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Case report

Syncope: a complication of chronic cough

A 54-year-old male with an 8-year history of productive cough was referred to the tertiary cough clinic. He had a smoking history of 60 pack-years and reported his cough began when he stopped smoking.

He reported expectorating an egg cupful of white sputum per day with occasional streaks of haemoptysis. His subjective cough severity score was 8/10, where 0 is no cough and 10 is the worst possible cough. He had no concomitant symptoms of breathless, wheeze or chest infections. He reported a sensation of burning in his throat, which preceded coughing bouts.

He had previously trialled inhaled and oral corticosteroids, and inhaled nasal steroids, none of which had any impact on his cough. He had also trialled high-dose proton-pump inhibitor therapy (omeprazole 40 mg twice daily) with regular Gaviscon advance, which did not ameliorate his cough symptoms. His past medical history included depression and gastro-oesophageal reflux disease for which he took mirtazapine 30 mg once daily and omeprazole 20 mg once daily. His reflux symptoms were well controlled.

On examination, his body mass index (BMI) was 31 $kg \cdot m^{-2}$. His chest was clear, and he had no peripheral stigmata of lung disease. He underwent a laryngoscopy which revealed heightened laryngeal sensitivity, but no evidence of nasal disease, subglottic oedema or hyperaemia which would suggest ongoing reflux [1]. In view of the history of haemoptysis, particularly in a former smoker, he underwent a computed tomography (CT) of the thorax, lung function and bronchoscopy (figures 1, 2, tables 1, 2).

Task 1
What do these CT images (figure 1) show?

a) Emphysema
b) Desquamative interstitial pneumonia
c) Mediastinal lymphadenopathy
d) Normal appearances

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Lung function tests were within normal limits for the patient's age, height and gender. The flow–volume loop demonstrates concavity of the expiratory loop. This typically indicates a degree of airflow obstruction and is typically seen in patients with emphysema and spirometric evidence of airflow obstruction ($FEV_1/FVC \leq 70\%$) [4, 5]. In this case, the patient probably has a degree of airflow obstruction in relation to his previous smoking history, which may indicate early COPD.

It is consensus practice that high-risk patients such as this should undergo bronchoscopic evaluation to exclude an endobronchial tumour, which is rarely observed despite normal CT imaging [6, 7]. In those with chronic cough, real world data suggests that bronchoscopy is a clinically valuable

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@ERSpublications
Cough syncope is a rare but serious and potentially life-threatening complication of chronic cough. Early identification, comprehensive diagnostic evaluation and appropriate driving advice are fundamental to protect patients and the public. https://bit.ly/3CDAqYa

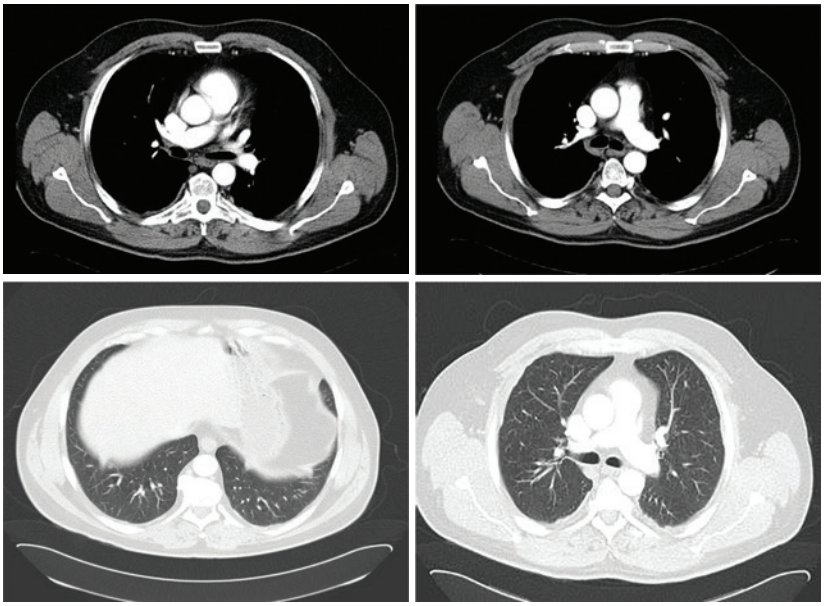

Figure 1 *Slices from CT of the thorax.*

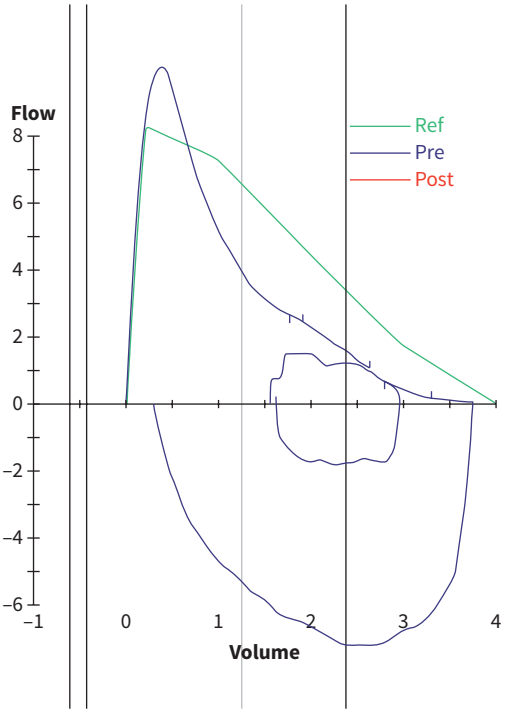

Figure 2 *Lung function testing (Ref: reference value; Pre: measured value; Post: post-bronchodilator value, not performed). Results are shown in table 1.*

tool in the right patient group, with macroscopic abnormalities, such as excessive dynamic airway collapse (EDAC), tracheobronchopathia osteochondropathia (TPO), tracheo bronchomalacia (TBM) and rarely foreign bodies, being present in 80% of cases, and eosinophilic bronchitis present in 4% of those undergoing this procedure [8]. The patient subsequently underwent bronchoscopy and bronchoalveolar lavage (BAL).

Task 2
What are the normal values for differential cell counts of a BAL?

a) Macrophages >85%, lymphocytes 10–15%, neutrophils <3%, eosinophils <1%, others <5%
b) Macrophages >65%, lymphocytes 5–10%, neutrophils 5–10%, eosinophils 15%
c) Macrophages 55%, lymphocytes 25%, neutrophils 10%, eosinophils 10%
d) Macrophages >85%, lymphocytes 10–15%, neutrophils <6%, eosinophils <3%
e) Macrophages >85%, lymphocytes 5–10%, neutrophils 5–10%, eosinophils <1%

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On further review of systems, the patient revealed that he had had six episodes of syncope upon coughing. He worked as a postman and walked 6 miles a day. He drove a van for work and reported one syncopal episode whilst driving.

Task 3
What driving advice should you give him at this point? Select more than one answer, if appropriate.

a) Must revoke his licence indefinitely
b) Must inform the Driver and Vehicle Licensing Agency (DVLA) immediately
c) Cannot drive for 6 months
d) Cannot drive for 1 year
e) Cannot drive for 5 years
f) Cannot drive until syncopal episodes resolved
g) Does not need to inform the DVLA but must not drive

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According to both EU and UK guidance this gentleman is a group 1 licence holder. According to UK regulations he must not drive for 12 months following the last episode of syncope and must inform the UK DVLA. Patient's driving licences are revoked until they are symptom free for the time specified. Under EU regulations he must also cease driving, however, may restart if there is no reoccurrence of syncope within 6 months [11].

Concurrent diagnoses of underlying conditions that precipitate syncope may affect this advice. The patient in this case is obese, which is associated with obstructive sleep apnoea (OSA). There are case reports in the literature of associations between refractory chronic cough (RCC) and OSA [13, 14]. This patient had no associated symptoms of OSA, such as excessive sleepiness, feeling unrefreshed, morning headaches, snoring and witnessed apnoeas. However, in cases where such symptoms are present, patients should be

investigated for OSA as this would alter treatment and the driving advice given.

Based on this guidance, the patient contacted the DVLA, who due to ongoing syncopal episodes, revoked his licence. As driving was essential for his work, he unfortunately lost his job. Due to subsequent financial difficulties, he could not afford to attend our specialist clinic (50 miles away from his home) for many years. This left him without appropriate treatment for his cough. He was subsequently referred to the service several years later with worsening cough syncope.

Task 4

You suspect that the patient is suffering from cough syncope, but would like to consider other conditions in your differential diagnosis. What are the red flag features that you would want to ask about in your history to identify other causes of syncope?

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Due to the damaging effects and potential serious nature of conditions potentially contributing to cough syncope, it is good practice that all patients reporting syncope undergo further diagnostic workup to exclude underlying treatable conditions.

These include:

- ECG to look for arrhythmias such as atrial fibrillation, heart block (prolonged PR interval or dissociation of P waves from QRS complexes), prolonged QT interval and evidence of right axis deviation and p pulmonale which may indicate pulmonary hypertension;
- Echocardiogram (ECHO) to look for features of fluid or inflammation in the pericardial sac, examine left heart function, and to look for features of pulmonary hypertension, and valvular disease such as aortic stenosis;
- A cardiac event monitor to capture arrhythmias that may be associated with syncope;
- A tilt table test to look for evidence of autonomic dysfunction; and
- If any neurological symptoms or signs are present, including headache, blurred vision, paraesthesia and weakness, to arrange urgent brain imaging as per local pathways.

Our patient underwent an ECG, ECHO, 48-h Holter monitor and tilt table testing, which were all within normal limits. The limitation of the 48-h monitor was he did not have a syncopal episode during this timeframe. His syncopal episodes continued, therefore, he underwent 14-day cardiac monitoring, which demonstrated occasional ventricular ectopics and one non-sustained run of ventricular tachycardia and he was therefore commenced on bisoprolol (figure 3). He had five episodes of dizziness during this timeframe but no syncope. He is awaiting an implantable loop recorder.

Table 1 *Result of the lung function testing for this 54-year-old Caucasian male*

Spirometry	Measurement	% of reference	SR
FEV_1, L	2.66	82	−1.16
FVC, L	3.76	93	−0.45
FEV1/FVC, %	71		
D_{LCO}, mmol·min^{-1}·kPa^{-1}	9.1	100	0.02
K_{CO}, mmol·min^{-1}·kPa^{-1}·L^{-1}	1.67	120	1.02
TLC (box), L	5.51	85	−1.42
RV (box), L	1.63	74	−1.37
RV/TLC, %	29		

SR: standard residuals (the deviation from predicted values (recorded−predicted)/residual standard deviation), FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lungs for carbon monoxide; TLC: total lung capacity; RV: residual volume.

Table 2 *Bronchoalveolar lavage (BAL) results*

Differential cell count	
Macrophages	83%
Neutrophils	1%
Lymphocytes	6%
Eosinophils	1%
Others	9%
Microscopic description	No malignant cells recognised

Total cell count: 0.11 million cells per mL.

Table 3 *EU standards for driving with recurrent cough syncope and DVLA guidance for group 1 (motorcycles, passenger cars and other small vehicles) and 2 (vehicles over 3.5 tonnes or vehicles designed for the carriage of more than nine passengers) drivers for patients with cough syncope*

EU standards [11]	Group 1 drivers	Driving allowed if no recurrence in 6 months
	Group 2 drivers	Permanent ban
UK DVLA guidelines [12]	Group 1 Drivers	Must not drive for 6 months following a single episode and for 12 months following multiple episodes and must notify DVLA
	Group 2 Drivers (bus and lorry)	Must not drive for 12 months following a single episode and for 5 years following multiple episodes and must notify DVLA

If more than one episode of cough syncope occurs within a 24-h period, this will be counted as a single event. However, if the episodes of cough syncope are more than 24 h apart, these are considered as multiple episodes. Adapted from [11, 12].

Table 4 *Adverse features in the history suggestive of alternative diagnoses*

Chest pain	Headache
Palpitations	Exertional onset
Protracted loss of consciousness >1–2 min	Syncope whilst supine or sitting
Significant history of structural heart disease	Polyuria/polydipsia
Significant breathlessness	Weight loss

Table 5 *Conditions that may mimic or exacerbate cough syncope*

Cardiac	Atrioventricular block Pulmonary hypertension Constrictive pericarditis Carotid sinus syndrome Postural hypotension Aortic stenosis Structural heart disease [16]
Neurological	Epilepsy Intracranial tumours [17] Subclavian steel syndrome [18] Autonomic dysfunction
Others	Drug induced (vasodilators, diuretics) Diabetes (resulting in autonomic dysfunction)

Information from [15].

In many cases of cough syncope, treating the cough itself will reduce or stop syncopal episodes entirely. There are, however, no current effective licenced treatments for chronic cough. Current unlicensed therapies include neuromodulators such as low dose slow-release morphine sulphate tablets (MST), gabapentin, pregabalin, and speech and language therapy.

This patient trialled pregabalin with no effect. Although MST reduced his subjective cough severity score from 8/10 to 6/10, he did not tolerate it well due to the side-effects of constipation and drowsiness.

Discussion

This case highlights one of the many challenges that patients with chronic cough face. Chronic cough (ongoing cough for 8 weeks or more) is a protracted and disabling condition, associated with many unpleasant features that have a profound effect on an individual's quality of life (QoL) [19, 20]. There are many potential causes and pathophysiological processes underlying chronic cough. Careful and systematic evaluation is required to exclude serious pathologies such as undiagnosed malignancy and to identify possible provoking factors such as gastro-oesophageal reflux disease, asthma, rhinosinusitis, eosinophilic bronchitis and medications [21]. Baseline assessment of the chronic cough patient should include history and examination; and baseline spirometry and chest radiography with cessation of any aggravating factors, such as smoking and angiotensin converting enzyme inhibitor usage [19, 21]. At this stage any underlying pathologies identified should be appropriately managed.

More in-depth assessment should then be considered including fraction of exhaled nitric oxide, serum and sputum eosinophils, high-resolution CT scan of the thorax, laryngoscopy, bronchoscopy and methacholine challenge [20, 21].

In up to 59% of patients, cough remains unexplained or refractory to evidence-based diagnostic and treatment strategies and is known as refractory or unexplained chronic cough (RCC/UCC) [21, 22]. Complications of RCC include depression, anxiety, sleep disturbance, urinary incontinence, and social disruption [23, 24]. Cough syncope is an important, but frequently overlooked, feature of chronic cough. Defined as loss of consciousness during coughing, cough syncope is a distressing and potentially fatal condition if an episode occurs whilst driving [25]. Despite this, it is under-represented in the literature, with no current consensus statements, or published guidance on how to investigate and manage these patients.

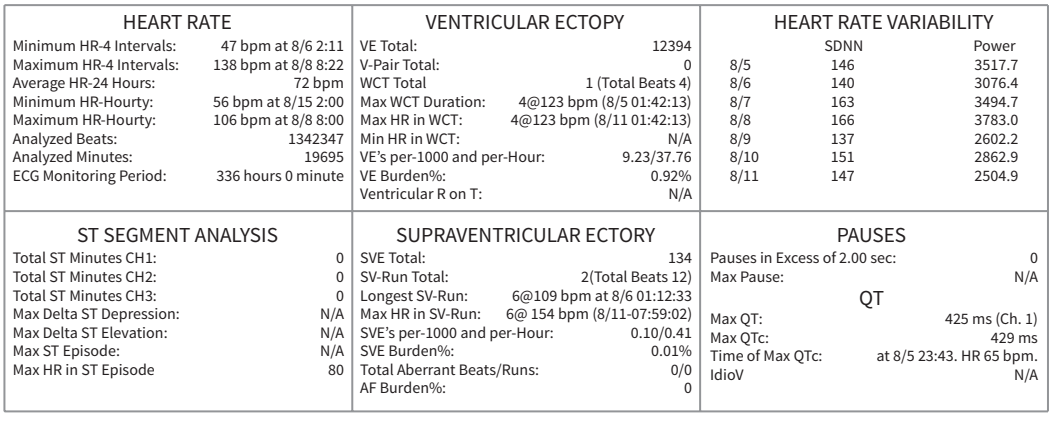

Figure 3 *Results of 14-day cardiac monitoring, revealing occasional ventricular ectopics (VEs), and an unsustained episode of ventricular tachycardia (VT). HR: heart rate; WCT: wide complex tachycardia; SDNN: standard deviation of the normal-to-normal RR intervals; SVE: supraventricular ectopic beats; AF: atrial fibrillation.*

Typically described as occurring predominantly in middle aged, overweigh males, the mechanism of cough syncope has been widely debated [26]. It was previously proposed that these episodes were a form of epilepsy, perhaps due to the jerking movements that patients often exhibit upon fainting [27]. However, this was disregarded when electroencephalograms performed during these episodes were normal [28]. By the mid-20th century, a number of small studies and case series suggested that post-tussive syncope was a consequence of markedly elevated intrathoracic pressures induced by coughing [29–31]. This results in reduced venous return and subsequent decreased cardiac output resulting in syncope [31]. The rapid alterations in intrathoracic pressure also stimulate baroreceptors triggering peripheral vasodilation and hypotension. The interaction of these mechanisms results in loss of consciousness [31]. A subsequent small study demonstrated a decreased chronotropic response to hypotension in cough syncope patients resulting in an inadequate heart rate response to maintain cardiac output [32]. Although the exact underlying pathophysiology of this condition remains unclear, it is generally thought to be due to a combination of the above factors.

As highlighted in this case, cough syncope has a multitude of potentially life-threatening precipitants, many of which are described in the literature. Careful history, examination and sequential investigation as outlined in this case is essential.

Although there are no current guidelines on the investigation of cough syncope, we propose a minimum set of tests to exclude differential pathologies (figure 4). History and examination should assess for adverse features that may suggest an underlying mechanism of syncope (table 4). Where symptoms of headache, visual disturbance, paraesthesia or limb weakness are present, a full neurological examination is also indicated. There are isolated reports in the literature of intracranial tumours presenting with symptoms of cough syncope so keeping a broad list of differentials is key [17].

There are several medications that may contribute to episodes of syncope during coughing. Anti-hypertensives, vasodilators and diuretics may worsen hypotension during coughing and medications that prolong the QT interval, such as selective serotonin reuptake inhibitors and macrolide antibiotics, may also exacerbate cough syncope. Reducing or stopping these medications where possible can be enough in some circumstances to stop syncopal episodes entirely. Angiotensin converting enzyme inhibitors are commonly associated with cough and should be discontinued or exchanged for a suitable alternative.

Occupation and driving history are a fundamental part of the clinical assessment and appropriate driving advice should be given in accordance with DVLA guidance [12]. This must be documented clearly in the medical notes. There have been isolated case reports in the literature of death caused by cough syncope whilst driving which have resulted in medico-legal cases [25]. This case highlights the huge implications that cough syncope can have on an individual's QoL. Sufferers may well depend upon driving in their professional or personal lives and the loss of a driving license may render many unable to work or attend hospital appointments.

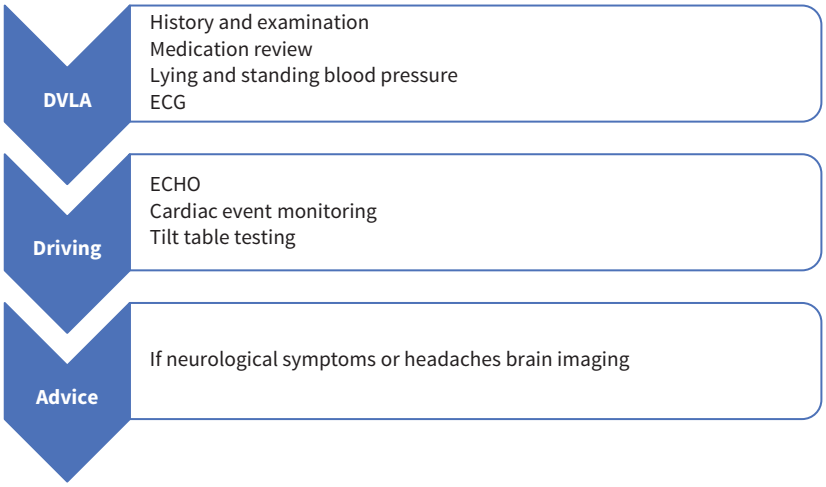

Figure 4 *Proposed set of investigations in all patients reporting cough syncope.*

Investigations should include ECG and cardiac event monitoring in all patients. As highlighted in this case the duration of cardiac event monitoring should be based on symptom frequency, as unless symptoms of pre-syncope and syncope occur daily a 24–48 h monitor is unlikely to capture a symptomatic period. Echocardiogram should be strongly considered is all cases and should always be performed in the presence of physical examination findings suggestive of structural heart disease and in those with an abnormal ECG.

In a small study of 29 patients with cough syncope, tilt table testing reproduced symptoms of pre-syncope or syncope in 62% of patients [33]. These symptoms were absent in all of the 29 controls [33]. The authors demonstrated that syncope and pre-syncope were associated with an abnormal vasopressor response leading to hypotension in all cases [33]. This suggests that tilt table testing is a useful investigation in those with suspected cough syncope as a diagnostic tool, but also to indicate underlying mechanisms.

Management of cough syncope should be tailored to individual provoking factors and to treating their chronic cough. As mentioned, those with postural hypotension who are on medications such as anti-hypertensives, vasodilators and diuretics may respond well to stopping or reducing these medications. There are no current licensed therapies for use in chronic cough. This patient had trialled MST and pregabalin. Opioid therapy is commonly used in specialist cough services and is recommended in international guidelines [20]. Evidence for its efficacy is lacking

and consists of a small, randomised controlled trial (RCT) demonstrating reduction in cough severity score and improvement in cough-related QoL [34]. However, many do not tolerate it due to side-effects such as constipation, nausea and lethargy as highlighted in this case. The alpha-2-delta ligands gabapentin and pregabalin are further unlicensed anti-tussive therapies recommended in the guidelines [20]. A single placebo controlled RCT demonstrated a subjective reduction in cough severity (visual analogue scale score) and improvement in cough-related QoL (Leicester Cough Questionnaire score) with gabapentin [35]. There are no head-to-head trials comparing pregabalin with placebo. A single RCT demonstrated that pregabalin combined with speech and language therapy (SLT) significantly reduced subjective cough measures compared with SLT alone, and although both groups showed significant reductions in objective cough frequency there were no significant differences between the two groups [36]. Again, these medications are often poorly tolerated, with side-effects that include unsteadiness and visual disturbances.

SLT has an emerging role as a non-pharmacological therapy in chronic cough. The first RCT evaluating SLT in RCC/UCC demonstrated significant reductions in reported and observed cough severity scores in 88% of participants [36]. However, no objective data regarding cough challenge response or 24-h cough frequency was collected, nor was any long term follow-up data to see if the effects persisted after completing a course of therapy [36]). A further multicentre RCT demonstrated significant reduction in 24-h cough frequency in patients undergoing SLT compared with placebo, an effect which extended to the 3-month follow-up period [37]. The potential drawbacks of this therapy are the amount of time and patient engagement required to complete a course of therapy and engage in the habits taught regularly, and the limited availability of therapists experienced in managing chronic cough. In a patient with severe symptoms such as cough syncope, SLT may not be appropriate due to the more urgent need to control the cough quickly.

Though treatment options for chronic cough are currently limited, the P2X3 antagonist gefapixant has recently completed phase 3 trials and has shown great promise in reduction of overall cough frequency and will hopefully be licenced in the near future [38, 39]. Hopefully this and other new therapies in development for RCC will provide more treatment options to control coughing in patients troubled by this serious complication.

Conclusion

Although rare/infrequent, cough syncope is a serious and potentially life-threatening complication of chronic cough which can have a major impact on sufferers' physical, psychological and financial well-being. Early identification, comprehensive diagnostic evaluation and appropriate driving advice are fundamental to protect patients and the public. Treatment should be focussed on treating the underlying chronic cough. Further work needs to be done to incorporate management of this condition into clinical guidelines. The financial and occupational implications of cough syncope must not be underestimated and centres that cater to the chronic cough population need to consider how they might signpost patients to appropriate support.

Answers

Answer 1

d. The CT scan is normal. The majority (71%) of patients with productive chronic cough in real world data from our clinic have normal CT imaging. However, CT imaging is important to exclude other serious pathologies, including malignancy, bronchiectasis, interstitial lung disease and emphysema, that may coexist. This is particularly relevant in smokers. It is important to note that prior work has demonstrated that up to 42% of patients with a normal chest radiograph will have abnormalities on CT of the thorax [2, 3].

<< Go to Task 1

Answer 2

a. BAL is a clinically useful tool with an established role in respiratory infection, interstitial lung disease and lung cancer. Within the chronic cough population, it has a select role in excluding eosinophilic bronchitis, lower respiratory tract infection and neutrophilic inflammation, which may require alternative treatment approaches [9]. The American Thoracic society (ATS) define cut-offs for normal BAL samples in their guidance as: eosinophil count <1%, lymphocytes 10–15%, neutrophils <3%, macrophages >85%, and others <5% [10].

<< Go to Task 2

Answer 3

b, d and f. This is dependent on country of practice. In the UK, the DVLA offer guidance for healthcare professionals and patients (table 3). This advice should be followed and conversations about driving should be clearly documented in the medical notes and in correspondence. In the European Union (EU), the Expert Group on Driving and Cardiovascular Disease have produced standards with recommendations for practice (table 3) [11].

<< Go to Task 3

Answer 4

There are many possible alternative diagnoses to consider including cardiac, neurological and systemic conditions that can contribute to syncope in this patient group. Red flag symptoms of alternative conditions are listed in table 4 and conditions that may mimic or exacerbate cough syncope are listed in table 5.

<< Go to Task 4

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Conflict of interest

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This article has been republished with a correction to one of the author first names.

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