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 (FEV1) 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 (FIO2) 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
COPD feature: A typical COPD exacerbation?

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 ($P_{a,\text{CO}_2}$) 3.9 kPa (29 mmHg); arterial oxygen tension ($P_{a,\text{O}_2}$) 6.4 kPa (48 mmHg); bicarbonate 26 mM; and arterial oxygen saturation ($S_{a,\text{O}_2}$) 88% on room air. The $P_{a,\text{O}_2}/F_{I,\text{O}_2}$ ratio was 30.3 kPa (228 mmHg). Arterial blood gases should be performed in all patients with $S_{a,\text{O}_2} <90\%$ 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 7.5x10$^3$ per dL; haematocrit 49%; haemoglobin 14.9 g per dL; platelets 196x10$^9$ 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.
COPD feature: A typical COPD exacerbation?

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

**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

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid conditions</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>History of frequent exacerbations</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Severity of COPD</td>
<td>Mild/moderate</td>
<td>Moderate/severe</td>
<td>Severe</td>
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</table>

<table>
<thead>
<tr>
<th>Physical findings</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Haemodynamic evaluation</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Use of accessory respiratory muscles, tachypnoea</td>
<td>Not present</td>
<td>++</td>
</tr>
<tr>
<td>Persistent symptoms after initial therapy</td>
<td>No</td>
<td>++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic procedures</th>
<th></th>
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<tbody>
<tr>
<td>Oxygen saturation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood tests§</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum drug concentrations¶</td>
<td>If applicable</td>
<td>If applicable</td>
</tr>
<tr>
<td>Sputum gram stain and cultures</td>
<td>No§†</td>
<td>Yes</td>
</tr>
<tr>
<td>ECG</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

+ 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; ¶: consider if patients are using theophylline, warfarin, carbamazepine, digoxin; †: consider if patient has recently been on antibiotics. Reproduced from [1] with permission from the publisher.

**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).
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 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 ($P_aO_2$ < 5.3 kPa (<40 mmHg)) and/or severe worsen hypercapnia ($P_aCO_2$ > 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.

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?
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.

**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).

**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 FIO₂ of 0.35 are: pH 7.49; PₐCO₂ 3.9 kPa (29 mmHg); PₐO₂ 7.8 kPa (59 mmHg); bicarbonate 26 mM; and SₐO₂ 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.
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 $P_{a}\text{CO}_2 > 6.0$ 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%?
COPD feature: A typical COPD exacerbation?

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 Pa,CO₂ ≥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 (Fl,O₂ 0.21) are: pH 7.42; Pa,CO₂ 4.8 kPa (36 mmHg); Pa,O₂ 7.2 kPa (54 mmHg); bicarbonate 26 mM; and Sa,O₂ 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 β₂-agonist.
b) An inhaled corticosteroid.
c) Tiotropium.
d) Oral warfarin for 3–6 months.
e) Long-term oxygen therapy (LTOT) for life.
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 FEV1) 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
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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])

- **A**ntibiotics
- **B**ronchodilators
- **C**orticosteroids
- **D**ifferential Diagnosis
- **E**ducation
- **F**ollow-up

**References**