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A typical COPD exacerbation?

Case history

A 68-year-old male arrives at the accident and emergency department complaining of deterioration in dyspnoea from British Medical Research Council (MRC) grade 2 to MRC grade 4 (see Box) during the 3 days prior to his presentation. The patient has a known history of chronic obstructive pulmonary disease (COPD), which was diagnosed 2 years previously (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III, severe COPD; post-bronchodilator forced expiratory volume in one second (FEV_1) 42% predicted when in stable condition) and receives treatment with a long-acting β-agonist, inhaled corticosteroids and tiotropium. During the previous 12 months, he has had three hospital admissions for COPD exacerbations. His medical history includes arterial hypertension treated with an angiotensin-converting enzyme inhibitor and type II diabetes mellitus treated with metformin.

Physical examination

The patient is dyspnoeic, using his accessory muscles while breathing, and has prominent ankle swelling. Auscultation reveals decreased breath sounds and bilateral expiratory wheezing. The patient has tachypnoea (32 breaths per min) and tachycardia (124 beats per min), with a blood pressure of 125/85 mmHg and an arterial oxygen saturation measured by pulse oximetry of 88% on room air (inspiratory oxygen fraction (F_{I,O_2}) 0.21).

Task 1
Is the patient experiencing an exacerbation of COPD?

The MRC dyspnoea scale for grading breathlessness

1. Not troubled by breathlessness except on strenuous exercise
2. Short of breath when hurrying or walking up a slight hill
3. Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
4. Stops for breath after about 100 m or after a few minutes on the level
5. Too breathless to leave the house, or breathless when dressing or undressing

Answer 1

The correct answer is yes. According to the definition, an exacerbation of COPD is an event in the natural course of the disease characterised by a change in the patient's dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management [1]; this is true for the present patient.

Task 2

Which of the following investigations would you order now? Choose as many as apply.

a) Chest radiograph.
b) Arterial blood gases.
c) ECG.
d) Routine haematology and biochemistry blood tests.
e) Blood cultures.

Answer 2

a) This is a correct answer. The patient's chest radiograph is shown in figure 1, illustrating hyperinflated lung fields with attenuation of peripheral vasculature, flattened diaphragms and increased retrosternal clear space, findings indicative of emphysema. A chest radiograph should be obtained in all cases of COPD exacerbation with diagnostic uncertainty, in order to exclude aggravating factors that should be treated promptly (*e.g.* pneumothorax, pneumonia or signs of congestive heart failure). None of these are present in the patient's radiograph.

b) This is a correct answer. The arterial blood gas results are: pH 7.49; arterial carbon dioxide tension (P_{a,CO_2}) 3.9 kPa (29 mmHg); arterial oxygen tension (P_{a,O_2}) 6.4 kPa (48 mmHg); bicarbonate 26 mM; and arterial oxygen saturation (S_{a,O_2}) 88% on room air. The $P_{a,O_2}/F_{i,O_2}$ ratio was 30.3 kPa (228 mmHg). Arterial blood gases should be performed in all patients with S_{a,O_2} <90% and in those with possible carbon dioxide retention.

c) This is a correct answer. The patient's ECG reveals sinus tachycardia with no other remarkable findings.

d) This is a correct answer. Routine laboratory tests should be obtained from any patient admitted for COPD exacerbation (table 2). Laboratory results are as follows: white blood cell count 7.5×10^3 per dL; haematocrit 49%; haemoglobin 14.9 g per dL; platelets 196×10^9 per L; glucose 278 mg per dL; urea 6.2 mM; creatinine 0.98 mg per dL; Na^+ 139 mEq per L; K+ 4.2 mEq per L; C-reactive protein 1.5 mg per L.

e) This answer is incorrect. Blood culture is not a first-choice examination for diagnosis of an acute exacerbation of COPD.

Table 1 Indications for hospitalisation in patients with COPD exacerbations

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnoea, change in vital signs
- Severe underlying COPD
- Onset of new physical signs (*e.g.* cyanosis and peripheral oedema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities (e.g. pneumonia, arrhythmia, congestive heart failure, diabetes mellitus, and liver or renal failure)
- Frequent exacerbations
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

Data obtained from [1, 2].

Table 2 Clinical history, physical findings and diagnostic procedures in patients with an exacerbation of COPD

	Level I	Level II	Level III
Clinical history			
Comorbid conditions#	+	+++	+++
History of frequent exacerbations	+	+++	+++
Severity of COPD	Mild/moderate	Moderate/severe	Severe
Physical findings			
Haemodynamic evaluation	Stable	Stable	Stable/unstable
Use of accessory respiratory muscles, tachypnoea	Not present	++	+++
Persistent symptoms after initial therapy	No	++	+++
Diagnostic procedures			
Oxygen saturation	Yes	Yes	Yes
Arterial blood gases	No	Yes	Yes
Chest radiograph	No	Yes	Yes
Blood tests¶	No	Yes	Yes
Serum drug concentrations§	If applicable	If applicable	If applicable
Sputum gram stain and cultures	No^f	Yes	Yes
ECG	No	Yes	Yes

+: unlikely to be present; ++: likely to be present; +++: very likely to be present. #: the more common comorbid conditions associated with poor prognosis in exacerbations are congestive heart failure, coronary artery disease, diabetes mellitus, and renal and liver failure; ¶: blood tests include cell blood count, serum electrolytes, renal and liver function; §: consider if patients are using theophylline, warfarin, carbamezepine, digoxin; ^{f}: consider if patient has recently been on antibiotics. Reproduced from [1] with permission from the publisher.

The diagnostic procedures indicated dependent on the severity of an exacerbation of COPD are presented in table 2.

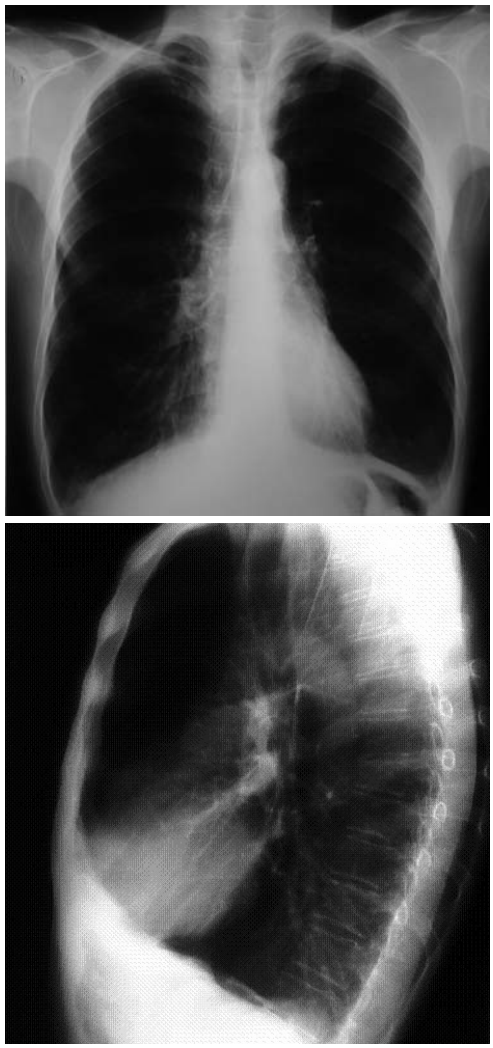

Figure 1
Chest radiograph (posteroanterior and lateral).

REMEMBER:
Exacerbations of COPD can be classified according to their severity. Level I: treated at home; level II: requires hospitalisation; level III: leads to respiratory failure [1].

Task 3
Where would you treat this patient?
a) At home.
b) In the respiratory/general medicine department.
c) At the accident and emergency observation unit.
d) In the intensive care unit (ICU).

Answer 3

b) Is the correct answer. This patient has several indications for hospitalisation: severe underlying COPD; frequent exacerbations (three admissions in the past year); older age; presence of diabetes mellitus with an abnormal plasma glucose value at presentation; marked increase in dyspnoea (from MRC II to MRC IV); significant hypoxaemia; presence of a new physical sign (ankle oedema). Table 1 presents the indications for hospitalisation in patients with COPD exacerbations, according to GOLD and American Thoracic Society/European Respiratory Society guidelines. Furthermore, diagnostic uncertainty may be an issue in this patient, since he does not present increased sputum production or purulent sputum, either of which could indicate of an infectious cause of exacerbation. Finally, he does not meet the criteria for ICU admission (table 3).

Table 3 Indications for ICU admission in patients with COPD exacerbation

- Severe dyspnoea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxaemia (P_{a,O_2} <5.3 kPa (<40 mmHg)) and/or severe/worsening hypercapnia (P_{a,CO_2} >8.0 kPa (>60 mmHg)) and/or severe/worsening respiratory acidosis (pH 7.25), despite supplemental oxygen and noninvasive ventilation
- Need for invasive mechanical ventilation
- Haemodynamic instability: need for vasopressors

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Task 4

Which of the following are appropriate initial therapeutic interventions for the management of this patient in the accident and emergency department? Choose as many as apply.

a) Supplemental oxygen.
b) Inhaled albuterol (salbutamol).
c) Oral prednisone.
d) Intravenous aminophylline.

Answer 4

a) This is a correct answer. Oxygen supplementation is crucial for the correction of the patient's hypoxaemia. The target is an S_{a,O_2} >90%, in order to assure a P_{a,O_2} >8.0 kPa (>60 mmHg), preferably with controlled oxygen therapy (*e.g.* with Venturi masks) along with close monitoring of the patient. Arterial blood gas measurement should be repeated 30–60 min after each change in oxygen flow settings, in order to check for adequate oxygenation and carbon dioxide retention. The patient receives supplemental oxygen with a Venturi mask at F_{I,O_2} 0.35.

b) This is a correct answer. The initial treatment of a COPD exacerbation includes the administration of short-acting β_2-agonists at short intervals, preferably with a spacer or hand-held nebuliser. Inhaled short-acting anticholinergics might be an alternative for this patient, owing to the presence of tachycardia on admission.

c) This is a correct answer. Systemic glucocorticosteroids should be added to the treatment regimen of all hospitalised patients with COPD exacerbations. Corticosteroids reduce treatment failures and improve FEV1, dyspnoea and arterial blood gases, especially in the first 6–72 h of treatment [3]. The oral route is preferable, with *i.v.* administration being an alternative in patients who cannot tolerate oral administration. The dose is 30–40 mg of prednisone (or equivalent) for 7–10 days.

d) This not a correct answer. Intravenous methylxanthines present a narrow therapeutic range and significant adverse effects; thus they are currently considered second-line treatment for COPD exacerbations, reserved for patients with a poor initial response to inhaled bronchodilators.

e) This is not a correct answer. There are no studies that support the use of long-acting bronchodilators for the in-hospital management of COPD exacerbations.

Task 5

Would you treat this patient with antibiotics?

Answer 5

The correct answer is no. The choice of treating a hospitalised patient with an acute exacerbation of COPD with antibiotics is based on his/her symptoms (type of exacerbation according to Anthonisen's classification) [4, 5]. The patient does not complain of increased sputum volume or purulent sputum and, therefore, this should be classified as Anthonisen type III exacerbation.

REMEMBER:

Hospitalised patients with a COPD exacerbation who should be treated with antibiotics are [2, 5]:

1) Patients with all three of the following symptoms: increased dyspnoea; increased sputum volume; and increased sputum purulence (type I Anthonisen exacerbation).

2) Patients with only two out of the three symptoms above (type II Anthonisen exacerbation) when increased purulence of sputum is one of the two cardinal symptoms.

3) Patients with a severe exacerbation that requires invasive or noninvasive mechanical ventilation.

4) Antibiotics are generally not recommended in type II Anthonisen exacerbations without sputum purulence or in type III patients (one or none of the above symptoms).

A recent meta-analysis reported that in COPD exacerbations with increased cough and sputum purulence, antibiotics reduce the risk of short-term mortality by 77%, and decrease the risk of treatment failure by 53% and the risk of sputum purulence by 44%, regardless of choice of the antibiotic agent [6]. The number needed to treat to avoid one treatment failure was three and the one to avoid one death was eight [6]. The review concluded that patients with COPD exacerbations characterised by increased cough and sputum purulence who are moderately to severely ill may benefit from the use of antibiotics.

Task 6

After a further 2 h, following administration of bronchodilators and corticosteroids, the patient does not respond to the initial treatment. He is still tachypnoeic and tachycardic. The new arterial blood gases on F_I,O_2 of 0.35 are: pH 7.49; P_a,CO_2 3.9 kPa (29 mmHg); P_a,O_2 7.8 kPa (59 mmHg); bicarbonate 26 mM; and S_a,O_2 91%. What would you do next (choose as many as apply)?

a) Order a blood D-dimer assay.

b) Order ventilation/perfusion scanning.

c) Order a computed tomography pulmonary angiography (CTPA).

d) Order a consultation from a cardiologist with echocardiography.

e) Consider noninvasive ventilation.

Answer 6

a) This is a correct answer. A blood D-dimer assay should be considered in all patients with a suspicion of pulmonary embolism (PE), after the assessment of clinical probability. It should not be performed in patients with high clinical probability [7, 8]. A negative high-quality D-dimer result reliably excludes PE in patients with low clinical probability [8, 9]. In the case of the present patient, COPD represents a risk factor for the development of PE and there is no obvious alternative diagnosis that may account for the patient's persistent hypoxaemia and hypocapnia. The D-dimer was 950 ng per mL (normal range in our laboratory 0–300 ng per mL).

b) This is not a correct answer. Despite the fact that a suspicion of PE has been raised for this patient, especially after the positive D-dimer result, ventilation/perfusion scanning is not useful for the diagnosis of PE in this patient. Ventilation/perfusion scanning is useful for the diagnosis of PE, provided that chest radiograph is normal and that there is no significant symptomatic concurrent cardiopulmonary disease [7, 8], which is not the case here.

c) This is a correct answer. In this patient with intermediate clinical probability with positive D-dimer, CTPA is the recommended initial lung imaging modality for nonmassive PE [7, 8]. It also allows the direct visualisation of emboli, as well as the detection of parenchymal abnormalities that may explain the patient's symptoms [9]. The patient's CTPA is shown in figure 2. A thrombus can be seen in the right pulmonary artery.

d) This is a correct answer. Consultation from a cardiologist with echocardiography may be useful in this case, in order to exclude the presence of congestive heart failure in the patient. However, it should be stressed that echocardiography (and especially transoesophageal echocardiography) is diagnostic in massive PE and it can demonstrate intrapulmonary and intracardiac thrombus, but in nonmassive PE it does not allow a firm diagnosis [7].

e) This answer is incorrect. Noninvasive mechanical ventilation should be considered for patients with acute hypercapnic respiratory failure with Pa,CO_2 >6.0 kPa (>45 mmHg) and respiratory acidosis (pH <7.35) despite optimal therapy and oxygen administration [1]. This is obviously not the case in the present patient.

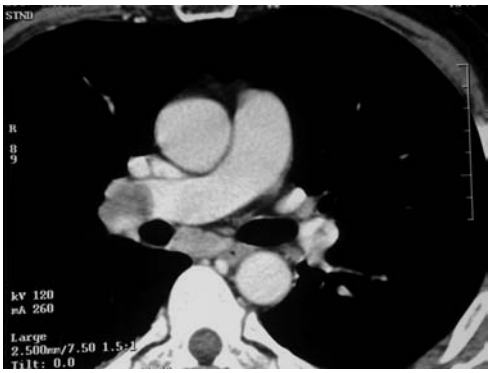

Figure 2
CTPA illustrating a thrombus in the right pulmonary artery.

Task 7

What proportion of hospitalised patients with unexplained severe COPD exacerbation present with PE? 3, 5, 10, 25 or 40%?

Answer 7

The correct answer is 25%. A French study evaluated 211 consecutive patients admitted to hospital for severe COPD exacerbations of unknown origin who did not require invasive mechanical ventilation. It showed that 25% of them met the diagnostic criteria for PE [10]. Clinical factors related to higher risk of PE were a history of previous thromboembolic disease, malignant disease and a decrease in P_{a,CO_2} ≥0.7 kPa (≥5 mmHg) [10]. Interestingly, none of the above parameters was present in the present patient, but the absence of response to the initial treatment, along with his otherwise unexplained deterioration, led us to the investigation of a possible PE.

The high prevalence of PE reported in the aforementioned study corresponds to otherwise unexplained severe COPD exacerbations and may not be an issue for patients with COPD with uncomplicated exacerbations [11]. A recent study investigated 123 consecutive patients admitted to the emergency departments of two academic hospitals for the presence of PE, regardless of clinical suspicion. This latter study reported a prevalence of PE of 6.2% in patients who had a clinical suspicion of PE and 1.3% in those not suspected [12]. Respiratory infections remain the most important cause of COPD exacerbations and rigorous investigation for possible PE should be reserved for patients with high clinical suspicion who do not respond to treatment [2, 11].

REMEMBER:

The differential diagnosis of patients with COPD exacerbation who do not respond to initial treatment includes other medical conditions that can mimic COPD exacerbations, including pneumonia, congestive heart failure, myocardial ischaemia, arrhythmias, pneumothorax, pleural effusion and PE [2, 13].

Task 8

The patient is treated with low molecular weight heparin and oral anticoagulant (warfarin), targeting an international normalised ratio (INR) of 2.0–3.0 [7]. The patient's dyspnoea, tachycardia and tachypnoea improve. The new arterial blood gases results (F_{I,O_2} 0.21) are: pH 7.42; P_{a,CO_2} 4.8 kPa (36 mmHg); P_{a,O_2} 7.2 kPa (54 mmHg); bicarbonate 26 mM; and S_{a,O_2} 88% on room air. After 12 days of hospitalisation a decision for discharge was taken. What would the optimal treatment regimen for this patient include? Choose as many as apply.

a) A long-acting β_2-agonist.

b) An inhaled corticosteroid.

c) Tiotropium.

d) Oral warfarin for 3–6 months.

e) Long-term oxygen therapy (LTOT) for life.

Answer 8

a) This is a correct answer. Long-acting inhaled bronchodilators are indicated for the treatment of patients with severe COPD and are more effective and convenient than short-acting inhaled bronchodilators [2].

b) This is a correct answer. Regular treatment with inhaled corticosteroids has been shown to reduce the frequency of exacerbations and improve health status for symptomatic COPD patients with an FEV_1 <50% pred and repeated exacerbations. The present patient has severe COPD and reports three hospital admissions for acute COPD exacerbations during the past 12 months [2].

c) This is a correct answer. Tiotropium is a long-acting anticholinergic bronchodilator that is more effective than short-acting inhaled anticholinergics. Furthermore, combining bronchodilators may improve efficacy and decrease the risk of side-effects compared with increasing the dose of a single bronchodilator [2].

d) This is a correct answer. Oral anticoagulation with warfarin should be given, targeting an INR of 2.0–3.0. As no specific risk factor has been identified for this patient, oral anticoagulation should be given for 3–6 months, since this is a first idiopathic episode of PE [7, 8].

e) This answer is incorrect. Supplemental LTOT should be prescribed in patients recovering from an acute exacerbation of COPD when the patient is receiving optimal therapy and has P_{a,O_2} <7.3 kPa (<55 mmHg) or P_{a,O_2} 7.3–7.8 kPa (55-59 mmHg) and the patient has developed cor pulmonale and/or polycythaemia. The goal is to maintain an S_{a,O_2} >90% during rest, sleep and exertion. However, the decision of LTOT for life should be taken with the patient in a stable condition. Therefore, the present patient should be reassessed in 30–90 days, checking arterial blood gases on room air; LTOT should be discontinued if the above conditions are not satisfied [1].

REMEMBER:

Conditions that should be met when considering patients for discharge include [1]:

- Symptoms returning to patients' baseline (e.g. eating, sleeping)
- Haemodynamic stability
- Oxygenation returning to baseline
- Inhaled β-agonist therapy required less frequently
- Ability to resume ambulation
- Ability to eat and sleep without frequent awakening by dyspnoea
- Off parenteral therapy for 12–24 h
- Patient (or home-care giver) understands correct use of medications
- Follow up and home-care arrangements have been completed (*e.g.* visiting nurse, oxygen delivery, meal provision)

Discussion

An important part of the management of a COPD exacerbation is the education of patients by the attending healthcare personnel prior to discharge. Ideally, education should include information about the nature of the disease, the use of inhalers and the proper use of LTOT, since patient education improves compliance with therapy [1]. Additionally, patients should be taught breathing and coughing techniques and be encouraged to adopt a healthy lifestyle (smoking cessation, nutrition, exercise, sleep habits, *etc.*). Such education programmes have been shown to be beneficial in reducing the use of healthcare services and improving health-related quality of life [14]. Furthermore, patients have to understand the nature of exacerbations and should receive an action plan in the event of an emergency. Improving patients' understanding of the nature of exacerbations and the benefits of early treatment may improve the outcome of exacerbations [15].

Finally, the management of an exacerbation of COPD is concluded by the proper arrangement of follow-up for the patients. The patient has to be seen at follow-up 4–6 weeks after discharge from the hospital. In this visit, the attending physician should assess lung function (especially post-bronchodilator FEV_1 for the proper staging of the disease, if not already known), the patient's ability to cope in his or her usual environment and understanding of treatment regimen and inhaler technique and the need for LTOT [2]. In a simplified rule of thumb, the management of COPD exacerbations should include antibiotics (where indicated), bronchodilators, systemic corticosteroids, a proper differential

diagnosis in patients who do not improve after initial treatment, education and follow-up arrangements [16].

REMEMBER:

The ABCs of management of COPD exacerbations (modified from [16])

Antibiotics
Bronchodilators
Corticosteroids
Differential Diagnosis
Education
Follow-up

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