the Netherlands in 2021, it was emphasized that there was a significant reduction in the prescription of antibiotics without treatment failure when CRP levels were considered in cases of COPD exacerbations in primary care outpatients, but it was reported that these findings needed to be confirmed before generalizing this recommendation.[21] Furthermore, it was reported that, when CRP was low, antibiotic use was safely reduced from 77.4% to 47.7%.[20]

PANEL RECOMMENDATIONS-7

The use of CRP as a biomarker to guide antibiotic therapy in outpatients presenting to the emergency department with a COPD exacerbation could lead to a significant reduction in antibiotic therapy.

5.3.3. Cardiac biomarkers

Acute exacerbation of COPD and left-sided heart failure commonly coexist in clinical settings. It has been shown that the plasma concentrations of N-terminal prohormone B-type natriuretic peptide (NT-proBNP) may be increased during COPD exacerbations, although not as much as in heart failure.[23,24] Moreover, the plasma concentrations of NT-proBNP are markedly increased in patients with COPD exacerbation and left ventricular failure compared with those in patients with COPD exacerbation alone.[25] We suggest that BNP/NT-proBNP tests should be used for performing differential diagnosis in patients with undifferentiated diagnosis presenting with dyspnea and in patients with both COPD and CHF to help distinguish whether the patient primarily has an exacerbation of CHF or that of COPD.

In the emergency department, troponins are often used in the evaluation of patients with acute dyspnea. The mean plasma concentrations of cardiovascular biomarkers were found to be elevated in patients with symptoms of COPD exacerbation at presentation. The plasma high-sensitive cardiac troponin I value was found to be elevated in 36.5% of the patients. Indeed, patients with COPD exacerbation and elevated markers of myocardial damage are at an increased risk for death, regardless of the severity of lung disease. Some studies have shown that possible acute myocardial damage plays a frequent and dramatic role, affecting short-term outcomes in COPD exacerbations.[26] Patients with elevated cardiac troponin levels during exacerbations have been found to have increased early and late mortalities. We recommend requesting a troponin test from patients with COPD exacerbation when ECG findings are abnormal, or the patient's dyspnea is more severe than expected. Although elevated troponins rarely detect acute cardiac pathology missed by ECG, they are associated with increased in-hospital and 30-day mortalities and should be considered while making decisions regarding the hospitalization of patients with COPD exacerbation.[27,28]

PANEL RECOMMENDATIONS-8

BNP/NTproBNP can help in the differential diagnosis of COPD exacerbation and heart failure in patients presenting to the emergency department with shortness of breath

Troponin test may be requested in COPD exacerbations in the presence of an abnormal ECG finding and/or in cases where the severity of the patient's underlying disease is not compatible with the severity of the exacerbation.

5.3.4. D-Dimer

Patients with COPD are at a risk for PTE due to systemic inflammation and accompanying comorbidities. The prevalence of PTE in patients with COPD and acutely worsening respiratory symptoms remains unclear. Among patients with COPD presenting to the hospital with acute worsening of respiratory symptoms, PTE was detected at a rate of 5.9%–16.1% using a predefined diagnostic algorithm.[29,30] In addition, it was observed that mortality and the length of hospital stay increased in patients with PTE presenting with COPD exacerbation of unknown etiology.[31,32]

In case of COPD exacerbation in patients with suspected PTE, plasma D-dimer measurement using defined diagnostic algorithms such as Wells or Geneva is recommended, preferably using the high-sensitive quantitative enzyme-linked immunosorbent assay method, to reduce the instances of unnecessary imaging in patients with low or moderate clinical probability. The negative predictive value of D-dimer levels is high in patients with low pretest probabilities. On the other hand, elevated D-dimer levels have a low positive predictive value, and the D-dimer test is not convenient for the confirmation of PTE. In addition, the measurement of D-dimer is not recommended for patients with high clinical probability because a normal result does not safely exclude PTE, even if a highly sensitive test is used.[33] In addition, D-dimer is often elevated in patients with cancer, hospitalized patients, those with severe infections or inflammatory conditions, and during pregnancy.[33]

PANEL RECOMMENDATIONS-9

Defined diagnostic algorithms such as Wells or Geneva should be used instead of direct

D-dimer level measurement in patients with suspected pulmonary thromboembolism who do not improve despite initial therapy in a COPD exacerbation.

5.3.5. Biochemical tests

There is extremely limited clinical evidence regarding the biochemical tests that should be used in the evaluation of patients with COPD exacerbation. Renal functions and electrolytes, which may contribute to mortality in clinically severe patients, can be considered for evaluation along with obtaining medical history and performing physical examination during the presentation to the emergency department.

Acute kidney injury (AKI) is also recognized as a serious complication of COPD exacerbation. AKI is reported to be an independent risk factor for in-hospital mortality in patients with COPD exacerbation.[34] The mortality rate was found to be 16.6% in cases with AKI and COPD exacerbation and 4.0% in cases without AKI, and AKI was one of the predictors associated with a 3.85-fold increased risk of in-hospital mortality. The prevalence of AKI is 1.9% in patients with COPD exacerbation. In addition, patients with COPD exacerbation and AKI have a 1.8-fold higher risk of death in the first 6 months after a COPD exacerbation compared with those without AKI.[35]

Patients with AKI have a high need for mechanical ventilation, hospitalization in the intensive care unit, long hospital and intensive care stays, and high in-hospital mortality risk.[36] We recommend evaluating renal function tests in patients with suspected COPD exacerbation presenting to the emergency department and in patients with severe exacerbation who are considered for hospitalization and intensive care unit admission.

Comorbidities are considered to be important problems in the management of COPD. It has been reported that patients with liver disease have a higher prevalence of COPD, and liver dysfunction has not been adequately evaluated in patients with COPD.[37] In addition, low-grade inflammation and oxidative stress, which are commonly observed in hepatic disorders and COPD, are considered to contribute to the development of liver dysfunction. Therefore, along with clinical evaluation, liver function tests may be requested from patients if needed.[38]

Hyponatremia (especially if severe) has been reported to be a predictive marker for a poor clinical course in COPD exacerbation; therefore, it is recommended to evaluate electrolyte imbalance and serum electrolytes in patients with COPD exacerbation. The incidence of hyponatremia was 15.8% in patients hospitalized for COPD exacerbation. It has been suggested that hyponatremia can be used as an independent predictor of mortality since patients with and those without hyponatremia have similar demographic characteristics; however, patients with hyponatremia have longer hospital stay, higher mechanical ventilation requirement, and higher mortality rate (both at admission and months after discharge) than patients without hyponatremia.[39]

PANEL RECOMMENDATIONS-10

Renal function tests and serum electrolytes should be evaluated in patients presenting to the emergency department with COPD exacerbation, especially in severe exacerbations for which hospitalization is considered.

References

1. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, *et al.* Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA 2013;309:2353-61.
2. Faner R, Tal-Singer R, Riley JH, Celli B, Vestbo J, MacNee W, *et al.*; ECLIPSE Study Investigators. Lessons from ECLIPSE: A review of COPD biomarkers. Thorax 2014;69:666-72.
3. Noell G, Cosío BG, Faner R, Monsó E, Peces-Barba G, de Diego A, *et al.* Multi-level differential network analysis of COPD exacerbations. Eur Respir J 2017;50:1700075.
4. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, *et al.* Persistent systemic issue is associated with poor clinical outcomes in COPD: A novel phenotype. PLoS One 2012;7:e37483.
5. Fattouh M, Alkady O. Inflammatory biomarkers in chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc 2014;63:799-804.
6. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, *et al.* Changes in forced expiratory volume in 1 second overtime in COPD. N Engl J Med 2011;365:1184-92.
7. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
8. Stiell IG, Clement CM, Aaron SD, Rowe BH, Perry JJ, Brison RJ, *et al.* Clinical characteristics associated with adverse events in patients with exacerbation of chronic obstructive pulmonary disease: A prospective cohort study. CMAJ 2014;186:E193-204.
9. Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: Cause, effects, and disease progression. Int J Chron Obstruct Pulmon Dis 2011;6:199-208.
10. Toft-Petersen AP, Torp-Pedersen C, Weinreich UM, Rasmussen BS. Association between hemoglobin and prognosis in patients admitted to hospital for COPD. Int J Chron Obstruct Pulmon Dis 2016;11:2813-20.
11. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, *et al.* Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: A randomised controlled trial. Lancet 2000;356:1480-5.
12. Cheng SL. Blood eosinophils and inhaled corticosteroids in patients with COPD: Systematic review and meta-analysis shih-lung. Int J Chron Obstruct Pulmon Dis 2018;13:2775-84.
13. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. Eur Respir J 2016;47:1374-82.
14. Hasegawa K, Camargo CA Jr. Prevalence of blood eosinophilia in hospitalized patients with acute exacerbation of COPD. Respirology 2016;21:761-4.

Table 5.4.1: Frequent electrocardiographic abnormalities and clinical significance in patients with chronic obstructive pulmonary disease exacerbation

ECG abnormalities	Clinical significance
Premature contractions	Atrial and ventricular ectopic beats are frequently seen in COPD patients.[2] Ectopic beats can trigger supraventricular and ventricular dysrhythmias
Sinus tachycardia	It develops due to hypoxia, acidosis, and tachypnea. It is expected to improve with appropriate treatment
Atrial fibrillation	Patients with chronic atrial fibrillation may have an increased ventricular rate during an exacerbation. Appropriate treatment protocols should be considered, and cardiology consultation should be requested in patients with newly developed atrial fibrillation
Multifocal atrial tachycardia	It is associated with a poor prognosis in COPD exacerbations[7]
Right atrial/ventricular hypertrophy, S1S2S3 pattern, right-axis shift	Right ventricular hypertrophy/dilatation supports the diagnosis of cor pulmonale[1,2]
Newly developed ST-segment/T wave changes	The main presenting complaint of acute coronary syndrome in elderly patients may be shortness of breath. In terms of acute coronary syndrome, repeated ECGs and troponin tests should be performed, and cardiology consultation should be requested if indicated

ECG=Electrocardiography, COPD=Chronic obstructive pulmonary disease

15. Viniol C, Vogelmeier CF. Exacerbations of COPD. Eur Respir Rev 2018;27:170103.
16. Kandemir Y, Doğan NÖ, Yaka E, Pekdemir M, Yılmaz S. Clinical characteristics of neutrophilic, eosinophilic and mixed-type exacerbation phenotypes of COPD. Am J Emerg Med 2021;45:237-41.
17. Long GH, Southworth T, Kolsum U, Donaldson GC, Wedzicha JA, Brightling CE, *et al.* The stability of blood eosinophils in chronic obstructive pulmonary disease. Respir Res 2020;21:15.
18. Brightling CE. Biomarkers that predict and guide therapy for exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc 2013;10:S214-9.
19. Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;174:867-74.
20. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, *et al.* C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. N Engl J Med 2019;381:111-20.
21. Prins HJ, Duijkers R, van der Valk P, Schoorl M, Daniels JM, van der Werf TS, *et al.* CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. Eur Respir J 2019;53:1802014.
22. Grolimund E, Kutz A, Marlowe RJ, Vögeli A, Alan M, Christ-Crain M, *et al.* ProHOSP study group. Long-term prognosis in COPD exacerbation: Role of biomarkers, clinical variables and exacerbation type. COPD 2015;12:295-305.
23. Pavasini R, Tavazzi G, Biscaglia S, Guerra F, Pecoraro A, Zaraket F, *et al.* Amino terminal pro brain natriuretic peptide predicts all-cause mortality in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis. Chron Respir Dis 2017;14:117-26.
24. Raluca H, Maria A, Magda B. Natriuretic peptides in heart failure coexisting with chronic obstructive pulmonary disease. Exp Clin Cardiol 2014;20:1606-14.
25. Guo X, Nie H, Chen Q, Chen S, Deng N, Li R, *et al.* The role of plasma N-terminal brain natriuretic pro-peptide in diagnosing elderly patients with acute exacerbation of COPD concurrent with left heart failure. Int J Chron Obstruct Pulmon Dis 2018;13:2931-40.
26. Laribi S, Pemberton CJ, Kirwan L, Nouira S, Turkdogan K, Yilmaz MB, *et al.* GREAT (Global Research on Acute Conditions Team) network. Mortality and acute exacerbation of COPD: A pilot study on the influence of myocardial injury. Eur Respir J 2017;49:1700096.
27. Wang M, Lin EP, Huang LC, Li CY, Shyr Y, Lai CH. Mortality of cardiovascular events in patients With COPD and preceding hospitalization for acute exacerbation. Chest 2020;158:973-85.
28. Adamson PD, Anderson JA, Brook RD, Calverley PM, Celli BR, Cowans NJ, *et al.* Cardiac troponin I and cardiovascular risk in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol 2018;72:1126-37.
29. Couturaud F, Bertoletti L, Pastre J, Roy PM, Le Mao R, Gagnadoux F, *et al.* Prevalence of pulmonary embolism among patients with COPD hospitalized with acutely worsening respiratory symptoms. JAMA 2021;325:59-68.
30. Aleva FE, Voets LW, Simons SO, de Mast Q, van der Ven AJ, Heijdra YF. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: A systematic review and meta-analysis. Chest 2017;151:544-54.
31. Fruchter O, Yigla M, Kramer MR. D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. Am J Med Sci 2015;349:29-35.
32. Hu G, Wu Y, Zhou Y, Wu Z, Wei L, Li Y, *et al.* Prognostic role of D-dimer for in-hospital and 1-year mortality in exacerbations of COPD. Int J Chron Obstruct Pulmon Dis 2016;11:2729-36.
33. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, *et al.* ESC scientific document group. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543-603.
34. Fabbian F, De Giorgi A, Manfredini F, Lamberti N, Forcellini S, Storari A, *et al.* Impact of renal dysfunction on in-hospital mortality of patients with severe chronic obstructive pulmonary disease: A single-center Italian study. Int Urol Nephrol 2016;48:1121-7.
35. Barakat MF, McDonald HI, Collier TJ, Smeeth L, Nitsch D, Quint JK. Acute kidney injury in stable COPD and at exacerbation. Int J Chron Obstruct Pulmon Dis 2015;10:2067-77.
36. Wan X, Chen D, Tan Y, Ma M, Zhang F, Liu Z, *et al.* Incidence, risk factors, and prognostic ımplications of acute kidney ınjury in patients with acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis 2020;15:1085-92.
37. Minakata Y, Sugiura H, Yamagata T, Yanagisawa S, Ichikawa T, Koarai A, *et al.* Prevalence of COPD in primary care clinics: Correlation with non-respiratory diseases. Intern Med 2008;47:77-82.
38. Viglino D, Jullian-Desayes I, Minoves M, Aron-Wisnewsky J, Leroy V, Zarski JP, *et al.* Nonalcoholic fatty liver disease in chronic obstructive pulmonary disease. Eur Respir J 2017;49:1601923.
39. Chalela R, González-García JG, Chillarón JJ, Valera-Hernández L, Montoya-Rangel C, Badenes D, *et al.* Impact of hyponatremia on mortality and morbidity in patients with COPD exacerbations. Respir Med 2016;117:237-42.

5.4. Electrocardiography evaluation

In patients presenting to the emergency department with shortness of breath, a 12-lead ECG should be performed urgently after airway safety, oxygenation, and hemodynamic stability are ensured. Common abnormal ECG findings observed in patients with COPD include right atrial enlargement, right ventricular hypertrophy, right bundle branch block, low voltage in extremity leads, S1S2S3 pattern, and right axis deviation.[1] These findings are reported to be more common in patients with severe COPD.[2] ECG findings of patients with COPD and their clinical significance are shown in Table 5.4.1.

It has been reported that acute coronary syndrome, heart failure, and dysrhythmias are more common in patients with COPD than in the normal population.[3] One of the common presenting complaints of acute coronary syndrome in the elderly population is shortness of breath.[4,5] Therefore, attention should be paid to ST-segment changes and T wave negativities on ECG since it may be associated with cardiac ischemia.

It has been reported that new-onset atrial fibrillation is common in patients with COPD exacerbation.[5] Moreover, new-onset atrial fibrillation is more common in patients with hypercapnia and low FEV1 values.[6] In patients presenting with a clinical presentation of COPD exacerbation and atrial fibrillation with rapid ventricular response on ECG, it should be considered that:

1. Increased ventricular response rate caused by hypoxia, tachypnea, or β2 agonist therapy based on chronic atrial fibrillation OR
2. New-onset (<48 h) atrial fibrillation may have developed.

For new-onset or presumably new-onset atrial fibrillation, the opinion of a cardiologist should be sought, a rate or rhythm control strategy should be established, and anticoagulant therapy should be initiated with appropriate indications to reduce the long-term risk of stroke. It should be noted that new-onset atrial fibrillation may decrease the ejection fraction and aggravate respiratory failure in patients with COPD and low cardiac reserve.[7]

PTE that may develop in patients with COPD may mimic the clinical presentation of COPD exacerbation or aggravate its symptoms. Therefore, caution should be exercised while evaluating ECG findings such as new-onset right bundle branch block, ST-segment depression in leads V_{1-3}, T wave negativity, and S1Q3T3 that may be associated with PTE.

Multifocal atrial tachycardia is one of the most common dysrhythmias observed in patients with COPD exacerbation. It has been shown that new-onset multifocal atrial tachycardia is associated with a poor prognosis in patients with COPD exacerbation.[8] The treatment of hypoxia and respiratory failure is more essential than the treatment using specific antiarrhythmic agents in the management of multifocal atrial tachycardia.[9]

PANEL RECOMMENDATIONS-11

In patients with suspected COPD exacerbation, a 12-lead ECG should be performed as soon as possible after stabilization is achieved

The frequency of dysrhythmia development in COPD patients is more frequent than in the normal population, so care should be taken against newly developing dysrhythmias

The presence of ECG findings of acute pulmonary thromboembolism and acute coronary syndrome that may mimic COPD exacerbation should be evaluated at the time of admission.

References

1. Goudis CA, Konstantinidis AK, Ntalas IV, Korantzopoulos P. Electrocardiographic abnormalities and cardiac arrhythmias in chronic obstructive pulmonary disease. Int J Cardiol 2015;199:264-73.
2. Holtzman D, Aronow WS, Mellana WM, Sharma M, Mehta N, Lim J, *et al*. Electrocardiographic abnormalities in patients with severe versus mild or moderate chronic obstructive pulmonary disease followed in an academic outpatient pulmonary clinic. Ann Noninvasive Electrocardiol 2011;16:30-2.
3. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. Lancet Respir Med 2015;3:631-9.
4. Bayer AJ, Chadha JS, Farag RR, Pathy MS. Changing presentation of myocardial infarction with increasing old age. J Am Geriatr Soc 1986;34:263-6.
5. Gregoratos G. Clinical manifestations of acute myocardial infarction in older patients. Am J Geriatr Cardiol 2001;10:345-7.
6. Terzano C, Romani S, Conti V, Paone G, Oriolo F, Vitarelli A. Atrial fibrillation in the acute, hypercapnic exacerbations of COPD. Eur Rev Med Pharmacol Sci 2014;18:2908-17.
7. Bhatt SP, Nanda S, Kintzer JS. Arrhythmias as trigger for acute exacerbations of chronic obstructive pulmonary disease. Respir Med 2012;106:1134-8.
8. McCord J, Borzak S. Multifocal atrial tachycardia. Chest 1998;113:203-9.
9. Custer AM, Yelamanchili VS, Lappin SL. Multifocal Atrial Tachycardia. 19 July, 2020. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.

5.5. Imaging

Posteroanterior chest X-ray should be routinely performed during the evaluation of patients with a prediagnosis of COPD exacerbation in the emergency department.[1] There is no specific finding that indicates exacerbation on the chest X-rays of patients presenting with COPD exacerbation. Therefore, the main purpose of performing chest X-ray imaging is to exclude differential diagnoses, leading to a clinical presentation of exacerbation. In particular, it is possible to detect new-onset pneumonic infiltrates, pneumothorax, pleural effusion, cardiomegaly, pulmonary edema, mass, abscess, and atelectasis using a chest X-ray.[1] Chest X-ray imaging should be performed after patients are administered oxygen, and their hemodynamic status is corrected. If the hemodynamic status of the patient is not stable for transferring to the radiography unit, portable chest X-ray imaging can be performed.

Thoracic computed tomography (CT) indications have not yet been clearly revealed in patients presenting to the emergency department with a prediagnosis of COPD exacerbation. In general, the routine use of thoracic CT is not recommended in COPD exacerbation cases.[2,3] However, for certain patients, noncontrast chest CT with low-dose radiation, if appropriate, may be considered in the following cases:

- If chest X-ray findings are not specific to COPD (infiltrates that cannot be clearly interpreted, interstitial pulmonary disease, pneumothorax, etc.)
- If there are signs of new-onset severe respiratory failure
- If other differential diagnoses that may mimic a COPD exacerbation are primarily considered

Minor pneumothorax, pneumonic infiltrates, bronchiectasis, atelectasis, pleural and pericardial fluids, cardiomegaly, mass, abscess, pneumomediastinum, and the location of the endotracheal tube in intubated patients, which may be missed in direct X-ray, can be detected using thoracic CT. It has been shown that noncontrast thoracic CT detects pneumonic infiltrates that cannot be detected on chest X-ray in one-third of patients with COPD exacerbation. It has been reported that noncontrast thoracic CT leads to a change in treatment in approximately 10% of cases with COPD exacerbation.[3] In another study, it was shown that 65% of patients with COPD exacerbation had pneumonic infiltrates of varying degrees.[4]

Bronchial wall thickening, emphysematous appearance, mucous plugging, and hyperinflation may support the diagnosis of COPD, and these may help diagnose COPD exacerbation along with the clinical features and medical history in patients without a previous diagnosis of COPD, but whose history suggests the presence of COPD and COPD exacerbation.[5,6]

Thoracic CT angiography should be performed during admission to the emergency department for patients with a high clinical probability of PTE and those with a low or moderate clinical probability of PTE but a high age-adjusted D-dimer value. Patients should be evaluated for contrast allergy, and renal function tests should be performed before using contrast materials. In cases where thoracic CT angiography cannot be performed, combinations of ventilation-perfusion scintigraphy, venous Doppler ultrasonography of the lower extremity, and echocardiography can be used.[7]

For patients with a prediagnosis of COPD exacerbation presenting to the emergency department with shortness of breath, echocardiography can be used in addition to clinical and laboratory evaluation for differential diagnosis in certain cases. Echocardiography can provide important information for the evaluation of left and right ventricular functions, especially in patients with suspected heart failure or PTE.

PANEL RECOMMENDATIONS-12

Chest radiography should be routinely performed in the evaluation of patients presenting with COPD exacerbation

Noncontrast thorax CT can be performed in these patients for the following indications:

- Suspicious findings that may be significant on the plain X-ray (cannot be explained by COPD)
- Newly developed severe respiratory failure
- Differential diagnoses that may mimic a COPD exacerbation

Thorax CT angiography or ventilation-perfusion scintigraphy may be performed for patients who are considered for further investigation for pulmonary thromboembolism. Renal function tests should be taken into account.

References

1. Radiopedia. Available from: https://radiopaedia.org/articles/copd-summary?lang=us. [Last accessed on 2021 May 05].
2. Ramakrishnan S, Janssens W, Burgel PR, Contoli M, Franssen FME, Greening NJ, *et al*. Standardization of clinical assessment, management and follow-up of acute hospitalized exacerbation of COPD: A Europe-Wide consensus. Int J Chron Obstruct Pulmon Dis 2021;16:321-32.
3. Park HJ, Kim SH, Kim HC, Lee BY, Lee SW, Lee JS, *et al.* Utility of computed tomography in a differential diagnosis for the patients with an ınitial diagnosis of chronic obstructive pulmonary disease exacerbation. Tuberc Respir Dis (Seoul) 2019;82:234-41.
4. Cheng T, Wan H, Cheng Q, Guo YI, Qian Y, Fan L, *et al.* Computed tomography manifestation of acute exacerbation of chronic obstructive pulmonary disease: A pilot study. Exp Ther Med 2016;11:519-29.
5. Hackx M, Ghaye B, Coche E, Muylem AV, Gevenois PA. Severe COPD exacerbation: CT features. COPD 2015;12:38-45.
6. Labaki WW, Martinez CH, Martinez FJ, Galbán CJ, Ross BD, Washko GR, *et al.* The Role of chest computed tomography in the evaluation and management of the patient with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2017;196:1372-9.
7. Turkish Thoracic Society Pulmonary Thromboembolism Diagnosis and Treatment Consensus Report. ISBN: 978-625-409-811-6. Release Date: January 2021. Available from: https://www.toraks.org.tr/site/community/downloads/wdIGg7bno0K_9zCY. [Last accessed on 2021 May 05].

5.6. Prognostic markers

There are many comorbid diseases, biomarkers, and derived scoring systems that predict the prognosis of a patient presenting to the hospital with a COPD exacerbation. Commonly used and validated risk scores that help evaluate mortality outcomes in COPD exacerbations are BAP-65, DECAF, and Ottawa COPD scores.[1-3]

According to many previously conducted studies that aimed at estimating prognosis, the most important criteria that predict a subsequent presentation to the hospital due to an exacerbation are the patient's previous presentations due to exacerbation.[4,5] Based on data from a study conducted by Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators in 2010, having an exacerbation once in the previous year is more risky than never having an exacerbation (odds ratio [OR]: 2.24, 95% CI: 1.77–2.84), and the risk increases exponentially in the case of two or more previous exacerbations (OR: 5.72, 95% CI: 4.47–7.31).[5]

According to the 5-year results of a retrospective cohort study involving 359 patients, age, severity of airway obstruction (<30% reduction in FEV1), history of diabetes mellitus, cancer, and elevated creatinine level and respiratory rate at presentation can predict death and readmission to the hospital. The variables predicting death, which is the secondary outcome of the study, are age (hazard ratio [HR]: 1.12, 95% CI: 1.05–1.19), a history of cancer (HR: 7.04, 95% CI: 2.22–22.36), and elevated procalcitonin levels (HR: 1.02, 95% CI: 1.00–1.03).[4]

Most prognostic studies conducted in patients presenting with COPD exacerbation have focused on whether the exacerbation was due to an infective and potentially bacterial etiology, patient readmission, and mortality outcomes. The colonization of respiratory pathogens in the airway of patients with COPD makes it difficult to use sputum samples for microbiological evaluation during exacerbations. For these reasons, the use of biochemical markers during exacerbation can give an idea about the origin of the exacerbation.[6]

Overview of key biomarkers

Although many biomarkers have been studied for the

prognostic evaluation of patients with COPD during the stable and exacerbation periods, the most prominent ones among these are procalcitonin and CRP. In addition, biomarkers can be used in diagnosing exacerbations, determining the etiology, understanding the severity of the disease, guiding the use of antibiotics, determining the length of hospital stay and complications, and predicting recurrence and mortality.[7]

5.6.1. Procalcitonin

Procalcitonin is a calcitonin precursor produced by the C cells in the thyroid tissue. Calcitonin expression is limited to the neuroendocrine cells in healthy individuals; however, under pathological conditions, its production is observed in the adipose tissue in the presence of bacterial lipopolysaccharides, microbial toxins, and inflammatory stimulators (interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]).[8,9] It is not detectable in the blood (<0.01 ng/mL) of healthy individuals, and although it may increase, its level rarely exceeds 0.5 ng/mL and has a half-life of 30 h in noninfectious conditions.[10]

In studies, procalcitonin-guided approaches have not usually been analyzed directly in the context of COPD exacerbations. Instead, COPD was considered as a subgroup of lower respiratory tract infections in these studies. On the other hand, it has been reported that procalcitonin-based protocols prevent the pneumonic transformation of COPD (area under the curve [AUC]: 0.93, 95% CI: 0.88–0.98) and shorten the duration of antibiotic administration but have no effect on mortality.[11]

Meta-analyses that were conducted subsequently also tried to confirm this information. According to the results of a meta-analysis by Mathioudakis *et al*., the use of procalcitonin-based protocols in COPD exacerbations reduced the use of antibiotics (RR: 0.56, 95% CI: 0.43–0.73) and decreased the number of days of antibiotic administration (difference in days: −3.83, 95% CI: −4.32–0.35) but had no effect on the total length of hospital stay and mortality.[12]

In the guideline, details on procalcitonin-guided care can be found in the clinical question under the title Section 5.6.4 (procalcitonin-guided antibiotic use in exacerbations).

5.6.2. C-reactive protein

There is evidence in the literature that suggests CRP can also be used in the diagnosis of COPD exacerbations. CRP has an AUC of 0.73 in the diagnosis of exacerbation, and when the threshold value is taken as 27.6 mg/L, it helps the diagnosis of exacerbation with 40% sensitivity and 90% selectivity.[13] However, there are conflicting results in the literature suggesting that CRP indicates a bacterial etiology in COPD exacerbations. When the CRP threshold value is taken as 10 mg/L, the sensitivity is 84%, and selectivity is 38% for bacterial etiology. The diagnostic value of CRP increases when TNF-α levels in sputum are evaluated along with it.[14,15] Although there are publications suggesting that increased CRP levels increase the frequency of readmissions and exacerbations, it has not been proven to have an effect on the development of complications and mortality.[7,16,17] Data on CRP are detailed in Section 5.3 (laboratory tests).

5.6.3. Other biomarkers

Apart from the biomarkers that are frequently used in exacerbations, there are many other biomarkers that are still being evaluated in terms of their diagnostic value. The most commonly studied biomarkers are IL-6, sTREM-1, BNP, pro-ANP, neopterin, copeptin, and proADM.[6,7] It has been reported that, among these, sTREM-1 levels may be associated with increased bacterial load in exacerbations;[18] and copeptin, pro-ANP, and IL-6 levels may be higher during exacerbations than in the stable period.[13,19] In a cohort study conducted by ECLIPSE investigators on patients with COPD, it was reported that, in addition to these findings, leukocyte count, neutrophil count, IL-6, CCL-18/PARC, CRP, IL-8, fibrinogen, and SP-D markers could predict 3-year mortality regardless of the patient's age; previous hospitalizations; and BODE index.[20] None of these biomarkers showed sufficiently high prognostic accuracy for the short-term management and safe discharge of patients with COPD exacerbation.

PANEL RECOMMENDATIONS-13

It is not appropriate to use any biomarker alone for prognostic purposes in the management of COPD exacerbations. In the light of available evidence, it may be considered to use procalcitonin and CRP levels together with other clinical signs in order to determine the etiology of exacerbation and to evaluate the possibility of re-admission to the hospital. The clinical question regarding the use of procalcitonin-guided antibiotics is discussed in Section 5.6.4 (Procalcitonin-Guided Antibiotic Use in Exacerbations).

References

1. Tabak YP, Sun X, Johannes RS, Gupta V, Shorr AF. Mortality and need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: Development and validation of a simple risk score. Arch Intern Med 2009;169:1595-602.
2. Steer J, Gibson J, Bourke SC. The DECAF score: Predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax 2012;67:970-6.
3. Stiell IG, Clement CM, Aaron SD, Rowe BH, Perry JJ, Brison RJ, *et al*. Clinical characteristics associated with adverse events in patients with exacerbation of chronic obstructive pulmonary disease: A prospective cohort study. CMAJ 2014;186:E193-204.
4. Flattet Y, Garin N, Serratrice J, Perrier A, Stirnemann J, Carballo S. Determining prognosis in acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis 2017;12:467-75.
5. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, *et al*. Evaluation of COPD Longitudinally to Identify

Predictive Surrogate Endpoints (ECLIPSE) ınvestigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
6. Lacoma A, Prat C, Andreo F, Domínguez J. Biomarkers in the management of COPD. Eur Respir Rev 2009;18:96-104.
7. Koutsokera A, Stolz D, Loukides S, Kostikas K. Systemic biomarkers in exacerbations of COPD: The evolving clinical challenge. Chest 2012;141:396-405.
8. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: Past, present and future. BMC Med 2011;9:107.
9. Vijayan AL, Vanimaya , Ravindran S, Saikant R, Lakshmi S, Kartik R, *et al.* Procalcitonin: A promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care 2017;5:51.
10. Bassetti M, Russo A, Righi E, Dolso E, Merelli M, D'Aurizio F, *et al.* Role of procalcitonin in predicting etiology in bacteremic patients: Report from a large single-center experience. J Infect Public Health 2020;13:40-5.
11. Hankey B, Riley B. Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 1: Use of a procalcitonin algorithm to guide antimicrobial therapy in COPD exacerbations can reduce antibiotic consumption with no increase in rates of treatment failure or mortality. Emerg Med J 2015;32:493-5.
12. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Vestbo J. Procalcitonin to guide antibiotic administration in COPD exacerbations: A meta-analysis. Eur Respir Rev 2017;26:160073.
13. Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;174:867-74.
14. Bircan A, Gokirmak M, Kilic O, Ozturk O, Akkaya A. C-reactive protein levels in patients with chronic obstructive pulmonary disease: Role of infection. Med Princ Pract 2008;17:202-8.
15. Sethi S, Wrona C, Eschberger K, Lobbins P, Cai X, Murphy TF. Inflammatory profile of new bacterial strain exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:491-7.
16. Perera WR, Hurst JR, Wilkinson TM, Sapsford RJ, Müllerova H, Donaldson GC, *et al.* Inflammatory changes, recovery and recurrence at COPD exacerbation. Eur Respir J 2007;29:527-34.
17. Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, *et al.* Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. Chest 2007;131:1058-67.
18. Phua J, Koay ES, Zhang D, Tai LK, Boo XL, Lim KC, *et al.* Soluble triggering receptor expressed on myeloid cells-1 in acute respiratory infections. Eur Respir J 2006;28:695-702.
19. Müller B, Süess E, Schuetz P, Müller C, Bingisser R, Bergmann A, *et al.* Circulating levels of pro-atrial natriuretic peptide in lower respiratory tract infections. J Intern Med 2006;260:568-76.
20. Celli BR, Locantore N, Yates J, Tal-Singer R, Miller BE, Bakke P, *et al*. ECLIPSE Investigators. Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;185:1065-72.

5.6.4. Chronic obstructive pulmonary disease exacerbation and procalcitonin-guided antibiotic use

Clinical question:

- P: Patients presenting to the hospital after an exacerbation of COPD
- I: Procalcitonin-guided antibiotic use,
- C: Standard care, and
- O: mortality was determined, and a literature review was conducted with the appropriate keywords.

In the full-text review conducted for the clinical question, it was found that some articles particularly covered patients with lower respiratory tract infections rather than COPD exacerbation,[1-4] and some articles randomized patients to antibiotic therapy versus no antibiotic therapy rather than direct procalcitonin-guided care.[3,5] Therefore, only randomized or observational studies comparing procalcitonin-guided treatment with standard care in patients who presented only with COPD exacerbation were included in the bias assessment. In RoB2 and ROBINS-I evaluations, it was understood that the articles had a medium-high risk of bias due to the way the articles were assigned to the groups, the awareness of the participants and practitioners of the interventions, and the problems in the evaluation of patients who were lost during follow-up.

In a study by Verduri *et al*., patients with COPD exacerbation were randomized either to groups receiving antibiotic therapy (n = 90) or to groups, in which procalcitonin-guided antibiotic treatment was initiated or discontinued (n = 88) and followed up for 6 months.[6] There was no difference between the groups in terms of at least one recurrent exacerbation, the primary end point of the study. Three deaths were reported in the procalcitonin group and two deaths in the standard care group (risk difference = 1.19, 95% CI: −3.67–6.05). In a study by Corti *et al*., patients with COPD exacerbations followed up for 28 days were randomized to procalcitonin (n = 62) and control (n = 58) groups, and the decision for using antibiotic treatment in the control group was based on the GOLD criteria.[7] According to the results of the study, the rate of antibiotic use was 41.9% in the procalcitonin group, whereas it was 67.2% in the control group. Death occurred in one patient in the first group and in two patients in the second group. In a similar study by Stolz *et al*., a total of 226 patients were randomized into groups, and the outcomes of the patients were evaluated within a 6-month period. Accordingly, it was found that procalcitonin-mediated care reduced antibiotic prescription (40% vs. 72%) and total antibiotic use (RR: 0.76, 95% CI: 0.64–0.92). Five patients from the procalcitonin group and nine patients from the standard care group died at the end of 6-month period (P = 0.409).[8]

In addition, some studies in the literature have tested procalcitonin- and CRP-guided approaches and compared them with the standard approach. In a study conducted by Zou *et al*. in 2018, patients presenting with COPD exacerbation were randomized into two groups; there was no difference between the groups in terms of the use of antibiotics and other drugs. In addition, it was observed that lengths of antibiotic use and hospital stay were shortened. Two patients in the biomarker group and one patient in the standard care group died.[9]

According to the results of a retrospective cohort study conducted by Ulrich *et al*. in 2019, in which records of 238 COPD exacerbation cases were evaluated, the duration of antibiotic administration did not decrease in patients who were evaluated by procalcitonin within a 6-month period, and no difference was observed in terms of mortality. On the other hand, it was observed that the number of 30-day readmissions was lower in the group, in which procalcitonin was measured compared to the group in which it was not measured (21% vs. 36%).[10]

When studies were evaluated based on their risk of bias, three studies without a high risk of bias were included in the meta-analysis.[6,8,9] Accordingly, it was found that the effect of procalcitonin-mediated care on mortality was not statistically significant (RR: 0.858, 95% CI: 0.378–1.946). No heterogeneity was found between the studies (I^2 = 0.0). The forest plot of the meta-analysis is shown in Figure 5.6.1.

EVIDENCE-BASED RECOMMENDATIONS FOR CLINICAL QUESTIONS-2

Since the use of procalcitonin-guided antibiotics in patients admitted to the hospital with COPD exacerbation does not reduce mortality compared to standard care, routine PCT level measurement is not recommended. However, procalcitonin-guided therapy can shorten the duration of antibiotic use and reduce readmission rates, so it can be used in the evaluation of patients.

References

1. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, *et al.* ProHOSP study group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: The ProHOSP randomized controlled trial. JAMA 2009;302:1059-66.
2. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, *et al.* Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: Cluster-randomised, single-blinded intervention trial. Lancet 2004;363:600-7.
3. Daniels JM, Schoorl M, Snijders D, Knol DL, Lutter R, Jansen HM, *et al.* Procalcitonin vs. C-reactive protein as predictive markers of response to antibiotic therapy in acute exacerbations of COPD. Chest 2010;138:1108-15.
4. Townsend J, Adams V, Galiatsatos P, Pearse D, Pantle H, Masterson M, *et al.* Procalcitonin-guided antibiotic therapy reduces antibiotic use for lower respiratory tract ınfections in a United States medical center: Results of a clinical trial. Open Forum Infect Dis 2018;5:ofy327.
5. Wang JX, Zhang SM, Li XH, Zhang Y, Xu ZY, Cao B. Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: A prospective randomized controlled trial. Int J Infect Dis. 2016;48:40-5.
6. Verduri A, Luppi F, D'Amico R, Balduzzi S, Vicini R, Liverani A, *et al.* Antibiotic treatment of severe exacerbations of chronic obstructive pulmonary disease with procalcitonin: A randomized noninferiority trial. PLoS One 2015;10:e0118241.
7. Corti C, Fally M, Fabricius-Bjerre A, Mortensen K, Jensen BN, Andreassen HF, *et al.* Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis 2016;11:1381-9.
8. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, *et al.* Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 2007;131:9-19.
9. Zou Y, Zhu Z, Zhang Y. Significance of serum procalcitonin combined with C-reactive protein in diagnosis of acute exacerbation of chronic obstructive pulmonary disease and guidance of antibiotics therapy. Int J Clin Exp Med 2018;11:11070-8.
10. Ulrich RJ, McClung D, Wang BR, Winters S, Flanders SA, Rao K. Introduction of Procalcitonin Testing and Antibiotic Utilization for acute exacerbations of chronic obstructive pulmonary disease. Infect Dis (Auckl) 2019;12:1178633719852626.

6. Treatment of Chronic Obstructive Pulmonary Disease Exacerbations

6.1. Short-acting inhaled β-2 agonists

The main cause of dyspnea in COPD exacerbation is bronchoconstriction. The contraction of the bronchial smooth muscles caused by airway inflammation is the cause of this condition.

β2-agonists are catecholamine-derived sympathomimetic bronchodilators.[1] β2-agonists bind to the receptors on the cell membranes of the endothelial, airway smooth muscle, epithelial, mast, and vascular smooth muscle

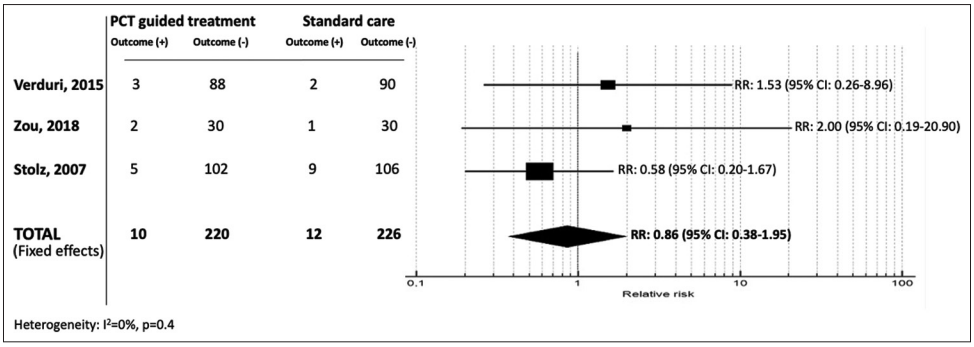

Figure 5.6.1: Forest plot of the relationship between procalcitonin-guided care and mortality

cells. However, they mainly bind to the airway smooth muscle cells. β-adrenergic agonists exert their effects by activating adenyl cyclase, which increases the level of intracellular cyclic adenosine 3′,5′-monophosphate (cAMP). cAMP activates protein kinase A, which phosphorylates some intracellular proteins and leads to smooth muscle relaxation. It is also considered that β-agonists suppress inflammation by inhibiting the release of mediators from human mast cells.

The effects of short-acting inhaled β2-agonists are evident within minutes, and their effect reaches the maximum level within 15-30 min. Their duration of action is 4-6 h. Although they have been used for many years, the maximal dose is generally avoided due to side effects and ineffective achievement of bronchodilation. It is known that salbutamol causes remarkable improvement in FEV_1, dyspnea, and quality of life compared to placebo in patients with COPD. It has been shown to reduce dyspnea and dynamic hyperinflation during exercise.[2] Short-acting β2-agonists, short-acting anticholinergics, and methylxanthines cause bronchodilation by inhibiting airway smooth muscle contraction. These drugs also act on secretions and mucociliary clearance.[3]

Short-acting β2-agonists were compared with short-acting anticholinergics in the Cochrane analysis of the use of short-acting bronchodilators in the treatment of COPD exacerbations since there is no study comparing short-acting β2-agonists with placebo. The effects on short-and medium-term respiratory functions were evaluated in the studies included in this analysis. In these small studies, no difference was observed in FEV_1 and peak expiratory flow rates when the use of β2-agonists and ipratropium bromide were compared. The increase in mean FEV_1 after administering a single dose of any drug has been reported to be between 150 and 250 ml.[4] Since high-quality randomized controlled trials are limited, the GOLD 2021 guidelines recommend the initiation of short-acting β2-agonists with or without short-acting anticholinergics as the first-line treatment for COPD exacerbations.[5]

Dosage and administration

Salbutamol

It is administered at a dose of 2.5 mg with a nebulizer (diluted to a total of 3 mL with saline) or 1–2 inhalations with an MDI (2 inhalations are commonly used, which may be increased up to 4 inhalations if necessary; 90 mcg per inhalation). If MDI is to be used with an air chamber, it is administered at a rate of 2–3 inhalations every hour and then every 2–4 h as needed based on treatment response.[5]

Increasing the dose of nebulized salbutamol to 5 mg has no significant benefit on spirometry or clinical outcomes.[6] Continuous nebulized β-agonist administrations may increase side effects and have not been shown to be advantageous in managing COPD.

Despite the evidence that the use of MDI devices is equally effective when compared to the use of nebulizers during COPD exacerbations, the use of nebulizers is preferred because many patients with COPD have difficulty using the appropriate MDI technique in the event of an exacerbation.[7,8]

6.2. Inhaled anticholinergics

Cholinergic bronchomotor tone is increased in COPD. Therefore, anticholinergics are used for bronchodilation. Plant alkaloids, atropine and scopolamine, are the fundamental compounds of anticholinergic therapy. Atropine methyl nitrate and ipratropium, oxitropium, and tiotropium bromides have a common quarternary ammonium structure. Most of the efferent anatomical nerves in humans are cholinergic. The fibers of the vagus continue along the airways and synapses in the peribronchial ganglion. Short postganglionic fibers reach the smooth muscle and mucous glands in the central airways. The release of acetylcholine from postganglionic nerve endings activates muscarinic receptors, causing smooth muscle contraction, mucus secretion from the mucous glands, and ciliary movement acceleration. Cholinergic bronchoconstriction occurs mainly in large airways. Anticholinergics inhibit cholinergic activity by binding to the acetylcholine-binding sites at muscarinic receptors and cause airway dilation. There are at least three types of muscarinic receptors with different physiological functions in the human lung – M1 receptors cause bronchoconstriction by providing peribronchial cholinergic transmission, M3 receptors on the smooth muscle cells, and submucosal glands cause smooth muscle contraction and mucus secretion, and unlike the other two receptors, M2 receptors limit vagal bronchoconstriction.[9] Since M2 receptors on the cholinergic nerve endings inhibit the release of acetylcholine, they act as a reuptake inhibitor receptor (autoreceptor). Thus, the blockade of M2 receptors increases the release of acetylcholine in the airways of humans. As atropine and ipratropium bromide are nonselective muscarinic antagonists, they block M2 receptors as well as M1 and M3 receptors. Therefore, the increased release of acetylcholine may resolve the muscarinic receptor blockade in the muscles. As a result, attempts have been made to develop muscarinic receptor antagonists that will selectively block either M3 or M1 and M3 receptors. Ipratropium and oxitropium bromides have activity against M1, M2, and M3 receptors. However, the absorption of ipratropium bromide from the oronasal mucosa is poor, and the ingested portion is also poorly absorbed. Moreover, after the inhalation of ipratropium bromide, its serum levels are quite

low, reaching peak levels in 1–2 h, with a half-life of approximately 4 h.[3]

Given the benefit of dual therapy in stable COPD, the use of short-acting muscarinic antagonists and short-acting β-agonists is recommended for exacerbations requiring treatment in an emergency department or in a hospital.[5,10,11]

Dosage and administration

When ipratropium is combined with salbutamol in nebulizer therapy (0.5 mg [500 mcg] ipratropium is mixed with 2.5 mg salbutamol and diluted to 3 mL), it is administered at a dose of 2–3 inhalations every hour and then every 2–4 h as needed.[12] Ipratropium is also available in an MDI form that can be used with a chamber at a dose of 2 inhalations every 4–6 h.

There was no difference in the effects of short-acting β2-agonists or anticholinergics on FEV_1 when their administration with MDI and nebulizers were compared. Patients with more severe COPD and severe exacerbation may receive nebulizer therapy although continuous use is not recommended.

It has been emphasized that treatment with MDI or dry powder inhalers should be preferred instead of nebulizers because of the risk of the presence of COVID-19 related aerosols, especially in nebulizer therapies for patients with COPD. In addition, it has been suggested that if the bronchodilator agent is to be administered through a nebulizer, air-driven bronchodilator nebulization should be preferred because of the potential risk of increased $PaCO_2$ posed by the oxygen-driven nebulization form. In cases where nebulizer therapy is administered, it is recommended that health-care professionals enter the room with full protection for 3 h following treatment administration.[5]

The number of studies conducted on whether inhaled long-acting bronchodilators are beneficial during exacerbations is limited. However, in patients using long-acting β2-agonists, anticholinergics, or their combinations, it is recommended not to discontinue these drugs during exacerbation or to start them immediately upon discharge from the hospital.[5]

6.3. Selection of antibiotics against exacerbations

Clinical question:

- P: Patients presenting to the emergency department with COPD exacerbation
- I: Antibiotic group (macrolides)
- C: Antibiotic group (cephalosporins, quinolones, and penicillins)
- O1: Mortality, O2: Readmission, and O3: Admission to the intensive care unit were determined, and a literature review was conducted using appropriate keywords.

During the full-text review conducted for the clinical question, 78 full texts were read for the first outcome, 28 for the second outcome, and 40 for the third outcome. The third outcome was not included in the scope of PICO, because there was no article directly answering the selection of antibiotics and intensive care unit admission. Ten articles were included in the bias assessment for mortality, and RoB2 bias tool was applied to seven of these articles and ROBINS-I bias scale to three of them [bias tables: Tables 2.1 and 2.2]. It was found that two studies carried a high risk of bias, and two studies had a moderate risk of bias.

Ruiz-González *et al*. compared levofloxacin with standard antibiotic (clarithromycin, cefuroxime, amoxicillin/clavulanate) treatment in their study of 116 patients with COPD exacerbation, mortality was similar in both groups (17.8% vs. 22.9%, $P = 0.53$).[1]

Two randomized controlled trials were evaluated for the hospital readmission outcome; one of them had a high risk of bias, the other a moderate risk of bias. Four observational studies had a moderate and severe risk of bias [Tables 2.1 and 2.2]. In a multicenter, randomized, placebo-controlled study, Vermeersch *et al*. compared 500 mg/day azithromycin that was started after the first 48 h in addition to standard care, followed by, after 3 days, a dose of 250 mg/2 days a week for 3 months ($n = 147$) with placebo ($n = 154$) in patients hospitalized with exacerbation. In this study, the effect of prolonged administration of azithromycin on treatment failure was evaluated. According to the results of this study, there was a decrease in the hospital readmission rate (13% vs. 28% (HR: 0.43, 95% CI: 0.25–0.75, $P = 0.0024$)), but mortality was similar (2% vs. 4%, $P = 0.5075$).[2] The recurrent occurrence of the composite index defined in the *post hoc* analysis of this study was evaluated. Recurrent hospital visits were observed in one patient in the azithromycin group and in two patients in the placebo group within a 3-month period. It was reported that there was a 53% decrease in the rate of hospital visits (RR = 0.47, 95% CI: 0.27–0.80; $P = 0.007$), which was especially true for patients with CRP > 50 mg/L (RR = 0.18, 95% CI: 0.05–0.60, $P = 0.005$) or patients with low blood eosinophil level (<300 cells/µL, RR = 0.33, 95% CI: 0.17–0.64, $P = 0.001$).[3]

In a randomized controlled study by Wilson *et al*. (*MAESTRAL*), conducted in patients with moderate/severe COPD and chronic bronchitis who presented with an exacerbation, met type 1 Antonisen criteria and were treated as outpatients, the outcome was determined as 8-week clinical success (adding corticosteroids and/

Table 6.4.1: Randomized controlled trials investigating the effects of the duration of antibiotic use on chronic obstructive pulmonary disease exacerbation

Article	Risk level**	Population	Exclusion criteria	Intervention	Comparison	Outcome*	Result
Gotfried *et al*., 2005[3]	Some concerns	COPD (FEV_1 <70%), chronic bronchitis, outpatient, exacerbation type: Anthonisen type I, II	Additional comorbid disease, bronchiectasis, lung cancer, severe disease requiring oxygen therapy, immunodeficiency, hepatic-renal disorders	Controlled release clarithromycin 1000 mg/day (5 days)	Clarithromycin 1000 mg/day (7 days)	Clinical/bacteriological cure/target pathogen eradication rate/side effect (17-21. days posttreatment)	A similarly high efficacy (clinical response 84%, bacteriological response 87% and pathogen eradication 88%). Side effects are less in controlled-release form than in rapid-release form
Lorenz, 1998[4]	Some concerns	Type 1 chronic bronchitis exacerbation (according to Winnipeq classification), outpatient, COPD disease severity not reported	Not reported	Cefixime 400 mg/day (5 days)	Cefixime 400 mg/day (10 days)	Clinical improvement and side effects at 6th, 11th (primary outcome) and 30th days after treatment	A similarly high clinical efficacy (91%-89%) and side effects
Gotfried *et al*., 2001[5]	Some concerns	Exacerbation of chronic bronchitis, exacerbation type: Anthonisen type 1, 2, 3. COPD disease severity was not reported. Patients were grouped according to corticosteroid use. The mean duration of exacerbation was 9 days, 83% of the cases had 0-3 exacerbations in the previous year, 68% were active smokers, 8% were using systemic corticosteroids	Pregnancy, immunodeficiency, pneumonia, liver failure, taking antibiotics for the last 7 days, taking other antibiotics simultaneously	Gatifloxacin (5 days)	Clarithromycin (10 days), gatifloxacin (7 days)	Clinical cure and microbiological eradication/ side effects (7th-14th days after treatment)	Similar high efficacy (89%-88%) and similar side effects
DeAbate *et al*., 1999[6]	Some concerns	Exacerbation of chronic bronchitis (over 18 years, Anthonisen type 1, 2, 3). COPD disease severity was not reported	Pregnancy, lactation, immunodeficiency, pneumonia, additional lung disease, taking antibiotics in the last 7 days, taking systemic corticosteroids, being hypersensitive to antibiotics, neutropenia, taking theophylline and warfarin, AIDS, uncontrolled diabetes, gastroenterological disease	Grepafloxacin (5 days)	Grepafloxacin (10 days)	Clinical/bacteriological cure and side effects during the treatment (3rd-5th days), after the treatment (1st-3rd days), follow-up (24th-26th days)	Clinical cure in 81%-83% and similar in both groups. Similar side effects

Contd...

Table 6.4.1: Contd...

Article	Risk level**	Population	Exclusion criteria	Intervention	Comparison	Outcome*	Result
Sethi *et al.*, 2005[7]	Low risk	Chronic bronchitis exacerbation (Anthonisen type 1, 2, 3), over 45 years, smoking (>15 pack/year). Presence and severity of COPD were reported. FEV1 >70% in 39% of patients, between 50-70% in 22.8%, below 50% in 22.8%. 16% of patients used corticosteroids in the previous year, 73% of them had exacerbation last year	Pregnancy, lactation, immunodeficiency, pneumonia, bronchiectasis, active tuberculosis, malignancy, cystic fibrosis, infectious mononucleosis, renal-hepatic failure, taking antibiotics in the last 7 days, taking systemic corticosteroids, hypersensitivity to antibiotics, AIDS, severe uncontrolled disease	Amoxicillin/ clavulanate 2000/125 mg/ day (5 days)	Amoxicillin/ clavulanate 875/125 mg/day (7 days)	Clinical improvement/ adverse effects at 9-11 days posttreatment, 14-21 days posttreatment (test of cure) and long-term follow-up (28-35 days)	Clinical improvement between 14th-21st days (primary outcome), similar in both groups: 93%. Adverse effects similar
Wasilewski *et al.*, 1999[8]	Some concerns	Chronic bronchitis exacerbation (patients over 12 years of age). COPD presence and severity not reported	Pregnant, lactating period, pneumonia, taking antibiotics in the last 7 days, hypersensitivity to antibiotics	Dirithromycin (5 days)	Erythromycin (7 days)	After treatment, 3rd-5th days and 10th-14th days, clinical improvement and side effects	Clinical response is in the range of 84%-72%, similar in both groups. Side effects rates are similar
Masterton and Burley, 2001[9]	Some concerns	Exacerbation of chronic bronchitis (patients over 18 years, Anthonisen type 1-2-3). COPD cases were included, severity unknown	Pregnant, lactating period, immunodeficiency, pneumonia, bronchiectasis, active tuberculosis, malignancy, cystic fibrosis, renal-hepatic failure, taking antibiotics in the last 3 days, taking azithromycin or ofloxacin in the last 7 days, severe malabsorption, antibiotic hypersensitivity, AIDS, uncontrolled serious illness	Levofloxacin (5 days)	Levofloxacin (7 days)	Clinical improvement after 1-3 days and 7-10 days after last dose and improvement after 4-5 weeks and side effects	Clinical improvement was 82.8%-84.8% and was similar in both groups. Side effects rates are similar. Those with COPD, cardiopulmonary disease, over 65 years of age and more than 4 exacerbations per year did not change the outcome
Chodosh *et al.*, 2000[10]	Low risk	Chronic bronchitis exacerbation (anthonisen type 1, 2, 3). COPD cases were included, severity unknown	Severe (functional capacity, class 4) patients, patients requiring iv antibiotics, patients using drugs that prolong QT, patients using systemic antibiotics in the last 24 h	Moxifloxacin (5 days)	Moxifloxacin (10 days) (3rd group: 10 days of clarithromycin)	Bacteriological and clinical response and side effects at 0-6 days and 7-17 days after treatment	Clinical improvement was in the range of 89%-91%-91% and was similar in all three groups. The 10-day treatment caused more drug-related side effects
Roede *et al.*, 2007[2]	Low risk	Hospitalized COPD exacerbation (Type-1). 50% of patients were GOLD spirometric grade 3-4, received oxygen and corticosteroid therapy	Drug allergy, cystic fibrosis, bronchiectasis, neutropenia, agammaglobulinemia, neutropenia, taking antibiotics in the last 24 h, life expectancy <1 month, requiring mechanical ventilator or intensive care unit admission	Amoxicillin/ clavulanate (3 days)	Amoxicillin/ clavulanate (10 days)	Clinical cure and side effects at 21st day and 3rd month	Clinical cure was 76%-80% for the 21st day and 62%-56% for the 3rd month. Length of hospital stay, systemic corticosteroid and oxygen use were similar in both groups. The side effect profile was mild and similar in both groups

*Points highlighted in red are primary outcomes, **Risk assessment was conducted by ROBINS-I[1]. FEV1=Forced expiratory volume at the 1st second, GOLD=Global initiative for obstructive lung disease, AIDS=Acquired immunodeficiency syndrome, COPD=Chronic obstructive pulmonary disease, QT=QT interval on ECG

or antibiotics to the treatment or increasing their dose, or hospitalization within 8 weeks due to respiratory reasons after the index event), and moxifloxacin and amoxicillin/clavulanic acid were compared. According to the results of this study, it was found that moxifloxacin was not less effective than amoxicillin/clavulanic acid (according to per-protocol-analysis: 20.6% vs. 22%, 95% CI: −5.89–3.83, according to intention-to-treat analysis: 20.4% vs. 21.6%, 95% CI: −5.50–3.03). Even in cases where the exacerbation was confirmed to be of bacterial origin, clinical failure rates were reported to be lower with moxifloxacin compared to amoxicillin/clavulanic acid (19% vs. 25.4%, $P = 0.016$ according to the intention-to-treat analysis).[4]

The findings could not be evaluated by meta-analytical methods because of the following reasons: The studies included different populations, comparison arms of randomized controlled trials were chosen as placebo,[5,6] old publications included chronic bronchitis exacerbations,[7-10] antibiotic groups were evaluated with different definitions in each study,[1,11] patients and exacerbations of varying severity levels were evaluated,[2,3,12] primary outcome was not compliance with antibiotherapy,[13] various times and criteria were selected as the primary and secondary outcomes (e.g., in-hospital mortality, short-term mortality, and mortality for 6 months),[12,14,15] and different criteria were selected for readmission.

EVIDENCE-BASED RECOMMENDATIONS FOR CLINICAL QUESTIONS-3

The panel did not make a recommendation due to the lack of sufficient evidence regarding the question of which antibiotic group would reduce mortality and prevent hospital readmission for patients who presented to the emergency department due to COPD exacerbation and were planned to start antibiotics. According to the antibiotic sensitivity pattern of the hospital and the region, antibiotic preference can be made by considering the principles of rational antibiotic use.

References

1. Ruiz-González A, Giménez A, Gómez-Arbonés X, Soler-González J, Sánchez V, Falguera M, *et al.* Open-label, randomized comparison trial of long-term outcomes of levofloxacin versus standard antibiotic therapy in acute exacerbations of chronic obstructive pulmonary disease. Respirology 2007;12:117-21.
2. Vermeersch K, Gabrovska M, Aumann J, Demedts IK, Corhay JL, Marchand E, *et al.* Azithromycin during acute chronic obstructive pulmonary disease exacerbations requiring hospitalization (BACE). A multicenter, randomized, double-blind, placebo-controlled trial. Am J Respir Crit Care Med 2019;200:857-68.
3. Vermeersch K, Belmans A, Bogaerts K, Gyselinck I, Cardinaels N, Gabrovska M, *et al.* Treatment failure and hospital readmissions in severe COPD exacerbations treated with azithromycin versus placebo – A *post hoc* analysis of the BACE randomized controlled trial. Respir Res 2019;20:237.
4. Wilson R, Anzueto A, Miravitlles M, Arvis P, Alder J, Haverstock D, *et al.* Moxifloxacin versus amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. Eur Respir J 2012;40:17-27.
5. van Velzen P, Ter Riet G, Bresser P, Baars JJ, van den Berg BT, van den Berg JW, *et al.* Doxycycline for outpatient-treated acute exacerbations of COPD: A randomised double-blind placebo-controlled trial. Lancet Respir Med 2017;5:492-9.
6. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: A randomised placebo-controlled trial. Lancet 2001;358:2020-5.
7. Elmes PC, King TK, Langlands JH, Mackay JA, Wallace WF, Wade OL, *et al.* Value of ampicillin in the hospital treatment of exacerbations of chronic bronchitis. Br Med J 1965;2:904-8.
8. Pines A, Raafat H, Plucinski K, Greenfield JS, Linsell WD, Solari ME. Demethylchlortetracycline, lymecycline and methacycline compared in patients with purulent exacerbations of bronchitis. Br J Dis Chest 1968;62:19-26.
9. Wilson R, Allegra L, Huchon G, Izquierdo JL, Jones P, Schaberg T, *et al.* Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. Chest 2004;125:953-64.
10. Allegra L, Konietzko N, Leophonte P, Hosie J, Pauwels R, Guyen JN, *et al.* Comparative safety and efficacy of sparfloxacin in the treatment of acute exacerbations of chronic obstructive pulmonary disease: A double-blind, randomised, parallel, multicentre study. J Antimicrob Chemother 1996;37 Suppl A:93-104.
11. Joyner KR, Walkerly A, Seidel K, Walsh N, Damshekan N, Perry T, *et al.* Comparison of narrow-versus broad-spectrum antibiotics in elderly patients with acute exacerbations of chronic obstructive pulmonary disease. J Pharm Pract. 2020 Jul 10:897190020938190.
12. Kiser TH, Reynolds PM, Moss M, Burnham EL, Ho PM, Vandivier RW, *et al.* Impact of macrolide antibiotics on hospital readmissions and other clinically ımportant outcomes in critically Ill patients with acute exacerbations of chronic obstructive pulmonary disease: A propensity score-matched cohort study. Pharmacotherapy 2019;39:242-52.
13. Bremmer DN, Moffa MA, Ma K, Bean HR, Snatchko J, Trienski TL, *et al.* Acute exacerbations of chronic obstructive pulmonary disease with a low procalcitonin concentration: Impact of antibiotic therapy. Clin Infect Dis 2019;68:725-30.
14. Rothberg MB, Pekow PS, Lahti M, Brody O, Skiest DJ, Lindenauer PK. Comparative effectiveness of macrolides and quinolones for patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). J Hosp Med 2010;5:261-7.
15. Stefan MS, Rothberg MB, Shieh MS, Pekow PS, Lindenauer PK. Association between antibiotic treatment and outcomes in patients hospitalized with acute exacerbation of COPD treated with systemic steroids. Chest 2013;143:82-90.

6.4. Duration of antibiotic treatment in exacerbation cases

Clinical question:

- P: Patients presenting to the hospital with symptoms of COPD exacerbation and are planned to be treated with antibiotics
- I: Short-term antibiotic therapy (5–7 days),
- C: Long-term antibiotic therapy (14 days),
- O: Mortality, hospital readmission, and intensive care unit admission were determined, and a literature review was conducted using appropriate keywords.

A total of 47 randomized clinical trials that conducted short-term and long-term use of the same antibiotic were

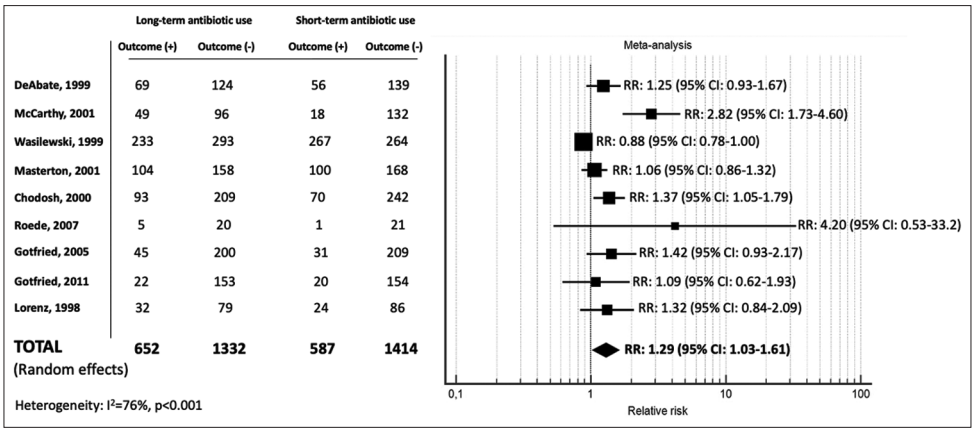

Figure 6.4.1: Forest plot for the effect of long- and short-term antibiotic use on the incidence of side effects

reviewed. Accordingly, ROBINS-I bias risk assessment was applied for nine studies that could be used to answer the research question.[1] Parameters related to the efficacy section of the studies were not included in the meta-analysis because of differences in the end times, outcome parameters, and study populations of the studies. Since the assessment of side effects was homogeneous, it was evaluated by performing a meta-analysis.

Evaluation based on outcomes

As seen in Table 6.4.1, none of the nine randomized clinical studies that were selected investigated the effects of using short-and long-term antibiotics against COPD exacerbations on mortality and hospitalization at the intensive care unit. Readmissions were not directly investigated. COPD exacerbations were included in only five of these nine studies, and the study group consisted of patients with only exacerbations of chronic bronchitis in the remaining four studies. Study populations generally consisted of outpatients, and only one study included inpatients. Most studies included patients over the age of 18 years, and one study included patients over the age of 12 years. Most of these groups did not include patients with COPD. Study populations usually consisted of patients with mild-to-moderate exacerbation, and few studies considered the effect of other treatments received by the patients (such as systemic corticosteroid use). End-of-treatment (immediately after the end of treatment), medium-term (test of cure; a while after the end of treatment), and long-term clinical and bacteriological improvements were chosen as the outcome in most of the studies; the outcomes of readmission, mortality, and admission to the intensive care unit were not evaluated in any of the studies. The common conclusion of the studies was that the short-term antibiotic use was as effective and well tolerated as long-term antibiotic use in moderate exacerbations and highly selected patients who have good clinical conditions and do not have a high risk of comorbidity. Accordingly, there is insufficient evidence to show that short-term antibiotic use is as effective as long-term antibiotic use in severe exacerbations requiring hospitalization and in patients with multiple complicating factors. As seen in Table 6.4.1, in a single randomized controlled study conducted with a group of hospitalized patients with severe disease receiving oxygen and corticosteroids, the result of clinical cure achieved using short-term antibiotics (3 days) was similar to that using long-term (10 days) antibiotics at 21 days and 3 months.[2] Clinical cure was at a rate of 76%–80% for day 21 and 56%–62% for month 3. Evaluation on day 21 was informative in terms of recurrence and may include a prediction for readmission.

A meta-analysis was conducted with nine studies without a high risk of bias to compare the incidence of side effects with short-and long-term antibiotic use. Accordingly, the collective results showed that long-term antibiotic use was associated with a higher incidence of side effects (RR: 1.288; 95% CI: 1.029–1.612, P = 0.027). There was heterogeneity between the studies (I^2 = 76%). The forest plot of the meta-analysis is provided in Figure 6.4.1.

EVIDENCE-BASED RECOMMENDATIONS FOR CLINICAL QUESTIONS-4

Short-term antibiotic use (5-7 days) is recommended in COPD exacerbations with a profile similar to the patient groups evaluated in the current studies on the subject (requiring outpatient treatment, without pneumonia and severe additional disease, without immune deficiency, without respiratory failure, and without antibiotic use in the last 7 days). On the other hand, there are insufficient studies to make recommendations on the effect of short-term therapy on clinical and bacteriological improvement in clinically more severe patients and exacerbations. The pharmacokinetic and pharmacodynamic properties of the antibiotics to be administered should also be considered.

References

1. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
2. Roede BM, Bresser P, El Moussaoui R, Krouwels FH, van den Berg BT, Hooghiemstra PM, *et al*. Three vs. 10 days of amoxycillin-clavulanic acid for type 1 acute exacerbations of chronic

obstructive pulmonary disease: A randomised, double-blind study. Clin Microbiol Infect 2007;13:284-90.
3. Gotfried M, Notario G, Spiller J, Palmer R, Busman T. Comparative efficacy of once daily, 5-day short-course therapy with clarithromycin extended-release versus twice daily, 7-day therapy with clarithromycin immediate-release in acute bacterial exacerbation of chronic bronchitis. Curr Med Res Opin 2005;21:245-54.
4. Lorenz J. Comparison of 5-day and 10-day cefixime in the treatment of acute exacerbation of chronic bronchitis. Chemotherapy 1998;44 Suppl 1:15-8.
5. Gotfried MH, DeAbate CA, Fogarty C, Mathew CP, Sokol WN. Comparison of 5-day, short-course gatifloxacin therapy with 7-day gatifloxacin therapy and 10-day clarithromycin therapy for acute exacerbation of chronic bronchitis. Clin Ther 2001;23:97-107.
6. DeAbate CA, Bettis R, Munk ZM, Fleming H, Munn NJ, Riffer E, *et al*. Effectiveness of short-course therapy (5 days) with grepafloxacin in the treatment of acute bacterial exacerbations of chronic bronchitis. Clin Ther 1999;21:172-88.
7. Sethi S, Breton J, Wynne B. Efficacy and safety of pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 milligrams twice daily for 5 days versus amoxicillin-clavulanate at 875/125 milligrams twice daily for 7 days in the treatment of acute exacerbations of chronic bronchitis. Antimicrob Agents Chemother 2005;49:153-60.
8. Wasilewski MM, Johns D, Sides GD. Five-day dirithromycin therapy is as effective as seven-day erythromycin therapy for acute exacerbations of chronic bronchitis. J Antimicrob Chemother 1999;43:541-8.
9. Masterton RG, Burley CJ. Randomized, double-blind study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis. Int J Antimicrob Agents 2001;18:503-12.
10. Chodosh S, DeAbate CA, Haverstock D, Aneiro L, Church D. Short-course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis. The bronchitis study group. Respir Med 2000;94:18-27.

6.5. Route of administration of corticosteroids in exacerbation cases

Clinical question:

- P: Patients presenting to the emergency department with COPD exacerbation
- I: Systemic corticosteroid use (oral or intravenous)
- C: Use of inhaled corticosteroids (nebulizer, MDI, and dry-powder inhaler)
- O1: Mortality, O2: Readmission, O3: Intensive care admission, O4: Side effects, and O5: Cost was determined, and a literature review was conducted using appropriate keywords.

After conducting a full-text review regarding the clinical question, 16 articles were found, of which 5 were found suitable for evaluation. During RoB2 and ROBINS-I evaluations, an article was found to have a high risk of bias due to problems such as using an inappropriate method for assigning the participants to groups, and since the participants and practitioners were aware of the interventions, and was therefore excluded from the evaluation. A moderate risk of bias was found in the other four articles due to problems with the method for assigning the participants to groups, outcome measurement, and selection of the results to be reported. In the articles that were reviewed, it was observed that inhaled corticosteroids were generally administered through nebulizers.

Among outcomes, there was the absence of articles investigating the corticosteroid administration method with mortality (outcome 1), intensive care unit admission (outcome 3), and cost (outcome 5). The data could not be analyzed by meta-analytical methods, because the studies included different populations, used different demographic characteristics in the diagnostic criteria for COPD,[1] evaluated exacerbations of different severity levels,[1-4] the drug doses used varied across studies, a placebo group was added to the comparison in two studies, but there was no placebo group in the other two studies, and the outcomes of the studies were different. Only one study examined the rate of hospital readmission, and no difference was found between nebulized budesonide and intravenous prednisolone administrations.[3]

In a study by Maltais *et al*. in which 199 patients with COPD exacerbation requiring treatment by hospitalization were randomized to nebulized budesonide, oral prednisolone, and placebo groups. The use of both nebulized budesonide and oral prednisolone was shown to have an improving effect on FEV1 compared to the placebo group, whereas the increase in FEV1 observed in the nebulized budesonide, and oral prednisolone groups were reported to be similar [mean difference = −0.06 L (95% CI: −0.14–0.02 L).[1] Similarly, it was reported that there was no difference between the two administration methods in terms of the length of hospital stay. In terms of side effects, nebulized budesonide was associated with fewer side effects, especially hyperglycemia.

In a study conducted by Stallberg *et al*. on only GOLD Stage II patients with COPD exacerbation who were determined to receive outpatient treatment, inhaled budesonide or oral glucocorticoid administrations in addition to inhaled formoterol administration were compared. Accordingly, it was reported that there was no difference in terms of the values of FEV1 increase in the 2nd week after treatment. Similarly, there was no difference between the groups in terms of symptoms, quality of life, treatment failure, need for additional medication, and time until first exacerbation.[2]

In a study by Günen *et al*. conducted in patients hospitalized due to COPD exacerbation, high-dose nebulized budesonide and oral prednisolone treatments in addition to bronchodilator therapy were compared, and the FEV1 values on day 10 were found to be significantly higher in patients who used nebulized budesonide.[3] However, the FEV1 change on day 10 after

Table 6.7.1: Contraindications for noninvasive mechanical ventilation

Respiratory and circulatory arrest
Severe hemodynamic instability (hypotension unresponsive to fluid replacement and vasopressors, systolic blood pressure <90 mmHg)
Life-threatening dysrhythmias
Presence of intractable respiratory secretions
Failure to protect the airway
Inability of the patient to continue treatment
Conditions where the NIMV interface cannot be used comfortably, such as facial burns/trauma/recent facial or upper airway surgery

NIMV=Noninvasive mechanical ventilation

treatment was evaluated instead of the final values since there was a difference in favor of nebulized budesonide between the initial FEV1 values of the patients in this study. In addition, it was observed that there was no significant difference between the two treatments. In terms of side effects, it has been reported that the use of nebulized budesonide was associated with a lower rate of hyperglycemia occurrence as a side effect. The length of hospital stay was similar in both groups.

In a study by Uçar *et al*. conducted in patients who were hospitalized due to moderate or severe COPD exacerbation, 4 mg/day nebulized budesonide, 8 mg/day nebulized budesonide, and 40 mg/day intravenous prednisolone administrations were compared, and it was shown that there was no difference between the groups in terms of outcomes such as improvement in FEV1 and ABG parameters before discharge and side effect profile (oral moniliasis and hyperglycemia).[4]

EVIDENCE-BASED RECOMMENDATIONS FOR CLINICAL QUESTIONS-5

No recommendations were made regarding the question of whether corticosteroid therapy should be given systemic or inhaled route in terms of mortality, intensive care unit admission, re-admission, and cost-effectivity outcomes in patients admitted to the emergency department due to COPD exacerbation

Although systemic corticosteroid use is recommended primarily in COPD exacerbation patients admitted to the emergency department, the available evidence suggests that systemic therapy is not superior to nebulized form for hospital readmission

In selected patients with difficulty in glycemic control, the use of high-dose nebulized corticosteroids in the management of exacerbations may be considered as an alternative to systemic corticosteroids.

References

1. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, *et al.* Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: A randomized controlled trial. Am J Respir Crit Care Med 2002;165:698-703.
2. Ställberg B, Selroos O, Vogelmeier C, Andersson E, Ekström T, Larsson K. Budesonide/formoterol as effective as prednisolone plus formoterol in acute exacerbations of COPD. A double-blind, randomised, non-inferiority, parallel-group, multicentre study. Respir Res 2009;10:11.
3. Gunen H, Hacievliyagil SS, Yetkin O, Gulbas G, Mutlu LC, In E. The role of nebulised budesonide in the treatment of exacerbations of COPD. Eur Respir J 2007;29:660-7.
4. Yilmazel Ucar E, Araz O, Meral M, Sonkaya E, Saglam L, Kaynar H, *et al.* Two different dosages of nebulized steroid versus parenteral steroid in the management of COPD exacerbations: A randomized control trial. Med Sci Monit 2014;20:513-20.

6.6. Other treatments

Methylxanthines

Methylxanthines (theophylline or aminophylline) are not recommended for use in exacerbations of COPD. The efficacy of intravenous aminophylline has not been established in randomized controlled trials. In addition, methylxanthines have been associated with side effects such as dysrhythmia, nausea, vomiting, palpitations, and tremors; therefore, they have no roles in the management of exacerbations.[13,14]

Magnesium

Magnesium exerts a bronchodilator effect by inhibiting calcium-induced contraction in the airway smooth muscles and reducing the release of acetylcholine from cholinergic nerve endings and histamine from mast cells. Although it has been included in the guidelines for managing severe asthma attacks for a long time due to this effect, there are limited studies in COPD. In a study in which nebulized magnesium sulfate was used in addition to short-acting ipratropium and salbutamol for managing exacerbation of COPD, it was shown that adding magnesium did not have a significant effect on FEV1.[15] In three studies where intravenous magnesium was administered in the treatment of COPD exacerbations, improvements in symptoms, reduction in the length of hospital stay, and improvements in peak flow rate and FEV1 were reported.[16,17] However, it is usually not included in the routine management of COPD exacerbations due to limited evidence.[18]

PANEL RECOMMENDATIONS-14

Short-acting inhaled β2-agonists and/or inhaled anticholinergics can be used as first-line inhaled bronchodilators in COPD exacerbations

Inhaler treatments to be administered in the emergency department can be performed with the help of MDI or nebulizers

Nebulization should not be done using an oxygen source

Methylxanthine derivatives (aminophylline and theophylline) should not be used in COPD exacerbations.

References

1. Nelson HS. Beta-adrenergic bronchodilators. N Engl J Med 1995;333:499-506.
2. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;153:967-75.
3. Bilgic H, Karadağ M, Umut S, Erdinç E. Chronic Obstructive Pulmonary Disease from Definition to Treatment. Bursa: Galenos Yayıncılık, Toraks Kitapları; 2008. www.toraks.org.tr.
4. McCrory DC, Brown CD. Inhaled short-acting beta2-agonists

versus ipratropium for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2001;2001(2):CD002984.
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2021 Report). Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. [Last accessed on 2020 Dec 06].
6. Nair S, Thomas E, Pearson SB, Henry MT. A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. Chest 2005;128:48-54.
7. Bardsley G, Pilcher J, McKinstry S, Shirtcliffe P, Berry J, Fingleton J, *et al.* Oxygen versus air-driven nebulisers for exacerbations of chronic obstructive pulmonary disease: A randomised controlled trial. BMC Pulm Med 2018;18:157.
8. Edwards L, Perrin K, Williams M, Weatherall M, Beasley R. Randomized controlled crossover trial of the effect on PtCO2 of oxygen-driven versus air-driven nebulisers in severe chronic obstructive pulmonary disease. Emerg Med J 2012;29:894-8.
9. Costello RW, Jacoby DB, Fryer AD. Pulmonary neuronal M2 muscarinic receptor function in asthma and animal models of hyperreactivity. Thorax 1998;53:613-6.
10. McCrory DC, Brown CD. Anti-cholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002;(4):CD003900.
11. Moayyedi P, Congleton J, Page RL, Pearson SB, Muers MF. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. Thorax 1995;50:834-7.
12. van Geffen WH, Douma WR, Slebos DJ, Kerstjens HA. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD. Cochrane Database Syst Rev. 2016 Aug 29;2016(8):CD011826.
13. Duffy N, Walker P, Diamantea F, Calverley PM, Davies L. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: A prospective randomized controlled trial. Thorax 2005;60:713-7.
14. Köktürk N, Gürgün A, Şen E, Kocabaş A, Polatlı M, Naycı SA, *et al.* The view of the Turkish Thoracic Society on the report of the GOLD 2017 global strategy for the diagnosis, management, and prevention of COPD. Turk Thorac J 2017;18:57-64.
15. Edwards L, Shirtcliffe P, Wadsworth K, Healy B, Jefferies S, Weatherall M, *et al.* Use of nebulised magnesium sulphate as an adjuvant in the treatment of acute exacerbations of COPD in adults: A randomised double-blind placebo-controlled trial. Thorax 2013;68:338-43.
16. Hogg J, Mulrennan S, Everett C. A single center double-blind placebo-controlled pilot study into the use of intravenous magnesium sulphate for the treatment of acute exacerbation of COPD (abstract). Eur Respir J 2004;24 Suppl 48:343p.
17. Skorodin MS, Tenholder MF, Yetter B, Owen KA, Waller RF, Khandelwahl S, *et al.* Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. Arch Intern Med 1995;155:496-500.
18. Dobler CC, Morrow AS, Farah MH, Beuschel B, Majzoub AM, Wilson ME, *et al.* Pharmacologic and Nonpharmacologic Therapies in Adult Patients with Exacerbation of COPD: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2019 Oct. Report No.:19(20)-EHC024-EF.

6.7. Noninvasive mechanical ventilation

NIMV is a positive-pressure ventilation support delivered through a noninvasive interface rather than an invasive interface (endotracheal tube, tracheostomy, etc.).[1-4] NIMV is widely used to treat, in particular, COPD exacerbations as well as acute cardiogenic pulmonary edema and acute respiratory failure in critically ill and immunocompromised patients.

Hypercapnic respiratory failure develops in approximately 20% of patients with COPD exacerbation.[5] NIMV should be prioritized for all patients with acute hypercapnic respiratory failure due to COPD exacerbation and without contraindications [Table 6.7.1]. NIMV can be applied in this group of patients in the case of the following three clinical conditions:[1,6] To prevent the development of acute respiratory acidosis, to prevent endotracheal intubation, and as an alternative to invasive ventilation in severely ill patients.

In many studies, NIMV has been shown to have significant positive effects on the need for endotracheal intubation and invasive ventilation, complications associated with invasive mechanical ventilation, length of hospital and intensive care unit stays, and mortality in COPD exacerbation cases. The latest ERS/ATS clinical practice guideline recommends bi-level NIMV in case of acute respiratory failure in patients experiencing acute respiratory acidosis due to COPD exacerbation (strong recommendation and high level of evidence).[7] With respect to patients diagnosed with COPD exacerbation, NIMV treatment should be considered in patients with blood pH $\leq$7.35, $PaCO_2$ >45 mmHg, and respiratory rate >20–24/breaths per min despite medical therapy. Although certain values have been reported for the lower limit value of pH for NIMV administration in previous years, there is currently no evidence-based lower pH limit, but it should be kept in mind that the lower the pH, the greater the risk of NIMV failure. Therefore, close monitoring should be performed, and preparations should be made for endotracheal intubation.[8] The success of NIMV is directly affected by factors such as identification of suitable candidate patients who may benefit from it, initiation of support at an early stage, and implementation by an experienced team.

Noninvasive mechanical ventilation in hypercapnic respiratory failure

In NIMV, workload of the inspiratory muscles, especially the diaphragm, is reduced by increasing tidal volume with inspiratory positive airway pressure (IPAP) during inspiration.[9] On the other hand, atelectatic lung areas are reduced, functional residual capacity is increased, alveolar ventilation is increased, and gas exchange is facilitated by applying expiratory positive airway pressure (EPAP) during expiration. In addition, EPAP facilitates overcoming the additional burden (intrinsic positive end-expiratory pressure) caused by hyperinflation of the respiratory workload and allows

the respiratory muscles to rest. It increases the respiratory system's response to carbon dioxide, and the sensitivity of the respiratory center increases.

Noninvasive mechanical ventilation use

Selection of interface and mask

The mask is the most important factor in the success of NIMV. It should be suitable for the shape of the patient's nose/face. Nasal, oronasal, full face, and helmet masks can be used. Patient preference, nasal or oral breathing pattern, risk of vomiting, degree of respiratory failure, patient compliance, and claustrophobia should be considered during mask selection. For selection, it should be noted that patient-ventilator compliance will increase, and events of asynchrony will decrease with the mask that is most suitable in terms of air leakage.[10]

Noninvasive mechanical ventilation ventilators

NIMV is applied with specially designed portable NIMV or intensive care ventilators. Portable ventilators designed for NIMV are home ventilators that allow the use of batteries and ventilation from the surrounding air without the requirement of a source of compressed gas. NIMV can be easily applied with the NIMV module in intensive care ventilators; they have more alarm and monitoring possibilities and offer features similar to bi-level devices in terms of the compensation of air leakage. It is preferred to apply NIMV with this type of ventilator to enable close monitoring, especially in patients with deep hypoxemic respiratory failure and high FiO_2 requirement.

Ventilator circuits

Single-line ventilators are usually used in portable NIMV ventilators, and expiration is usually provided through an expiratory port or with an active valve. Double-line circuits are usually used in NIMV ventilators with life support or in intensive care ventilators. Separate lines are used for inspiration and expiration; there is a small dead space and no rebreathing.

Modes of noninvasive mechanical ventilation

In hypercapnic respiratory failure, *BiPAP* is the basic ventilation mode for NIMV in portable devices. It provides different levels of positive airway pressure during inspiration and expiration (IPAP and EPAP, respectively). NIMV is applied with pressure support (PS) ventilation in many intensive care ventilators. Similar to BiPAP, different levels of positive airway pressure are provided during inspiration and expiration. The pressure applied during inspiration is called PS, and the absolute pressure added to EPAP during inspiration is different.

For initial settings, low pressures of EPAP (4–5 cmH_2O) and IPAP (8–12 cmH_2O) are used at the beginning, and if necessary, EPAP and tidal volume are increased (by approximately 8 ml/kg according to the ideal body weight) according to oxygen saturation, and IPAP is increased according to the $PaCO_2$ value. The difference between IPAP and EPAP in bi-level devices is set as PS in intensive care ventilators. In COPD exacerbations, the *rise time* should be kept short, and the inspiration time should be started at <1.0 s.[10] In patients with adaptation problems, the expiratory flow trigger setting on the device should be titrated for the patient, if necessary. The ramp setting should be reset in applications using home ventilators.

Monitoring of the patient during acute noninvasive mechanical ventilation

The first 1–2 h is the most important period for NIMV response assessment, and assessment should be based on the patient's clinical status and ABG. Clinical signs of response to NIMV therapy include improvement in the patient's consciousness, regression of respiratory rate, decrease in the use of accessory respiratory muscles, and decrease in respiratory effort. In the first 2 h, pH, $PaCO_2$, and PaO_2 should be evaluated through ABG analysis. Improvement in acidosis and hypercapnia is considered as treatment success.

PANEL RECOMMENDATIONS-15

Unless contraindicated, administration of NIMV should be considered a priority in the following patients with COPD exacerbation:

- In patients with acute hypercapnic respiratory failure (pH $\leq$7.35, $PaCO_2$ >45 mmHg)
- In hypoxemic patients who are resistant to standard oxygenation methods, whose respiratory distress continues, and who are candidates for respiratory muscle weakness.

References

1. Nava S, Fanfulla F, editors. Noninvasive Artificial Ventilation: How, When, Why? Springer Verlag, Italy: Springer; 2014.
2. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet 2009;374:250-9.
3. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, *et al.*; BTS standards of care committee member, British Thoracic Society/Intensive Care Society Acute Hypercapnic Respiratory Failure guideline development group, On behalf of the British Thoracic Society standards of Care committee. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax 2016;71 Suppl 2:ii1-35.
4. Bello G, De Pascale G, Antonelli M. Noninvasive ventilation: Practical advice. Curr Opin Crit Care 2013;19:1-8.
5. Roberts CM, Stone RA, Buckingham RJ, Pursey NA, Lowe D. Acidosis, non-invasive ventilation and mortality in hospitalized COPD exacerbations. Thorax 2011;66:43-8.
6. Nava S, Navalesi P, Conti G. Time of non-invasive ventilation. Intensive Care Med 2006;32:361-70.
7. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, *et al.* Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50:1602426.

8. Ergan B, Nasiłowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev 2018;27:170101.
9. Brochard L, Isabey D, Piquet J, Amaro P, Mancebo J, Messadi AA, *et al.* Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 1990;323:1523-30.
10. Carlucci A, Pisani L, Ceriana P, Malovini A, Nava S. Patient-ventilator asynchronies: May the respiratory mechanics play a role? Crit Care 2013;17:R54.

6.8. Invasive mechanical ventilation

The decision for using invasive mechanical ventilation in acute respiratory failure due to COPD exacerbation is similar to that in other causes of respiratory failure. Intubation and invasive ventilation are the first options for patients who present with severe respiratory failure and a possibility of respiratory arrest. In milder cases, NIMV should be tried first, and intubation and invasive mechanical ventilation should be considered if there is no improvement in clinical findings and gas exchange (blood gas evaluation) within 1–2 h. Various criteria have been proposed to predict the possibility of NIMV therapy failure in patients;[1] however, in clinical practice, if the respiratory workload is not relieved (such as no reduction in respiratory rate, continued use of accessory respiratory muscles, abdominal respiration, sweating, patient-ventilator asynchrony, and worsening of consciousness) and at least partial improvement in respiratory acidosis is not achieved after a 2 h NIMV, endotracheal intubation should be considered without much delay.

Reference

1. Ozyilmaz E, Ugurlu AO, Nava S. Timing of noninvasive ventilation failure: Causes, risk factors, and potential remedies. BMC Pulm Med 2014;14:19.

6.9. High-flow nasal oxygen therapy

HFNOT is another less invasive practice for delivering oxygen and respiratory support to critically ill patients. The device typically consists of an active flow generator, active heated humidifier, a single-limb heated circuit, and nasal cannula.[1] The initial devices were able to operate at a flow rate of 30–60 L/min, but currently, there are devices that produce higher flow rates. It provides physiological advantages such as improvements in gas exchange and respiratory effort, decrease in respiratory rate, and increase in lung volume compared to high-flow oxygen therapy with a face mask in patients with acute hypoxemic respiratory failure.[2] In addition, the patient's ability to talk, eat, and be more comfortable during HFNOT ensures better patient compliance in HFNOT compared to that in NIMV. Although NIMV has been shown to provide improvement of respiratory physiology than HFNOT,[3] increased transpulmonary pressure is a major problem in patients with a high respiratory effort, and it may worsen lung injury in some patients.[4] In a randomized controlled study comparing conventional oxygen therapies in patients with respiratory failure and without hypercapnia, it was reported that there was no difference in intubation rates, but the outcome in terms of 90-day mortality was better than that of NIMV (HR: 2.50, 95% CI: 1.31–4.78).[5] In a meta-analysis evaluating six randomized controlled trials, the intubation rate was found to be better with HFNOT than with conventional oxygen and similar to NIMV in patients with acute hypoxemic respiratory failure.[6]

HFNOT is usually recommended as an alternative to reservoir mask in patients with acute respiratory failure and without hypercapnia.[7] NIMV is primarily recommended in patients with hypercapnia. However, the results of studies on its use in patients at risk of hypercapnia have been promising in recent years. HFNOT and NIMV cause similar physiological changes in stable hypercapnic patients;[8] in addition, in observational studies, it has been shown to cause partial improvement in $PaCO_2$ in hypercapnic patients.[9-11] In a systematic review evaluating two randomized controlled trials and six observational studies, it was reported that there was no difference between HFNOT and NIMV in terms of blood gas analyses and change in respiratory rate in patients with hypercapnic respiratory failure. On the other hand, NIMV was found to be more effective in reducing mortality (although there was no statistical difference) (OR: 1.33, 95% CI: 0.68–2.60).[12] The reason for the difference between the two methods may be the characteristics of the patients, but it should also be considered that it may be the differences in the device used. In HFNOT, high flow rates may have a more favorable effect on improvement in case of hypercapnia with prolongation of expiration, and high oxygen fractions may cause disturbance in case of hypercapnia. In a recent study, it has been reported that in HFNOT, the flow rate remains constant while the oxygen fraction is increased, which causes a deterioration in $PaCO_2$.[13] A clinical question comparing the use of HFNOT with standard oxygen therapy and NIMV in exacerbations was evaluated, and recommendations were made in Section 6.9.1.

References

1. Nishimura M. High-flow nasal cannula oxygen therapy devices. Respir Care 2019;64:735-42.
2. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, *et al.* Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med 2017;195:1207-15.
3. Thille AW, Yoshida T. High pressure versus high flow: What should we target in acute respiratory failure? Am J Respir Crit Care Med 2020;201:265-6.
4. Grieco DL, Menga LS, Raggi V, Bongiovanni F, Anzellotti GM,

Tanzarella ES, *et al*. Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. Am J Respir Crit Care Med 2020;201:303-12.
5. Frat JP, Ragot S, Girault C, Perbet S, Prat G, Boulain T, *et al*. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: A post-hoc analysis of a randomised trial. Lancet Respir Med 2016;4:646-52.
6. Ou X, Hua Y, Liu J, Gong C, Zhao W. Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: A meta-analysis of randomized controlled trials. CMAJ 2017;189:E260-7.
7. O'Driscoll BR, Howard LS, Earis J, Mak V; British Thoracic Society Emergency Oxygen Guideline Group; BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 2017;72:i1-90.
8. Pisani L, Fasano L, Corcione N, Comellini V, Musti MA, Brandao M, *et al*. Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. Thorax 2017;72:373-5.
9. Pisani L, Betti S, Biglia C, Fasano L, Catalanotti V, Prediletto I, *et al*. Effects of high-flow nasal cannula in patients with persistent hypercapnia after an acute COPD exacerbation: A prospective pilot study. BMC Pulm Med 2020;20:12.
10. Şancı E, Ercan Coşkun F, Bayram B. Impact of high-flow nasal cannula on arterial blood gas parameters in the emergency department. Cureus 2020;12:e10516.
11. Kim ES, Lee H, Kim SJ, Park J, Lee YJ, Park JS, *et al*. Effectiveness of high-flow nasal cannula oxygen therapy for acute respiratory failure with hypercapnia. J Thorac Dis 2018;10:882-8.
12. Huang Y, Lei W, Zhang W, Huang JA. High-flow nasal cannula in hypercapnic respiratory failure: A systematic review and meta-analysis. Can Respir J 2020;2020:7406457.
13. Attaway AH, Faress J, Jacono F, Dasarathy S. Acute responses to oxygen delivery via high flow nasal cannula in patients with severe chronic obstructiv pulmonary disease-HFNC and severe COPD. J Clin Med 2021;10:1814.

Table 7.1: Potential indications for evaluation for hospitalization

Sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness
Acute respiratory failure
New-onset physical examination findings (e.g., cyanosis and peripheral edema)
An exacerbation not responding to initial medical therapy
Presence of serious comorbidities (e.g., heart failure and recent arrhythmias)
Insufficient social support

6.9.1. High-flow nasal oxygen therapy in exacerbation cases

Clinical question:

- P: Patients presenting to the hospital with an exacerbation of COPD
- I: Use of HFNOT
- C1: Standard O_2 therapy, C2: NIMV therapy
- O: Composite endpoint (mortality, number of readmissions, and need for intensive care unit admission) was determined, and a literature review was conducted with appropriate keywords.

In the literature review, no randomized clinical trials or observational studies were found to completely address the clinical question and in which the efficacy of HFNOT and standard oxygen therapy were compared in patients presenting with COPD exacerbation. However, a

Table 7.2: Criteria for evaluation of exacerbation severity and indication for hospitalization

Criteria	Home treatment	Hospitalization (hospital ward)	Hospitalization (high-dependency unit)	Hospitalization (intensive care unit)
Severity of respiratory failure	None/stable	Not stable	Unstable±need for NIMV	Unstable±need for NIMV±need for IMV
pH	>7.35	7.30-7.35	7.20-7.30	<7.20
Respiratory rate	<25	<25	25-35	>35
GCS score	15	15	10-14	<10
Use of accessory respiratory muscles	None	None/slightly	Slightly	Evident
Oxygenation	PaO_2 >60 mmHg or SpO_2 >90% in room air	PaO_2 >60 mmHg or SpO_2 >90% with oxygen support	NIMV requirement for PaO_2 >60 mmHg or SpO_2 >90%	NIMV/IMV requirement for PaO_2 >60 mmHg or SpO_2 >90%
Additional diseases	None	None/yes	Yes	Yes
Right heart failure	None	None/yes	None/yes	Yes
Newly developed dysrhythmia	None	None/yes	None/yes	None/yes
Kidney dysfunction	None	None/yes	None/yes	None/yes
Hemodynamics	Stable	Stable	Stable/unstable	Unstable
Clinical follow-up				
Symptoms after first treatment	Improving	There is a transient improvement	There is a transient improvement/no improvement	No improvement
Saturation	No need for follow-up	2-4 h interval follow-up requirement	Need for continuous follow-up	Need for continuous follow-up
Blood gases analyzes	No need for monitoring	8 h interval monitoring is required	2-4 h interval monitoring is required	Continuous monitoring (arterial line)
Social support	Adequate	Inadequate	Adequate/inadequate	Adequate/inadequate

NIMV=Noninvasive mechanical ventilation, IMV=Invasive mechanical ventilation, GCS=Glasgow Coma Scale

randomized trial that was indirectly related to the clinical question was reviewed. In a randomized controlled study, Pilcher *et al*. compared the effects of HFNOT and standard oxygen therapy on $PaCO_2$ using data from 24 patients. In this study, patients received the same amount of standard oxygen therapy in the first 15 min and were randomized to HFNOT and standard oxygen groups at the end of the 15th min. $PaCO_2$ and SpO_2 values of the patients at presentation and at the 30th min were evaluated, and the measurements were made using oximetry on the ear skin and not by blood tests. There was a statistically significant decrease in $PaCO_2$ levels at the end of the 30-min treatment period in the HFNOT group compared to the standard oxygen therapy group (−1.4 mmHg (95% CI: −2.2 to −0.6), $P = 0.001$), but there was no statistically significant difference between the groups in terms of respiratory rate and SpO_2 levels ($P = 0.099$ and $P = 0.96$, respectively).[1]

In the literature review on the second part of the clinical question, a randomized controlled trial, a prospective cohort study, and a retrospective cohort study comparing HFNOT with NIMV were included in the evaluation.[2-4] According to the RoB2 and ROBINS-I evaluations, the articles were found to have a moderate-to-high risk of bias. In addition, it was observed that the level of evidence of the data obtained was not sufficient since the outcomes in some studies were indirectly related to the outcome of our clinical question.

The efficacy of HFNOT and NIMV applications were compared in a multicenter randomized controlled study by Doshi *et al*. Although this study is the only randomized controlled trial that can answer the clinical question, it answers the question with a limited level of evidence since neither the patient population nor the outcomes completely match. All patients with respiratory failure, including those with COPD, who present to the emergency department were included in the study. Patients with COPD constituted 38.7% (79/204 patients) of these patients. The primary outcome in the study was treatment failure, which was defined as needing intubation within 72 h, treatment failure, and needing to switch to the other treatment arm. Secondary outcomes were change in $PaCO_2$ and pH and the presence of other symptoms of respiratory distress. Accordingly, although the study did not have an outcome that directly addressed the clinical question, attempts were made to make inferences from the outcome of treatment failure. In the study, a total of 204 patients (104 in the HFNOT group and 100 in the NIMV group) were included in the randomization. The intubation rate was 6.7% in the HFNOT group and 13.0% in the NIMV group (difference in risks −0.06, 95% CI: −0.14–0.02); the treatment failure rate was 26% versus 17%, respectively (difference in risks 0.09, 95% CI: −0.02–0.20). When the pCO_2 changes were evaluated in terms of providing indirect, if not direct, information about patients with COPD, it was observed that the baseline $PaCO_2$ values in both groups decreased during the treatment period, with no statistically significant difference. At the end of 4 h, the baseline $PaCO_2$ value decreased from 53.4 mmHg to 46.3 mmHg in the HFNOT group, whereas it increased from 58.7 mmHg to 66.2 mmHg in the NIMV group [$PaCO_2$ difference between the groups at the end of 4 h: −6.2 mm Hg (95% CI: −33.0–39.0)]. In conclusion, no significant differences were found between the HFNOT and NIMV groups in terms of all outcomes, and it was concluded that HFNOT was not inferior to NIMV.[2]

The prospective observational study by Lee *et al*. is a study that addresses the clinical question both in terms of patient population and outcomes. In the study, the efficacy of HFNOT and NIMV treatments was compared in terms of intubation rate and 30-day mortality in 92 patients presenting with COPD exacerbation and moderate hypercapnia. The intubation rate was 25% in the HFNOT group, whereas it was 27.1% in the NIMV group ($P = 0.857$). The 30-day mortality was 15.9% and 18.2%, respectively, in these patients ($P = 0.845$). There was no significant difference in terms of pH, pO_2, and pCO_2 levels of the patients between the groups when compared based on the measurements made after 6 and 24 h. Consequently, it was concluded that both treatment options had similar efficacy in terms of both intubation and 30-day mortality rates.[3]

In another retrospectively designed study, the efficacy of HFNOT and NIMV treatments was compared in terms of 28-day mortality in 82 patients with COPD and moderate hypercapnia. The 28-day mortality was 15.4% in the HFNOT group, whereas it was 14% in the NIMV group, and no statistically significant difference was found between the groups ($P = 0.824$). In addition, treatment failure was found to be similar across the groups (28.2% and 39.5%, respectively; $P = 0.268$).[4]

EVIDENCE-BASED RECOMMENDATIONS FOR CLINICAL QUESTIONS-6

Considering the medium-high risk of bias in existing studies and the weak evidence, NIMV is recommended to be tried primarily in the management of hypoxemic or hypercapnic patients admitted to the hospital with COPD exacerbation. HFNO therapy can be administered in patients who cannot tolerate noninvasive mechanical ventilation.

References

1. Pilcher J, Eastlake L, Richards M, Power S, Cripps T, Bibby S, *et al*. Physiological effects of titrated oxygen via nasal high-flow cannulae in COPD exacerbations: A randomized controlled cross-over trial. Respirology 2017;22:1149-55.

2. Doshi P, Whittle JS, Bublewicz M, Kearney J, Ashe T, Graham R, *et al.* High-velocity nasal ınsufflation in the treatment of respiratory failure: A randomized clinical trial. Ann Emerg Med 2018;72:73-83.e5.
3. Lee MK, Choi J, Park B, Kim B, Lee SJ, Kim SH, *et al.* High flow nasal cannulae oxygen therapy in acute-moderate hypercapnic respiratory failure. Clin Respir J 2018;12:2046-56.
4. Sun J, Li Y, Ling B, Zhu Q, Hu Y, Tan D, *et al.* High flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease with acute-moderate hypercapnic respiratory failure: An observational cohort study. Int J Chron Obstruct Pulmon Dis 2019;14:1229-37.

7. Discharge and Hospitalization in Chronic Obstructive Pulmonary Disease Exacerbation Cases

7.1. Criteria for hospitalization and intensive care admission

The decision to discharge or hospitalize after exacerbations of COPD depends on several variables. Treatments are administered in the hospital and emergency department to provide adequate oxygenation and reduce airway obstruction and bronchospasm by targeting normal blood pH level. For these purposes, oxygen therapy, bronchodilators, corticosteroids, antibiotics, and mechanical ventilation support are provided.

The clinical features that can be used in the evaluation of exacerbation severity for the decision between home treatment or hospitalization (ward and intensive care unit) made in the emergency department are given in Tables 7.1 and 7.2.[1-6] If the patient falls into different categories based on the evaluation of different parameters, the responsible physician should make the decision individually. Patients who do not have sufficient support to continue their appropriate treatment at home should be considered for hospitalization even if they do not meet the relevant clinical criteria; however, local resources should also be taken into account. Signs of acute respiratory failure, respiratory distress, need for high-flow oxygen therapy, impaired consciousness, cor pulmonale, need for continuous nurse supervision, need for hospitalization for other reasons (for example, cardiovascular comorbidity), and inadequate social support (patients with accommodation problems, nutrition problems, and substance abuse) are indications that home treatment is not appropriate.[1]

For evaluating the indication for hospitalization in exacerbation cases, it should be remembered that the following criteria may indicate different treatment areas in patients, and not all criteria may be found in every patient; therefore, the decision should be made by the clinician who is assessing the patient. However, in hospitals where there is no intermediate intensive care or observation unit, intermediate intensive care admissions can be provided in wards, or intensive care areas considering the need for close follow-up of the patient.

7.2. Discharge from the emergency department and follow-up

Before discharge, patients should be clinically stable, laboratory results should be within the normal limits, the abnormalities should be defined, necessary plans should be made for preventing tobacco use and other risk factors, and it should be ensured that maintenance therapy after discharge (inhalation technique, compliance with treatment, treatment and follow-up plan for comorbidities, and requirement to continue oxygen therapy) has been understood. The patient should be informed about nutrition, vaccination, lifestyle, physical activity, and/or pulmonary rehabilitation and, if possible, referred to a pulmonary rehabilitation program. In cases with a suspicion in diagnosis and/or in whom adequate clinical response in symptoms and/or exacerbations has not been achieved with the treatments administered and who are candidates for pulmonary rehabilitation, lung volume reduction approach, and lung transplantation should be referred to tertiary hospitals.

Follow-up of the patient at the outpatient clinic within 1–4 weeks after discharge should be planned. Tobacco use, drugs, and lifestyle, as well as vaccination, pulmonary rehabilitation, and oxygen therapy requirement of the patient should be evaluated during the follow-up at the outpatient clinic.

PANEL RECOMMENDATIONS-16

Hospitalization decision varies according to both physiological and respiratory parameters, as well as the patient's social support and local conditions after discharge. The criteria in Table 7.2 can be used for discharge and hospitalization decisions. Since it is known that these criteria are not separated very sharply from each other, patients and clinical situations can switch within the criteria. Although these criteria were compiled from evidence-based sources, they were not validated. The panel recommends that physicians make a patient-specific decision using available scientific data on this issue.

References

1. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, *et al.* Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017;49:1600791.
2. Website: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2021 Report. Available from: http://goldcopd.org. [Last accessed on 2021 May 25].
3. Ergan B, Nasiłowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev 2018;27:170101.
4. Garcia-Gutierrez S, Quintana JM, Barrio I, Bare M, Fernandez

N, Vidal S, *et al*. Application of appropriateness criteria for hospitalization in COPD exacerbation. Intern Emerg Med 2013;8:349-57.
5. Garcia-Gutierrez S, Quintana JM, Bilbao A, Unzurrunzaga A, Esteban C, Baré M, *et al*. IRYSS-COPD appropriateness study (IRYSS-COPD) group. Validity of criteria for hospital admission in exacerbations of COPD. Int J Clin Pract 2014;68:820-9.
6. Montserrat-Capdevila J, Godoy P, Marsal JR, Barbé F. Predictive model of hospital admission for COPD exacerbation. Respir Care 2015;60:1288-94.

Author contribution statement

Conceptualization (NOD, YV), data curation (NOD, YV, NK, EA, AÖA, ŞKÇ, GA, AB, HA, EŞ, BE, BB, SY, AG, MP), formal analysis-methodology (SK), resources (GA, ŞKÇ, HA), supervision (EA, AÖA, NK), writing (NOD, YV).

Conflicts of interest

COI statements are stated in the Appendix 1.

Ethical approval

Non applicable.

Funding

None declared.

The Turkish version of this guideline was published in the websites of EMAT and TTS in 2021.

Appendix 1: Conflict of interest statements (for the last 3 years, in order of surname)

Author	Supported company	Support type
Haldun AKOĞLU	Pfizer Onkoloji	Medical manager (2008-2011)
Ersin AKSAY	Astra-Zeneca, Sanofi	Honorarium, payment to institution
Aylin Özgen ALPAYDIN	Abdi İbrahim	Payments for presentations
Nurettin Özgür DOĞAN	Roche Diagnostics	Honorarium, payment to institution
Begüm ERGAN	Breas, Abdi İbrahim, Chiesi	Honorarium, payments for educational presentations, payment to institution
Nurdan KÖKTÜRK	Chiesi, Astra-Zeneca, Abdi İbrahim, Deva, Glaxo-Smith-Kline	Honorarium, consulting, payment to the institution
Elif ŞEN	Glaxo-Smith-Kline, Astra-Zeneca, Chiesi	Honorarium, payment to institution
Mehmet POLATLI	Astra-Zeneca, Deva	Honorarium, payment to institution
Yelda VAROL	Abdi İbrahim	Honorarium, payment to institution