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MANAGEMENT OF RECURRENT INFECTIVE EXACERBATIONS OF BRONCHIECTASIS

B McIntyre & NA Jarad

Abstract

The rate of non cystic fibrosis (CF) bronchiectasis is increased due to increase diagnosis and to aging. This is a chronic respiratory condition associated with abnormal irreversible bronchial airway dilatation. The condition is characterised by recurrent airway infections, persistent symptoms of cough and sputum production and a subsequent decline in respiratory function. It often results in patients requiring multiple hospital admissions. As a foundation junior doctor you may be expected to manage patients with bronchiectasis. This article is a case-based discussion on a patient presenting repeatedly with infective exacerbations of bronchiectasis.

It covers recognition of the unwell patient with an infective exacerbation and details the investigations and management that should be instigated. Bronchiectasis may be the result of a previous respiratory infection or an underlying systemic disease however in many cases it is idiopathic. Management of bronchiectasis should be targeted at both the acute presentation of an infective exacerbation as well as improving chronic respiratory symptoms and preserving respiratory function. Treatment should be tailored to the patient and their symptoms and is multimodal including airway clearance techniques, mucolytics and antibiotics. There is evidence that long term oral and nebulised antibiotic use is beneficial in sub groups of patients with bronchiectasis.

Case history

Mrs M is a 63 year old lady known to have post-infective bronchiectasis since childhood. She was seen in one stop emergency clinic (the HOT respiratory clinic) with increased breathlessness, chest tightness and increased sputum production of muco-purulent sputum. She also reported sleep disturbance and fatigue. Her symptoms had progressively worsened over the past 8 weeks and she had been seen repeatedly in HOT clinic requiring several hospitalisations for intravenous (IV) antibiotics.

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Her chest problems included asthma, sinusitis, and allergic broncho-pulmonary aspergillosis (ABPA). She had been recently diagnosed with hypertension. Her spirometric values were variable, but her best FEV1 was 2.36L (105%). This typically declined during exacerbations.

Her drug history included symbicort 2 puffs BD, carbocisteine 375mg PO TDS, azithromycin 500mg PO 3 x weekly, nebulised colistin, BD, hypertonic saline 1-2/day, montelukast 10mg PO OD, nasonex 2 sprays OD, lisinopril 5mg PO OD bendroflumethiazide 2.5mg PO OD and HRT patches. Her blood tests on admission showed raised inflammatory markers WBC 16.18, CRP 100, with a preserved renal function creatinine 63. A chest radiograph was performed which showed no focal consolidation however it was noted that a recent high resolution computed tomography (HRCT) confirmed multi-lobar bronchiectasis. Sputum samples cultured mucoid and non-mucoid strains of pseudomonas aeruginosa. Acid fast bacillus was not isolated.

The management of her acute exacerbations consisted of a combination of beta-lactam (ceftazidime, piperacillin and tazobactam) with an aminoglycoside (tobramycin). The duration of her treatment was 10-14 days. The growth of pseudomonas aeruginosa was frequently seen in her sputum samples. In an attempt to improve her exacerbations other nebulised antibiotics were tried. This included tobramycin and gentamycin with little improvement. Finally an attempt was made by nebulised small dose of piperacillin and tazobactam. The dose was 1.125 gram twice daily. This has, unexpectedly, resulted in a reduction in the number of exacerbations and in stabilisation of her FEV1 values.

Discussion

Bronchiectasis is the permanent dilatation and thickening of airways associated with sputum production, chronic cough, bacterial colonization and recurrent infection. The disease is increasingly recognised with the widespread use of chest CT scans. Bronchiectasis is an age-related disease slightly higher incidence in females (figure 1). The increase in age is also associated with a set of age-related co-morbid conditions including cardiovascular disease, mobility problems, frailty and depression. All these affect any management programme for this chronic condition.

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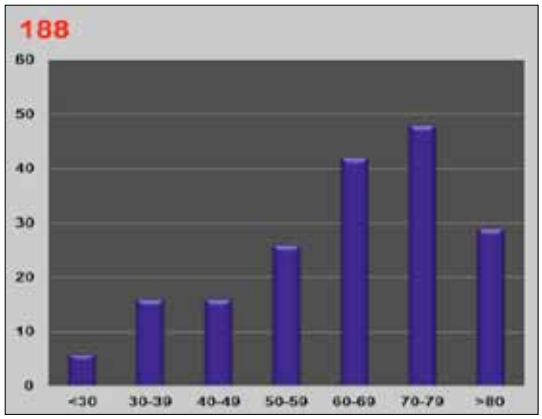


Figure 1: Age distribution of 188 patients with bronchiectasis in the authors' unit.

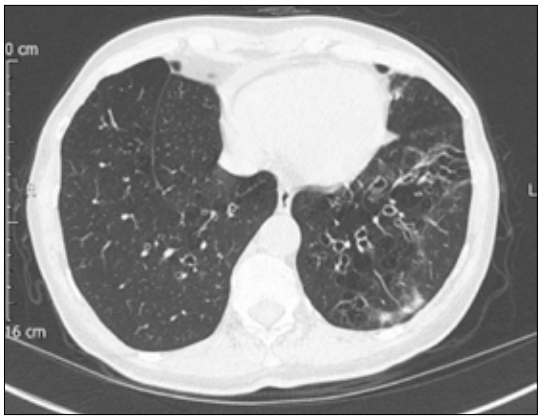
Clinical features suggestive of bronchiectasis are outlined in table 1. It is important to acknowledge that these features are not diagnostic as they can be seen in other respiratory disease, but would prompt investigations of bronchiectasis.

Clinical Features In Bronchiectasis
Copious sputum
Frequent exacerbations
Finger clubbing
Persistent basal crackles
Unexplained obstructive defect on spirometry
Haemoptysis
Frequent growth of bacteria in sputum samples

Table 1: Clinical features suggestive of bronchiectasis.

Chest X rays can show prominent linear opacities, but can be normal in mild and moderate disease. The diagnostic procedure is a HTCT scan. Three features would make the diagnosis of bronchiectasis likely -1. Evidence of airway dilatation and airway oedema when compared with adjacent pulmonary vessels. 2. Failure of airway tapering. 3. Visible airways within a short distance of the pleural surface.

(a)



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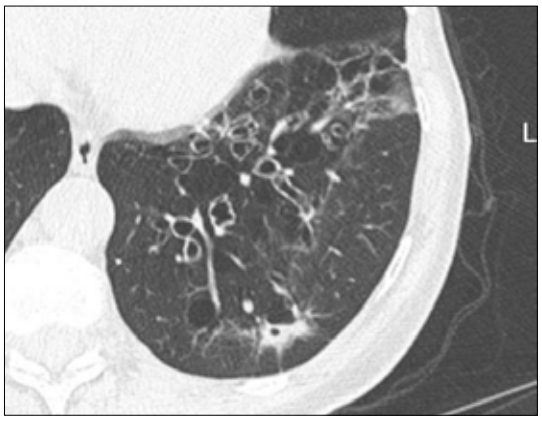

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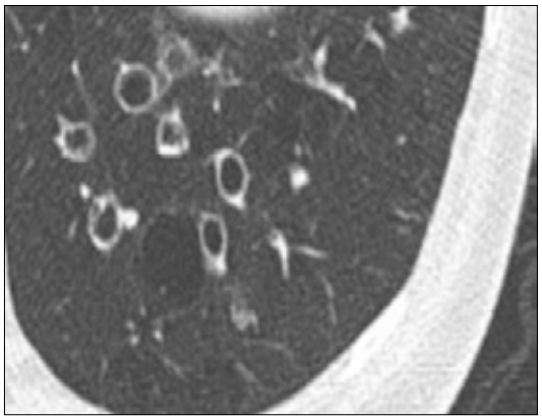

Figure 2: (a) Widespread bronchiectasis with failure of tapering, signet ring appearance and dilatation of the bronchi visible near to the pleural surface. (b) Dilatation of the airways with a failure of airway tapering and (c) signet ring appearance.

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Causes

The mechanism behind bronchiectasis formation is unknown. A vicious cycle of airway injury, inflammation and infection is thought to play a role. The impairment of the function of the muco-cilliary escalator contributes further to the mechanism of the disease.

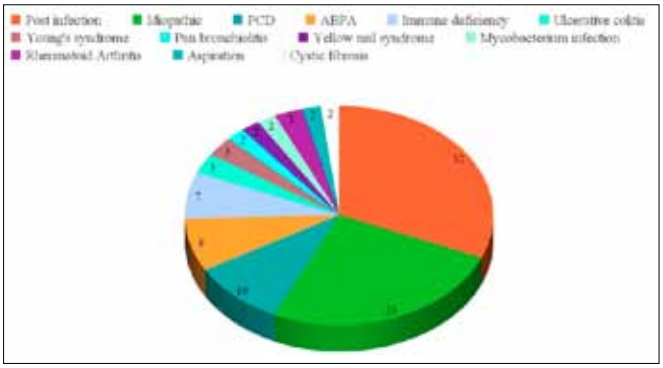

Figure 3: Aetiologies of bronchiectasis in a cohort of 165 adult patients investigated at the Royal Brompton hospital. (1) ABPA (allergic broncho-pulmonary aspergillosis), PCD – primary ciliary dyskinesia.

Establishing the cause of bronchiectasis may be difficult and in a large proportion of patients the cause is unknown, idiopathic. A number of studies have looked at the prevalence of the different causes of bronchiectasis, figure 3 shows the prevalence in a cohort of UK adult patients. (1) In Mrs M's case the cause of bronchiectasis was probably a post child hood pertussis infection, she also suffered from ABPA however given the widespread distribution of her bronchiectasis this was unlikely to be the main contributing cause.

Bacterial growth

This is a common and highly significant feature of bronchiectasis. Repeated isolation and culturing of bacteria in the sputum are common. Figure 4 illustrates the distribution of 'ever grown' bacteria in one year in the authors' unit. Repeated growth of bacteria is associated with an increase in day time symptoms and an increase in the frequency of exacerbations. The effect of bacterial growth on decline in lung function tests and on mortality rate are possible but have not yet been investigated. Repeated growth of pseudomonas aeruginosa is seen in patients with severe lung disease as a marker of disease severity. It is probably associated with a more rapid decline in their lung function tests.

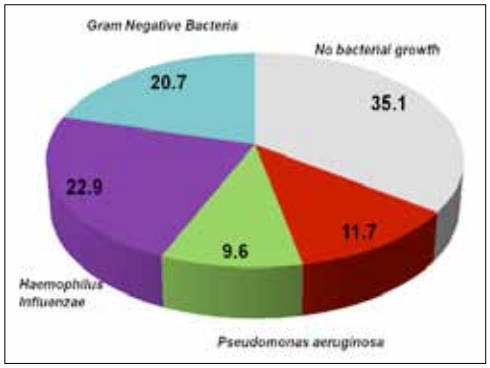

Figure 4: The growth of bacteria in the sputum of 188 patients over 12 months in the authors' unit. Numbers indicate a percentage of patients. Gram negative bacteria represent E coli or proteus vulgaris. As for pseudomonas aeruginosa they are divided into mucoid (green) and non-mucoid (red) strains.

Prognostic features

Establishing prognosis in bronchiectasis is important. Patients with high prognostic scores should have closer and more frequent clinical monitoring as well as a lower threshold for introducing treatment such as antibiotics. The multi-dimensional score The (FACED score) is shown in table 2 and is used in the author's unit. (2)

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Parameter	Score		
FEV1 (% predicted)	> 50% (0)	< 50 % (2)	
Age (years)	< 70 (0)	> 70 (2)	
Colonised with pseudomonas aeruginosa	No (0)	Yes (1)	
Extension of disease	One to two lobes (0)	> 2 lobes (1)	
MRC Dyspnoea Score	<3 (0)	> 3 (1)	
Total score			/7

Table 2: The FACED score. F for FEV1, A for age, C for colonisation with pseudomonas aeruginosa, E extent of the disease expressed by the number of lobes involved on CT scan and D for MRC dyspnoea score. Mild disease would score (1-2), moderate disease scores (3-4) and severe disease scores (5-6). Clear increase in mortality is seen in patients with increased FACED score.

Management of bronchiectasis

Long term management of bronchiectasis aims to preserve respiratory function, reduce the number of exacerbations, improve symptoms and quality of life and improve survival. Depending on the disease impact, management can be in primary care (by family doctors) or secondary care (hospital doctors). Patients who should be referred for management in secondary care are listed in the table below:

Referral for secondary care
Patients with bronchiectasis < 50 years of age
Patients with recurrent exacerbations ≥ 3 a year
Deteriorating bronchiectasis with declining lung function
Patients with chronic Pseudomonas aeruginosa colonisation, opportunistic mycobacteria or MRSA colonisation
Patients receiving prophylactic antibiotic therapy (oral/nebulised)
Allergic Broncho-Pulmonary Aspergilliosis (ABPA) - defined as asthma symptoms + total IgE >500Ku/L
Comorbid rheumatoid arthritis, immune deficiency, inflammatory bowel disease and primary ciliary dyskinesia.

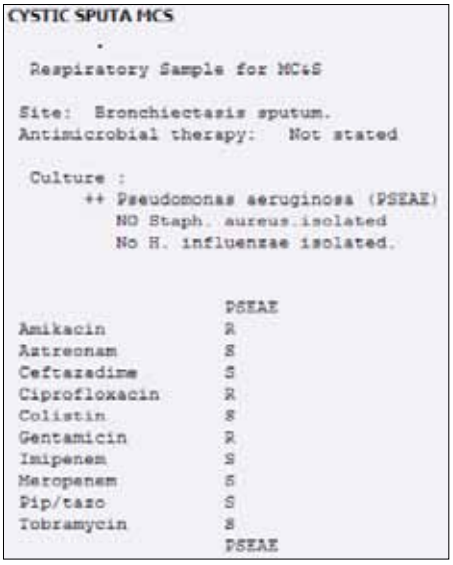
Table 3: Suggested circumstances for referral of patients for specialist bronchiectasis clinic – adapted from reference 4.

Infective exacerbations

An infective exacerbation of bronchiectasis is clinically defined as a sustained worsening of respiratory symptoms such as the volume and purulence of sputum, breathlessness, cough and fatigue. Occasionally haemoptysis would be a feature. Currently there are no biological markers to diagnose exacerbations. Chest X ray changes and raised blood inflammatory markers are subtle and unreliable.

Sputum cultures should preferentially be taken before antibiotics are started but they should not delay antibiotic therapy in an unwell patient. Mild exacerbations can be treated by oral antibiotics. Co-amoxiclav, doxycycline and macrolides are given to patient with no or infrequent (less than one a year) growth of pseudomonas aeruginosa. Quinolones such as ciprofloxacin may be helpful in patients with sensitive pseudomonas aeruginosa although resistance quickly emerges with repeated courses. The duration of the treatment should be for 10-14 days. (3)

Exacerbations unresponsive to oral antibiotics or severe exacerbations with impaired cardio-respiratory hemodynamic features require intravenous antibiotics. Single antibiotics are used in patients with non-pseudomonal growth. An example would be intravenous co-amoxiclav. A single or a combination of anti-pseudomonal antibiotics is usually helpful in pseudomonas aeruginosa. Examples are outlined in figure 5 and table 3.



CYSTIC SPUTA MCS

Respiratory Sample for MC&S

Site: Bronchiectasis sputum.
Antimicrobial therapy: Not stated

Culture :
++ Pseudomonas aeruginosa (PSEAE)
NO Staph. aureus isolated
No H. influenzae isolated.

	PSEAE
Amikacin	R
Aztreonam	S
Ceftazadime	S
Ciprofloxacin	R
Colistin	S
Gentamicin	R
Imipenem	S
Meropenem	S
Pip/taso	S
Tobramycin	S
	PSEAE

Figure 5: An example of a microbiology panel (Mrs M). This patient would respond to any of the combinations in table 4.

Essential antibiotics	Added antibiotic
Ceftazidime 2 grams three times daily	Tobramycin 4 milligrams/kg once daily
Pipracilline-Tazobactam 4.5 gram three times daily	Gentamicin 5 milligrams/kg once daily – examine urea and electrolytes due to increased nephro-toxicity.
Aztreonam 1 gram twice daily	
Meroponem 2 gram three times daily	

Table 4: Examples of a single or combination of antibiotics to treat patients with exacerbation of bronchiectasis in patients chronically infected with pseudomonas aeruginosa.

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Combination antibiotic therapy

Dual antibiotic therapy is not routinely recommended in the management of bronchiectasis exacerbations. If multiple pathogens are isolated then a single antibiotic should be selected to cover all pathogens. Combination therapy may be of benefit in infections caused by resistant pseudomonal bacterial strains or for those with repeated exacerbations despite using single treatment. Combination therapy in this situation has been shown to increase efficacy, extending the time until subsequent exacerbations and to reduce antibiotic resistance (3).

Infection with pseudomonas aeruginosa in bronchiectasis

Pseudomonas aeruginosa in bronchiectasis is worth discussing. The isolation and colonisation of pseudomonas aeruginosa in patients with bronchiectasis, is seen in advanced disease and may be associated with a worse prognosis.

It is debatable whether or not to instigate eradication of pseudomonas aeruginosa with antibiotics upon its first growth. The placebo arm of previous antibiotic studies (reference 6) showed spontaneous disappearance of this bacteria from the sputum in many patients. Therefore, the authors support the views that eradication strategies should be reserved to patients where this bacteria is isolated at two occasions within one year. Prospective studies on the value of eradication are needed.

If eradication therapy is unsuccessful then patients can stay on long term nebulised antibiotics as a suppressive therapy. Sending serial sputum cultures is useful to be able to monitor microbial colonisation and response to treatment.

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Long term therapy for bronchiectasis

Long term therapies are provided for patients with persistent daily symptoms, persistent bacterial growth and with frequent exacerbations. The strongest evidence available is for use of nebulised antibiotics and for long term macrolides (azithromycin and erythromycin).

Long term antibiotics in bronchiectasis have been shown to reduce microbial load as well as improving symptoms and reducing the number of infective exacerbations (5).

The strongest evidence for antibiotic use exists for nebulised gentamycin (6), nebulised colomycin (7) and nebulised or inhaled ciprofloxacin (8). Of significance, studies demonstrated that whilst these antibiotics are effective, they are also safe. Evidence of systemic side effects (renal toxicity and auto toxicity) is rare. In addition, emergence of resistance in clinical trials was shown in a recent systematic review to be comparable to placebo (9).

In the authors' unit, nebulised gentamycin 80 mg twice daily is used as a first line, followed by colomycin 1-2 mega unit twice daily and then by nebulised tobramycin 100 mg twice daily.

Macrolides have been shown to reduce the frequency of exacerbations by their anti-inflammatory capabilities rather than by being anti-microbial agents. Azithromycin 500 mg alternate days 10, or 250 mg once daily 13 has been shown to significantly reduce the number of exacerbations. In addition, erythromycin 250 mg twice daily gave similar results when given over a 12 month period (12).

Long term macrolides are associated with increased resistance in the population (13) and should be used with caution in patients with cardiovascular disease.

Therefore:

1. For patients who suffer with excessive daily symptoms and frequent bacterial growth, nebulised antibiotics are indicated.
2. For patients with frequent exacerbations, macrolides are helpful.
3. For patients with both features a combination of nebulised antibiotics and oral macrolides are indicated.

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The authors' policy is to review these patients after 12 months of the specific treatment. Recurrence of growth or increase frequency of exacerbations would mitigate re-starting the treatment.

Other maintenance management strategies

Less strong evidence exist for other modalities of treatment. This' include physio and physical therapy (exercises) and mucolytic agents. These are outlined in table 5.

Given the age of patients, caution should be exercised when providing treatment for patients especially those with old age related morbidities.

Physiotherapy	Input from specialist chest physiotherapists on airway clearance techniques. Pulmonary rehabilitation may be useful in patients who suffer from breathlessness with an MRC score more than 3.
Airway Management	In patients with evidence of reversible airways obstruction. • Salbutamol PRN • Ipratroprium PRN
Mucolytic	In patients with thick viscous secretions or difficulty expectorating. • Nebulised hypertonic saline 7% 4ml BD • Carbocisteine 750mg TDS • N-acetylcysteine 200 mg twice daily
Macrolide Antibiotics	Consider in patients having ≥3 infective exacerbations a year. • Azithromycin 500mg alternate days • Erythromycin 250mg BD
Nebulised Antibiotics	Nebulised antibiotics used in patients with daily symptoms and chronic bacterial colonisation • Gentamicin 300 mg BD • Colistin (colomycin) 1 mega unit BD • Tobramycin 300 mg twice daily • Tazocin 1.125 - 2.25 gram twice daily

Table 5: Evidence based maintenance management of bronchiectasis.

Conclusions

Non-CF bronchiectasis is associated with significant morbidity. Management requires a multidisciplinary as well as multimodal therapeutic approach. It aims to reduce the number of exacerbations along with improving a patient's daily symptoms and quality of life. Identifying infective exacerbations early is key to ensuring appropriate investigations and treatments are implemented.

Long term management involves patient specific directed treatment taking into account their microbial profiles, frequency of exacerbations and response to therapy. Long term antibiotic use has demonstrated a valuable role in the management of the condition.

Current data has come from relatively small clinical trials and so more large scale clinical trials are required to further support the role of long term antibiotic use along with the development of other treatments. The risk of chronic use of antibiotics has been debated. Macrolides are used for their immuno-modulating capabilities but cause drug resistance. The risk of drug resistance in nebulised antibiotics are probably less common.

MCQ Questions

1) Which of the following are associated with a better prognosis in bronchiectasis:

a) FEV1 <50%
b) Colonisation with Pseudomonas aeruginosa
c) Disease localised to > 2 lobes
d) Age < 70 years
e) MRC dyspnoea score > 3

2) Which of the following is not known as a common cause of bronchiectasis:

a) Kartagener's syndrome
b) Cystic fibrosis
c) Hypogammaglobulinaemia
d) Asthma
e) Gastro-oesophageal reflux disease

Answers

1. Being < 70 is associated with a better prognosis in bronchiectasis.

Prognostic factors in bronchiectasis can be analysed using the FACED score. The FACED score was developed by a study that used a multidimensional score to determine what variables contribute to a worse prognosis in patients with bronchiectasis. The variables identified were age >70 years, a radiological diagnosis of > 2 lobe involvement, presence of chronic colonisation with pseudomonas, dyspnoea with an MRC score >3 and forced expiratory volume in 1 second (FEV1) <50%.

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2. Asthma is not a known cause of bronchiectasis.

Although asthma can be associated with bronchiectasis and both are characterised by chronic inflammation they have key features which distinguish them. Asthma is associated with bronchoconstriction, hypersensitive and narrow airways, bronchiectasis on the other hand is associated with dilated airways and bacterial colonization.

Kartageners syndrome causes bronchiectasis due to inadequate clearance of mucous from impairment of the cilia motility. The more viscous mucus secretions in cystic fibrosis lead to bronchiectasis. Immune deficiencies such as hypogammaglobulinaemia and aspiration from gastroesophageal reflux disease have also been found to predispose to bronchiectasis.

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PULMONARY VASCULITIS: DIAGNOSTIC APPROACH

S Mukherjee

Pulmonary Vasculitis: Diagnostic Approach
Good Clinical Care

Abstract

Pulmonary vasculitides are a rare group of disorders characterized by inflammation and necrosis of the vessels of pulmonary circulation. Diagnosis of pulmonary vasculitis poses a challenge to the physician due to varied and non-specific presentations. As these conditions are rare, the physician is often riddled by the vasculitis mimickers, which unfortunately, are more common.

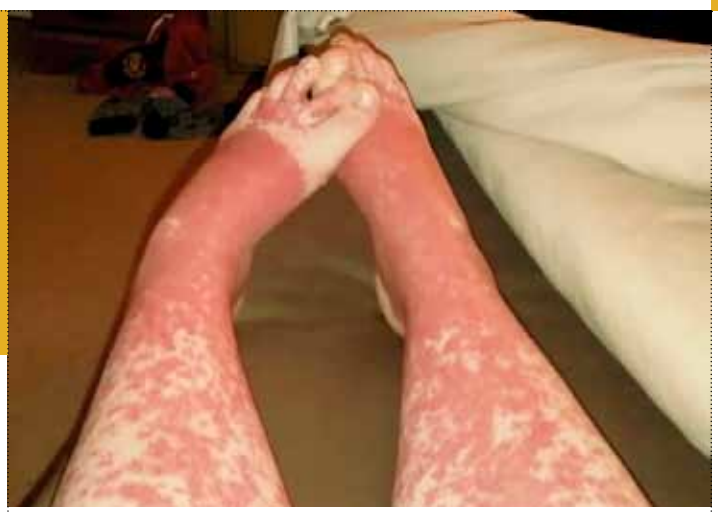
Clinicians should develop a methodology and a systemic approach taking into consideration the clinical and the radiological pattern along with targeted investigations. This article aims to outline the scenarios leading to suspicion of vasculitis and also the subsequent work-up required for confirmation of the same.

Keywords: *Vasculitis, Wegener's Ganulomatosis, Diffuse Alveolar Haemorrhage, Anti-Neutrophil Cytoplasmic Antibodies.*

Introduction

Pulmonary vasculitides are a rare group of disorders characterized by inflammation and necrosis of the vessels of pulmonary circulation. Diagnosis of pulmonary vasculitis poses a challenge to the physician due to varied and non-specific presentation and the fact that they are rare (incidence of 20 to 60 cases per million) (1,2).

The pulmonary vasculitides are categorized into small, medium, and large vessel vasculitis according to the size of the vessels predominantly involved or by the patho-physiologic mechanism of the disorder (e.g., pauci-immune or immune complex–mediated disease). The small vessel anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides most commonly affect the lung (Table 1).



Isolated pauci-immune pulmonary capillaritis#
Granulomatosis with polyangiitis#
Microscopic polyangiitis#
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)#
Idiopathic pauci-immune rapidly progressive glomerulonephritis#
Systemic lupus erythematosus
Rheumatiod arthritis
Polymyositis/dermatomyositis
Primary antiphospholipid syndrome
Scleroderma
Henoch–Schonlein purpura
Immunoglobulin A nephropathy
Behcet's syndrome
Hypersensitivity vasculitis
Essential cryoglobulinaemia
Inflammatory bowel disease

Table 1: Common causes of pulmonary vasculitis
#: Antineutrophil cytoplasmic antibody-associated vasculitis

Small vessel vasculitis (SVV) of the lungs can be a presenting feature of systemic vasculitis, collagen vascular diseases or any other autoantibody associated conditions; however, primary, idiopathic medium and large-vessel vasculitis, primary immune complex–mediated vasculitis, and secondary vasculitis are all capable of presenting with lung involvement (3-5). On the contrary, pauci-immune isolated pulmonary capillaritis (PIPC) can manifest as isolated pulmonary involvement with the characteristic clinical manifestations of diffuse alveolar hemorrhage (DAH). However, other immune-mediated disorders like Goodpasteur's syndrome (GS) with pulmonary renal involvement can mimic ANCA associated vasculitis (AAV) (3,6).

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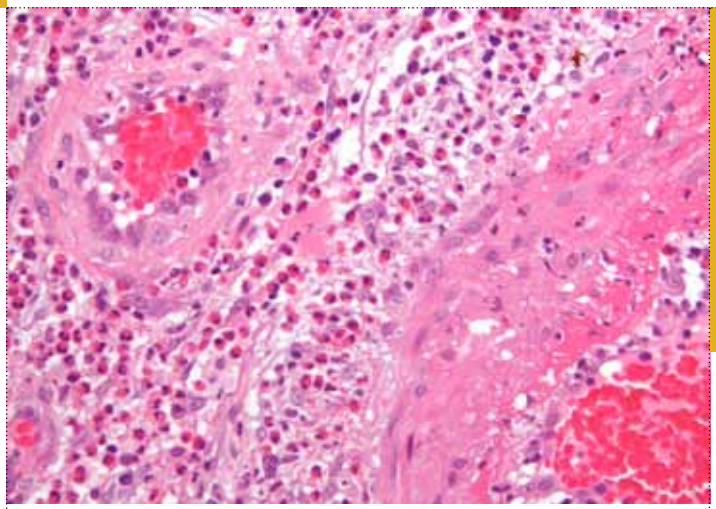

Physicians need a high index of suspicion particularly when the manifestations overlap with more common conditions like infections, malignancy and collagen vascular disease (CVD). Diagnosis is often clinical and needs integration of clinical, laboratory, radiological and histopathological data collated together to arrive to a definitive diagnosis. Furthermore, due to the varied manifestations of ANCA positivity, other organ involvement and difficulty in obtaining a proper histopathological sample, diagnosis of the specific type of vasculitis throws further challenge to the physician.

When should the physician suspect vasculitis?

The following scenarios should prompt the physician to actively look for AAV.

Diffuse Alveolar Hemorrhage

Most of the pulmonary vasculitis at some point can cause DAH characterized by hemoptysis, pulmonary infiltrates which are generally bilateral and a drop in the hematocrit and/or hemoglobin level. As mentioned before, PIPC typically presents with DAH (5,7). A high index of suspicion will be needed to direct appropriate investigations particularly with atypical presentations.

Acute Glomerulonephritis

All patients with pulmonary infiltrates should be screened for active urine sediment, which should include red blood cell (RBC) cast, hematuria, proteinuria (>500 mg/24 hours) along with serum urea and creatinine. A clinical picture of Rapidly Progressive Glomerulonephritis (RPGN) can develop along with pulmonary infiltrates and AAV is one of the commonest causes. Besides AAV, the differential diagnosis of RPGN also includes idiopathic pauci-immune glomerulonephritis (i.e., isolated small-vessel renal vasculitis), systemic lupus erythematosus (SLE), GS, post-infectious glomerulonephritis, IgA nephropathy, Henoch-Schonlein purpura (HSP), essential cryoglobulinemia, and membranoproliferative glomerulonephritis (8-10).

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The term pulmonary-renal syndrome refers to patients with both DAH/ pulmonary capillaritis and glomerulonephritis. The differential diagnosis includes the AAV, GS, and SLE (5).

Deforming or Ulcerating Upper Airway Lesions

In patients with Granulomatosis with Polyangiitis (GPA), previously termed as Wegener's Granulomatosis (WG), refractory chronic sinusitis with upper airways inflammation, ulceration, epistaxis and otitis can be characteristic features. There could be associated soft tissue and/or radiological bone destruction leading to characteristic deformities. Characteristically, patients with GPA develop typically subglottic or tracheal stenosis. Nasal polyposis can be associated with Churg Strauss syndrome (CSS) (5).

Palpable Purpura

Palpable purpura is most commonly seen in cutaneous small vessel vasculitis. Although association is with drug reactions, these lesions can also be found in the setting of AAV, cryoglobulinemia, connective tissue diseases (CTD), infections, and malignancy (5).

Mononeuritis Multiplex

Mononeuritis multiplex can be a presenting feature where the typical presentation is with a foot or wrist drop; the involvement of two or more nerves in this condition can be simultaneous or sequential. Sometimes sensory features can predominate (5,11).

Retro-orbital mass

GPA should be considered as one of the principal diagnoses in a patient presenting with retro-orbital mass; however, differential diagnoses should also include infections (e.g. orbital cellulitis, mucormycosis), tumours (lymphoma, pseudotumours, optic nerve glioma, metastasis) and other conditions like Langerhans cell histiocytosis, sarcoidosis and Graves opthalmopathy (7).

Multiple cavitary/non cavitary pulmonary nodules

This has been discussed in the radiology section.

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ANCA testing on patients presenting with one or more of the above scenarios will increase the positive predictive value and reduce the false-positive rate of the test, with no reduction in sensitivity or specificity (12). It cannot be over-emphasized that manifestations are variable, temporally heterogeneous and evolve over time.

Clinical assessment in vasculitis

Although certain clinical features as mentioned above are strongly suggestive of vasculitis, many patients, unfortunately, do not present with those features and signs and symptoms can be quite subtle. Even the smaller group of patients who indeed have the classic clinical features, there are a few conditions which can easily mimic vasculitis (e.g., CTD, infection, malignancy, drug toxicity, sarcoidosis, and interstitial lung diseases) particularly in the presence of multi organ involvement.

History taking should include relevant symptoms related to organ involvement, detailed drug history including recreational drugs and family and personal history of malignancies, Careful examination should be directed which should include cardiovascular, renal, neurological, dermatological and opthalmological examination with particular focus on the classic signs of vasculitis as mentioned above. Excluding infections can be a real challenge as it can sometimes lead to a positive ANCA response and a picture of leukocytoclastic vasculitis (7).

This is particularly important if the treating physician is planning to initiate immunosuppressive therapy. Similarly exclusion of drug-induced vascultis (e.g. propylthiouracil) is also crucial as clinical picture might be similar to that of infection induced vasculitis. Laboratory testing is also one of the key areas to investigate vasculitis; this is to define organ involvement as well as to determine any CTD related vasculitis. These are listed in table 2. Tests should include in addition, antiglomerular basement membrane antibodies, which are indicative of GS, and is helpful when evaluating alveolar hemorrhage, hematuria, or pulmonary renal syndrome (7).

Complete blood count with differential
Liver function tests
Urinalysis with microscopic examination
Urea and creatinine
Cryoglobulins
Serology for hepatitis B and C
Anticyclic citrullinated peptide for rheumatoid arthritis
Anti SS-A/Ro and anti-SS-B/La for SLE and Sjogren syndrome
Anti-Scl-70 (topoisomerase)
Anticentromere antibodies (systemic sclerosis)
Aldolase and creatinine phosphokinase for polymyositis
Complement levels for SLE.

Table 2: Laboratory tests for pulmonary vasculitis.

Chest imaging: when to suspect vasculitis?

Although plain chest radiographs are quite insensitive in identifying typical patterns of vasculitis, one of the characteristic features that is sometimes overlooked in chest radiographs is the presence of migratory infiltrates; although more common etiologies would include eosinophilic pneumonias, organizing pneumonias, pulmonary adenocarcinoma with lepidic growth pattern (previously termed as bronchioloalveolar carcinoma), vasculitis should always be considered particularly if there are clinical and biochemical evidence of multi-organ involvement.

Careful comparison of the serial chest radiographs is necessary to detect migratory infiltrates. A high resolution CT scan is an essential tool in imaging as this will identify many features, which might not be straightway visible on the plain chest radiograph. These would include multifocal ground glass changes and nodules, which can be further characterized. Radiological appearances can be classified into three main categories, which can further help to narrow the differential diagnosis (13).

Localized nodular and patchy opacities: angiitis-granulomatosis group

Radiological findings include multiple nodules, often with cavities (Figure 1), and pleural-based consolidation resembling pulmonary infarcts. GPA and CSS will characteristically cause this appearance. In GPA, Approximately 90% of patients have lung involvement and typical findings are bilateral, multiple, rounded opacities ranging from a few millimeters to 10 cm in diameter (14).

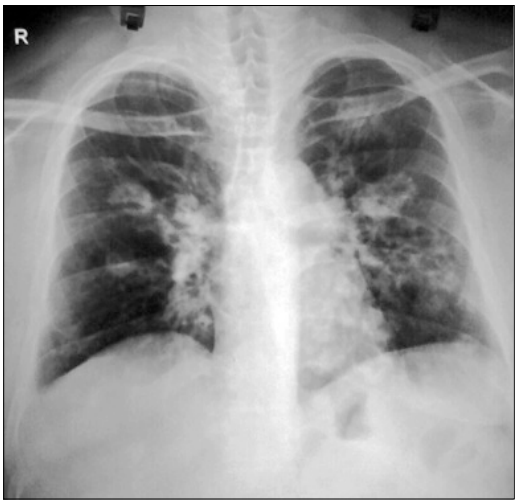

Figure 1: Chest radiograph of a 54 year old male with active Granulomatosis with polyangiitis showing bilateral multiple cavitary lung lesions.

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Cavitation of nodules with a thick wall and irregular inner lining is not infrequent. The nodules/masses and the focal pulmonary airspace opacities represent active inflammatory lesions. Reduction/resolution is a reliable indicator of response to immunosuppressive treatment. Secondary infection in the cavitry nodules can cause progressive consolidation or new air-fluid levels in pre-existing cavities, mimicking progression of AAGV (14-16). Multiple cavitary nodules can raise the possibility of cavitary metastases (melanoma, renal and thyroid cancers, squamous cell lung cancer), rheumatoid arthritis with necrobiotic nodules or the multinodular form of bronchioloalveolar cell carcinoma (now termed as adenocarcinoma with lepidic growth pattern).

Septic pneumonia, fungal pneumonias like cryptococcus, pulmonary tuberculosis, or multifocal parenchymal infarctions should also be considered in the differential diagnosis (16). Furthermore, many infections, including those caused by mycobacteria and Cryptococcus, can mimic endobronchial GPA and biopsy of all new ulcers is recommended to minimize the possibility of missing these diagnoses. In CSS, typical radiological findings include multiple nodular lesions and non-segmental air space consolidation in a peripheral distribution similar to eosinophilic pneumonia. In contrast to GPA, cavitation of nodules is rare (16).

Diffuse air space consolidation: diffuse pulmonary hemorrhage due to capillaritis

A wide variety of disease processes can cause DAH (Table 2). The acute stage of DAH is characterized by patchy or diffuse air space consolidation. The lung periphery and apices are often spared. The lesions are usually bilateral although they may be asymmetrical (Figure 2). In microscopic polyangiitis (MPA), DAH is present in one-third of the patients, tends to be severe and is often life threatening. DPH does not occur in classic polyarteritis nodosa (16,17). Furthermore, just the presence of focal ground glass opacities (GGO) can be a manifestation of DAH and can be seen in 25%–50% of cases of GPA (14, 16, 17).

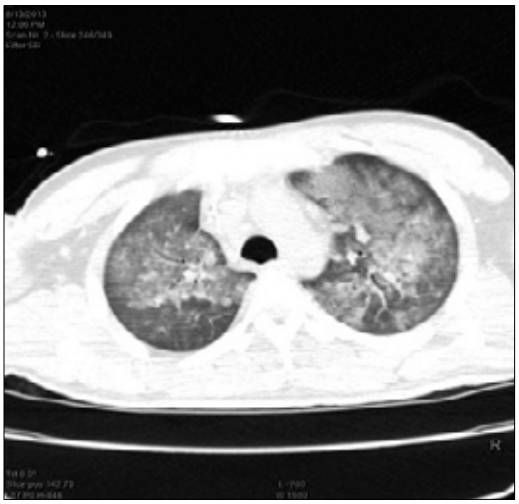

Figure 2: High resolution CT scan of chest in a 22 year old male with pulmonary vasculitis showing bilateral widespread ground glass opacities suggestive of diffuse alveolar haemorrhage.

DAH is a rare (2%) but catastrophic complication of SLE with reported mortality rates of 60-90% (17); It is most commonly seen concomitantly with other pulmonary manifestations of SLE such as acute lupus pneumonitis, pulmonary edema and infections, but is occasionally the initial manifestation of SLE. Amongst the non-vasculitic processes, GS is probably the commonest cause of DAH and should always be included in the differential diagnosis (13). Radiological differential diagnosis of DAH would include other disease processes leading to diffuse/bilateral air-space consolidation on chest radiograph/CT scan such as infective consolidation, pulmonary edema, organizing pneumonia, eosinophilic pneumonia and pulmonary adenocarcinoma with lepidic growth pattern.

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Aneurysm or stenosis of the large pulmonary arteries: Takayasu arteritis, Behcet's disease

Takayasu's disease and Behcet's syndrome can be suspected by the presence of segmental or subsegmental pulmonary arterial stenosis or aneurysms on CT pulmonary angiography. There can be thickening and enhancement of vascular wall; delayed enhancement of a thickened aortic or pulmonary arterial wall, as depicted on scans obtained 20–40 minutes after contrast medium injection, is characteristic of the active inflammatory phase of the disease. In addition, a mosaic appearance with decreased lung attenuation can be due to localized reduced lung perfusion. In the healed fibrotic phase, CT scan can detect vascular wall calcification. Behcet's disease, in addition, can manifest with superior vena caval occlusion and focal air space opacities due to pulmonary infarct/hemorrhage (18,19).

Focal or diffuse ground glass opacities

Probably the most challenging to the physician is the presence of widespread GGO on the HRCT (Table-3). This is due to the fact that differential diagnoses are wide and many common conditions including pulmonary edema can lead to these changes and unless a strong suspicion prevails, diagnosis of an underlying vasculitis is likely to be missed.

Primary idiopathic small vessel vasculitis
Granulomatosis with Polyangiitis (Wegener's Granulomatosis)
Churg-Strauss syndrome
Microscopic polyangiitis
Isolated pauci-immune pulmonary capillaritis
Goodpastures syndrome
Henoch-Schonlein purpura
Systemic lupus erythematosus
Rheumatoid arthritis
Antiphospholipid antibody syndrome
Mixed connective tissue disease
Polymyositis/dermatomyositis
Essential cryoglobulinemia
Behcet's disease
Coagulopathy

Table 3: Common causes of diffuse alveolar haemorrhage.

Upper airways: trachea-bronchial mass/irregularities of the mucosa

CT scan demonstrating trachea-bronchial mass/irregularities of the mucosa would be highly suggestive of GPA. Subglottic stenosis occurs in approximately 10–20% of patients with GPA, and can be the only manifestation (20).

Non-specific imaging signs

Pleural effusion can be present in 20-50% cases of GPA with segmental or sub-segmental bronchial wall thickening in approximately 70% of patients (21). Unilateral or bilateral pleural effusion is seen at CT in up to 50% of cases of CSS and may be caused by cardiomyopathy or eosinophilic pleuritis (22, 23). Centrilobular nodules and a tree-in-bud sign pattern may be seen in GPA and CSS in up to 10% of patients, usually mixed with other changes such as nodules, masses, ground glass opacity and bronchial wall thickening (14, 22, 23).

Non-specific imaging signs are a real challenge to the physician as differential diagnoses are wide and a strong index of suspicion is necessary to direct further confirmatory evidence. Some disease entities such as GPA and Behcet's disease can have features from more than one categories. However, this classification is useful for radiologists and will help to narrow the differential diagnosis in patients with suspected pulmonary vasculitis.

Role of ANCA in pulmonary vasculitis

Anti-neutrophil Cytoplasmic Antibody (ANCA) are autoantibodies directed against antigens found in the cytoplasmic granules of neutrophils and monocytes (24). Using indirect immunofluorescence, two major fluoroscopic patterns can be recognized: a diffuse cytoplasmic staining (C-ANCA), and a perinuclear/nuclear staining (P-ANCA). In patients with vasculitis, C-ANCA are directed against neutrophil proteinase (3) (a neutrophil azurophilic granule constituent) whereas P-ANCA predominantly recognizes myeloperoxidase (a lysosomal granule constituent) (25). Small vessel vasculitis is subclassified based on the presence or absence of ANCA. GPA, MPA, CSS and idiopathic necrotizing crescentic glomerulonephritis (INCGN) are associated with circulating ANCA, and are collectively called ANCA-associated systemic vasculitis (AASV). ANCA is a sensitive and specific marker for AASV (3-5).

Diagnostic value of ANCA in pulmonary vasculitis is included in Table 4.

C-ANCA	*Positive in 60-70% patients with classical GPA* *Negative in 10-20% patients with GPA* *Can be positive in about 30% patients with MPA and CSS*
P-ANCA	*Positive in CSS, INCGN and MPA*
Negative GPA ANCA assay	*(10-20%), CSS (40-50%)*
ANCA positivity other than vasculitis	
Inflammatory bowel disease	
Sclerosing cholangitis	
Rheumatoid arthritis	
SLE	
Sub-acute bacterial endocarditis	

Table 4: Diagnostic value of ANCA in pulmonary vasculiis.

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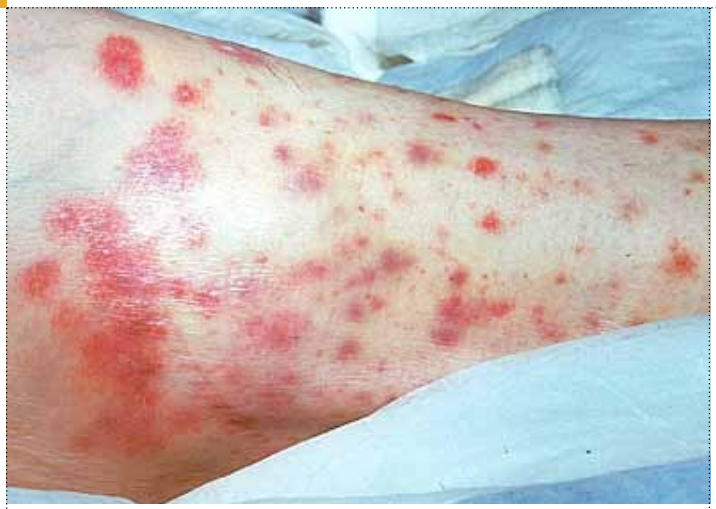

As mentioned before, ANCA testing is most useful when applied selectively to high-risk populations or with symptoms suggestive of vasculitis, which increases its positive predictive value (7).

Bronchoscopy

The primary role of bronchoscopy is to exclude infections. However, it is an important tool to diagnose DAH and can reveal endobronchial lesions in GPA which can be biopsied. Furthermore, it is a useful procedure to exclude other non-infectious pathologies mimicking vasculitis like eosinophilic pneumonias.

Organ biopsy

Biopsy of extra-renal and extra-pulmonary sites is easy to perform, more accessible and carries a lower morbidity. Therefore the physician is often tempted to perform biopsy of these sites. However, there is lower likelihood of making a definitive diagnosis of vasculitis from biopsy of these sites (26). Transbronchial lung biopsies, although more convenient, are generally unsuitable for making a diagnosis of vasculitis as specimen size is small and samples are often crushed (27).

Endobronchial biopsy might be useful particularly with vasculitis involving the major airways like GPA. If there are clinical and laboratory evidence of glomerulonephritis, percutaneous renal biopsy is a useful tool for the physician. The histopathology can demonstrate necrotizing vasculitis; moreover, the finding of a segmental necrotizing glomerulonephritis without immune deposits (i.e. pauci-immune glomerulonephritis) reflects a systemic vasculitis in most cases (28-30). Furthermore, immunofluorescence and electron microscopic examination can be performed on the specimens to detect IgA deposition in HSP, linear IgG deposition in GS and complement deposition in SLE (7).

Surgical lung biopsy

Surgical lung biopsy has low mortality and morbidity and will clearly provide a diagnosis in most of the cases of pulmonary vasculitis. However, as most of the patients with vasculitis are unwell, surgical lung biopsy can be difficult to perform.

Conclusion

There is a high morbidity and mortality associated with vasculitis despite considerable advances in diagnosis and management. Therefore, early diagnosis and identification of specific type of vasculitis is crucial for improving outcome for these patients. However, as these conditions are rare, the physician is often riddled by the vasculitis mimickers, which unfortunately, are more common. Clinicians should develop a methodology and a systemic approach taking into consideration the clinical and the radiological pattern along with targeted investigations, which can span several other medical and surgical specialties. This should be again a concerted effort in a comprehensive multidisciplinary approach.

MCQ

1. Differential diagnosis of multiple cavitary lesions on chest radiograph would include:

A) Septic emboli.
B) Granulomatosis with polyangiitis.
C) Metastatic cancer.
D) Churg-Strauss syndrome.
E) Sarcoidosis.

2. The following statements are true about pulmonary vasculitis:

A) Pulmonary involvement occurs in about 90% of patients of GPA.
B) Diffuse alveolar hemorrhage is almost universal in pauci-immune isolated pulmonary capillaritis.
C) Upper airway involvement can occur in Churg-Strauss syndrome.
D) Migratory pulmonary infiltrates may be seen.
E) P-ANCA is more sensitive than C-ANCA.

3. Vasculitis with renal and pulmonary involvement can be commonly seen in:

A) Churg-Strauss Syndrome.
B) Systemic Lupus Erythematosus.
C) Goodpasteur's syndrome.
D) Polyarteritis nodosa.
E) Microscopic polyangiitis.

4. Causes of mononeuritis multiplex would include:

A) Granulomatosis with polyangiitis
B) Churg-Strauss Syndrome
C) Essential cryoglobulinemia
D) Diabetes mellitus
E) Lymphoma

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5. P-ANCA can be positive in the following conditions:

A) Granulomatosis with Polyangiitis
B) Idiopathic pauci-immune rapidly progressive glomerulonephritis
C) Churg-Strauss syndrome
D) Ulcerative colitis
E) Goodpasteur's syndrome

Answers

1. Answer: all of above. *Churg-Strauss syndrome and sarcoidosis uncommonly can develop cavitary lesions.*

2. Answer: All of above. *P-ANCA is positive in 10-20% cases of GPA and can be detected in other non-vasculitis conditions like Goodpasteur's syndrome.*

3. Answer: A, B, E. *Goodpasteur's syndrome is not a vasculitis. Renal involvement is not uncommon in Churg-Strauss syndrome. In microscopic polyangiitis, kidneys are affected in up to 90% of patients. Pulmonary involvement is rare in polyarteritis nodosa.*

4. Answer: All true.

5. Answer: A, B, C, D, E. *P-ANCA is less sensitive and specific than C-ANCA.*

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EARLY DIAGNOSIS OF OBSTRUCTIVE SLEEP APNOEA

A Jayadev, S Law & HK Makker

Abstract

Obstructive Sleep Apnoea Syndrome (OSAS) describes a disordered sleep breathing pattern associated with recurrent apnoea and a range of symptoms including daytime somnolence. It is becoming increasingly common as the prevalence of obesity rises. Evidence demonstrates a significant impact on quality of life and increased risk of several co morbidities which can be improved with safe non-invasive treatment in the form of continuous positive airway pressure (CPAP). As a foundation doctor you will inevitably see patients with symptoms of OSAS and this article provides you with the tools to highlight those at risk and make the diagnosis early.

Key words: *Obstructive sleep apnoea, clinical features, early diagnosis.*

Case

You are asked to see a 57-year-old Caucasian male taxi driver in sleep clinic presenting with daytime somnolence. He reports feeling tired all the time with frequent napping in front of the television. This has progressed over a three years and he attended today as he is struggling to concentrate at work; even in the morning he feels un-refreshed. His wife recently started sleeping in the spare bedroom due to his loud snoring. He has hypertension and takes amlodipine, drinks 21 units of alcohol weekly and has never smoked. He has no other symptoms of note and has never fallen asleep driving or been involved in any road traffic accidents.

On examination his BMI is 33 and neck circumference 49 cm; oxygen saturations are 97% on air and blood pressure is 139/86 mmHg. Chest and cardiovascular examination is normal. There was no pallor or goitre. On examination of the oral cavity the uvula, tonsils and arches were all visualised.

Early Diagnosis Of Obstructive Sleep Apnoea
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The patient was sent for routine biochemistry and advised not to drive before returning to clinic with his wife. In a joint consultation she reported loud snoring with frequent worrying pauses where he appeared to stop breathing; these are followed by loud grunting and rapid breathing in a repeating cycle. She also noted he was more irritable and struggled to maintain concentration during conversations. Biochemistry was normal and his Epworth Sleepiness Scale (1) score was 18 demonstrating moderate daytime sleepiness.

A diagnosis of Obstructive Sleep Apnoea Syndrome (OSAS) was suspected and the patient was referred for sleep studies. Limited sleep studies demonstrated on average 18 apnoea's with associated oxygen desaturations of 5-10% per hour of sleep. This represented an apnoea-hypopnea index (AHI) of 18 and a diagnosis of moderate OSAS was made (2).

He was advised to lose weight, reduce his alcohol intake, cardiovascular risk was assessed and he was started on Continuous Positive Airway Pressure (CPAP); he was also advised to inform the DVLA and stop driving until further notice. Follow up 2 weeks later he had tolerated the CPAP well with good compliance and was feeling more energetic with reduction in daytime sleepiness score. Six weeks later, his daytime symptoms had completely resolved and following repeat DVLA assessment was permitted to return to driving.

What is the diagnostic criteria for OSAS?

What risk factors does he have?

What is the most predictive symptom of OSA in this case?

What is the most predictive sign of OSA in this case?

What is the likely cause of this patient's OSAS?

Do you know any other causes?

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This is a very common presentation and management scenario in the respiratory out-patient sleep clinic. The questions for consideration are addressed in the discussion below.

Definition

Obstructive Sleep Apnoea (OSA) or Obstructive Sleep Apnoea Hypopnea (OSAH) fall under the umbrella of sleep disordered breathing. They form part of spectrum of conditions with 'simple snorers' at one end, thought to affect approx. 40% of the adult population, (3) and those with repetitive complete obstruction of the upper airway throughout the night, at the other. (4)

Along this spectrum will occur the point at which the repetitive obstruction and recurrent arousal from sleep will result in symptoms leading to a diagnosis of Obstructive Sleep Apnoea Syndrome (OSAS). (4) It is important to appreciate the difference between OSA, which is used to describe sleep study findings consistent with recurrent apnoeic episodes, and the clinical syndrome, which occurs when patients are symptomatic.

"Apnoea" means cessation of breathing, and in OSA terms, this is defined as periodically interrupted breathing of at least 10 seconds. (4,5) It is usually caused by decreased stability and collapse of the upper airway (pharynx). Partial occlusion of the pharynx results in reduced ventilation called hypopneas, defined as at least 50% airflow reduction for at least 10 seconds. (5) Patients with OSAS usually have a combination of both. (3)

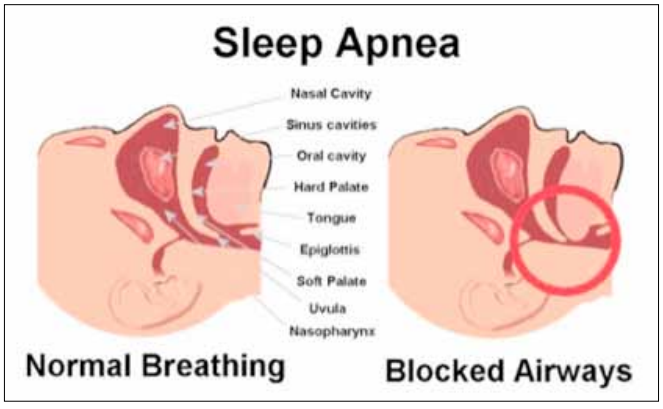

Figure.1: Mechanism of OSA.

These apnoeas and hypopneas are associated with desaturations that are terminated by semi-awakening, resulting in fragmented sleep, which in turn gives rise to daytime somnolence. Some narrowing of the upper airway during sleep is common as it is thought that all postural muscles (including pharyngeal dilator muscles) relax during sleep. (4,5) However, there are a few reasons that may cause excessive partial or complete obstruction of the upper airway and OSAS and are detailed in table 1.1.

Small Pharyngeal Size When Awake (IE. Physiological Relaxation During Sleep Is Enough To Cause OSA)	Excessive Narrowing Of Airway With Muscle Relaxation At Sleep Onset
Fatty infiltration of pharynx and external pressure from fat/muscle.	Obesity or excessive neck muscle mass can overwhelm residual dilator action
Large tonsils	Neuromuscular diseases can reduce dilator muscle tone, eg. myotonic dystrophy, stroke
Craniopfacial abnormalities, e.g micrognathia, retrognathia	Muscle relaxants, such as sedatives and alcohol
Extra submucosal tissue, eg myxoedema/ mucopolysaccharidosis	Increasing age

Table 1.1: Causes of OSA, from Oxford Handbook of Respiratory Medicine (4).

Need for the early diagnosis

It is well established that recurrent nocturnal hypoxaemia, that occurs in untreated OSA, leads to increased sympathetic output resulting in hypertension, increased risk of CVA, arrhythmias, pulmonary hypertension, cardiac failure and sudden cardiac death to name a few. (3,5) OSAHS is an independent risk factor for insulin resistance and type 2 diabetes, and OSA-induced brain injury is now a recognized clinical entity. (5,6,7)

Excessive daytime somnolence is regarded as the most important symptom as it can significantly impair quality of life, leading to difficulties in personal relationships, often secondary to irritability and loud snoring, impaired social functioning and sometimes employment dismissal. (3,5) Patients with OSAHS have a 3-7 times increased risk of road traffic accidents and often complain of feeling un-refreshed on wakening which may be associated with headaches and true nocturia (i.e. reversal of day/night ratio). (3,4,5)

Early diagnosis and treatment is of paramount importance because of significant dysregulation of cardiovascular and metabolic homeostasis, as well as the impact on quality of life that untreated OSAHS. (6) Evidence shows that treatment of OSA significantly improves early signs of atherosclerosis and is needed to reduce the risk of subsequent cerebrovascular and cardiovascular diseases. (8,9) Specifically in acute stroke, OSA has been found to impair rehabilitation and increase mortality, and early diagnosis and treatment would be favourable to improve recovery and reduce mortality. (10)

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OSA is a worldwide problem, thought to affect between 2-14% of the general population, yet most patients remain undiagnosed, with recent estimates that only 20-30% of individuals have been diagnosed in the UK. (3,11) As its prevalence is strongly correlated with obesity, it is increasing, particularly in America and developed countries, and is thought to be third most common serious respiratory disease after Asthma and COPD. (3,4) However, it is important to note that the diagnosis is not confined to the obese with approx. 30% of patients being non-obese. (3)

An improvement in rates of early detection and diagnosis is needed to reduce adverse health and social consequences of OSAS. One of the problems lies in the fact that it has only relatively recently, in the last decade or so, been recognized as a major health problem and there is reduced awareness by all, including health professionals. (3) Given that there is an effective treatment available in the form of CPAP (Continuous Positive Airways Pressure) therapy, several screening tools have become available to aid this process. These are discussed below, but firstly it is the history and examination that should alert the clinician and prompt further investigation. If presenting features were detected it could lead to earlier diagnosis.

Presenting features

Table 1.2 and Figure 2 highlight the most commonly reported symptoms and signs in OSA.

Common Symptoms
Excessive sleepiness
Loud snoring – often witnessed by partner
Intermittently awakes from sleep 'choking'
Poor concentration
Unrefreshing sleep
Nocturia

Less Common Symptoms
Nocturnal Sweating
Reduced Libido
Oesophageal reflux
Apnoeic episodes observed by spouse

Table 1.2: Common Symptoms of OSA adapted from Oxford Handbook of Respiratory Medicine (4).

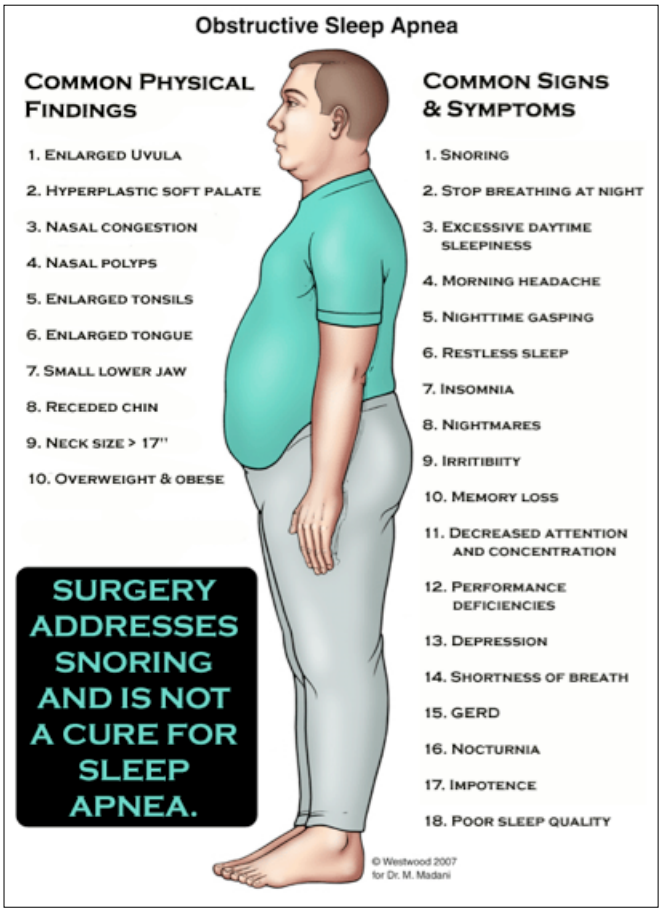

Figure 2: Typical Clinical features in patients with OSA (2).

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As these are fairly broad and can be non-specific, it is useful to consider the predictive value of each of these symptoms and signs. There has been much published in this field and one of the original and most comprehensive reviews, concluded that no single factor was usefully predictive of obstructive sleep apnoea. (12) However, combining clinical features and oximetry data could confidently identify one third of patients as having OSA or not. (12)

The review found that examination of the upper airway was not helpful in predicting the likelihood of OSA, and that BMI was a significant independent correlate with AHI (Apnoea-Hypopnea Index, discussed below). (12) This correlates with other studies where the Snoring Severity Score (SSS) and BMI were reported as the two most accurate predictors of OSA. (13) In one study a SSS of 4 or BMI of 26, was found to have a positive predictive value(PPV) 82.3% and negative predictive value (NPV) of 84.2% for moderate/severe OSA. (13) Patients at high risk were identified as having a BMI ³ 32, (89% PPV), or SSS ³ 7 (92% PPV). (13) Although other studies have not reported such high values with average snoring PPV of 84% but NPV of 39.6%. (14)

Self reported snoring has been shown to have a strong association with sleep apnoea in most reports, but it was significant only if it occurred every night (12). Other variables that showed a significant difference between sleep apnoea and non-sleep apnoea patients are shown in the table below along with the associated positive predictive value for each.

Symptom	Positive Predictive Value (%)	Negative Predictive Value (%)
Observed Apnoeas	64	53
Snoring	63	56
Weight increase as snoring worsened	64	55
Sleeping position (Sleeping on back = higher risk)	77	47
Awoken with heartburn	71	50
Falls asleep driving	70	51

Table 1.3: Questionnaire data showing significant differences between sleep apnoea and non-sleep apnpoea. (12)

There is also a significant relationship between alcohol consumption, BMI and age in men, but in women the only significant factors were age and neck circumference (12). Interestingly tendency to doze in situations other than driving occurred equally in both groups, with no significance of personality changes, nocturia, nocturnal enuresis, nasal symptoms and headaches.

Yet other studies have reported nocturia as a comparable to snoring as a screening tool with a PPV of 80.6% and NPV of 27.9%, where patient reported nocturia frequency predicted OSA severity above and beyond BMI, sex, age, and self reported snoring (14).

Diagnosis

The history and examination can therefore lead to a high clinical suspicion but current guidelines indicate that the diagnosis should be made by a specialist. This is to limit potential over (and under) diagnosis of OSAS given the high prevalence of non-pathological snoring, sleepiness and obesity.

The gold standard for diagnosis is considered by some to be a 'full sleep study' or body polysomnography which entails overnight oximetry, heart rate, body and abdominal movements, leg movements, snoring, oronasal airflow, EEG, EOG and EMG (4). All these investigations can be useful for difficult cases and excluding other causes of daytime sleepiness such as narcolepsy, neurological disorders, depression, periodic limb movement disorder. (3)

However the reality is that these tests are expensive, not easily accessible and not indicated for most patients. There is no evidence that a diagnosis of OSA requires full polysomnography, and overnight oximetry alone will often suffice.

In overnight oximetry a 4% dip in oxygen saturation equates to a 10 second obstruction in airflow. (5) The frequency of Apnoeas and Hypopneas that occur in an hour is calculated as the Apnoea Hypopnea Index (AHI). A diagnosis of OSA is made on the basis of AHI> 5 with unexplained daytime sleepiness or any of 2 symptoms. (5)

Severity of OSA can be classified as follows:

Mild: AHI 5-14

Moderate: AHI 15-30

Severe: AHI> 30

Management

NICE have recommended CPAP as the treatment for OSAHS in a health Technology Appraisal, implemented in 2009. (3) These guidelines recommend CPAP is offered to patients with AHI>15, i.e. moderate or severe OSAHS.

The exception is that it can be offered to those with mild disease if they have significantly impaired quality of life, or lifestyle or other measures have been unsuccessful or considered inappropriate. (3)

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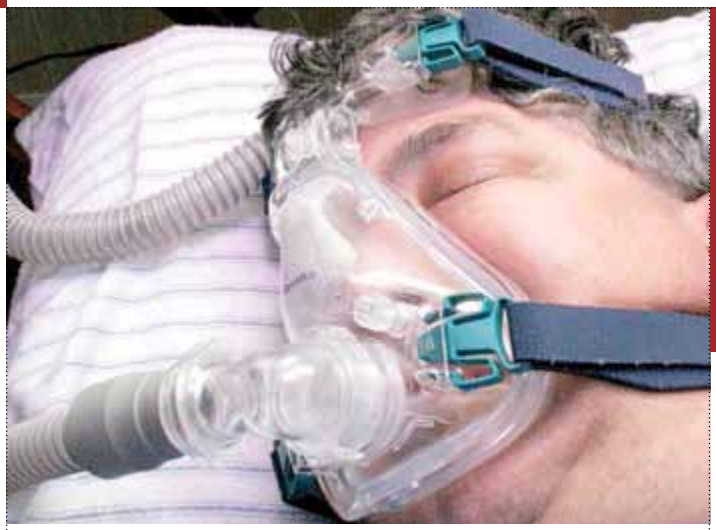

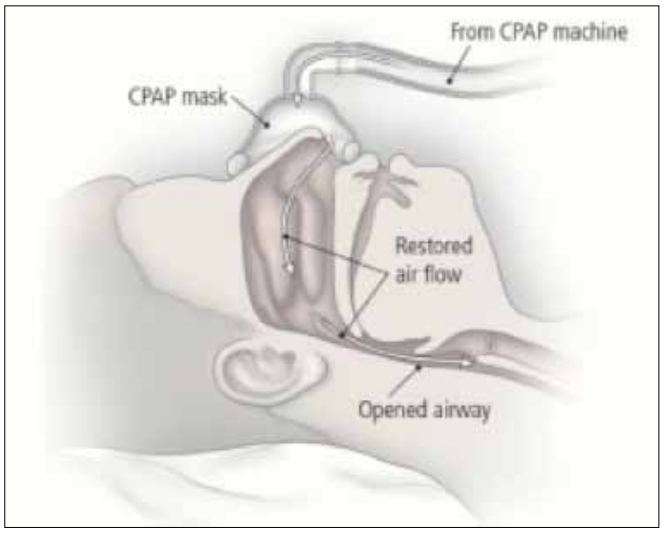

Figure 3: Continuos Positive Airway Pressure (CPAP) machine prevents sleep apnoea by blowing air into the airway to keep it from collapsing.

All patients should be given lifestyle advice, such as alcohol reduction and weight loss. Other non surgical options include mandibular advancement devices with surgical management of OSAHS being bariatric surgery, for which they would need specialist metabolic referral.

The gold standard treatment for OSAHS is CPAP therapy and it is recommended for a minimum of 4 hours a night.

The commitment to treatment is usually life-long once a diagnosis is made unless the underlying cause can be corrected, such as weight loss, or tonsillectomy if appropriate. As patients are known to struggle on initiation of therapy care needs to be taken with education and encouragement to persevere. (3)

This can be achieved with greater awareness of the benefits of treatment, which has been shown to improve dyspnoea during sleep, sleep quality, reduce hypertension, improve cognition, mood and quality of life. (5,15) It also improves driving safety. (5)

It is the clinicians' responsibility to tell the patient that they must inform the DVLA once a diagnosis of OSA is made. However, it is the responsibility of the patient to actually inform them, and usually they will be asked to stop driving until their symptoms are controlled. (3)

CPAP withdrawal is thought to lead to rapid recurrence of OSA with not only return of subjective sleepiness, but is associated with impaired endothelial function, increased urinary catecholamines, hypertension and heart rate. (16)

Screening

The fact that OSAHS is easily treatable and treatment if effective in preventing adverse long-term morbidity, better detection methods are needed to improve accurate diagnosis. A large Danish study concluded that patients with sleep disordered breathing show significant morbidities at least 3 years prior to their diagnosis, with evidence suggesting that particular emphasis for screening should be placed in endocrinology and metabolic specialities. (17)

Several tools are available to help screen patients and perhaps the most widely used and accepted is the Epworth Sleepiness Scale (ESS). This is an effective short scale used to determine excessive daytime sleepiness, with a score above 10 indicating higher than normal somnolence and need for further investigation. However, the Berlin Questionnaire, STOP-Bang Questionnaire (SBQ), and STOP questionnaire are becoming increasingly popular.

There are only a few studies comparing the effectiveness of these tools. One Egyptian study concluded the sensitivity of Berlin, STOP and STOP-Bang questionnaires was very high, yet, the low specificity resulted in increased false positives and failure of exclusion of individuals at low risk. (18) Luo et al found that the STOP-Bang questionnaire has superior predictive value compared with ESS, Berlin Questionnaire and STOP questionnaire and proposed further use for screening for OSAHS in the general population. (19)

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Most tools are readily accessible on the internet and particularly British Lung Foundation websites which can calculate the STOP-Bang and ESS score immediately. Hopefully with better awareness and increased screening, the large proportion of undiagnosed patients, particularly those from ethnic minority backgrounds, can receive the appropriate treatments. 'Few other medical treatments produce such profound improvements in Quality of life, social functioning and relationships' (3).

MCQ's

1: Which of the following interventions is not recommended in the treatment of obstructive sleep apnoea?

a) CPAP
b) Weight Loss
c) Nocturnal Oxygen
d) Reduction of alcohol intake
e) Treatment of modifiable cardiovascular risk factors

2: What is the gold standard diagnostic test to diagnose OSAS?

a) Polysomnography
b) Pulmonary Function Tests
c) Epworth Sleepiness Scale
d) History and examination
e) Limited sleep studies

3: A patient presents with severe daytime somnolence and a diagnosis of severe OSAS is made with CPAP commenced. What advice regarding driving must you give this patient?

a) Continue to drive do not inform the DVLA
b) Inform the DVLA and continue to drive
c) Inform the DVLA and stop driving for 1 year
d) Inform the DVLA and stop driving until you have been adequately treated and reassessed
e) Inform the DVLA and stop driving for 1 month

4: OSAS patients are at increased risk of which of the following?

a) Hypertension
b) Stroke
c) Sudden Cardiac Death
d) Road traffic accidents
e) All of the above

5: A 52 year old male is started on CPAP for severe OSAS. His symptoms rapidly improve and he enquires about how long he requires the treatment for. How would you advise?

a) Stop when symptoms completely resolved
b) Stop after 6 months of therapy
c) Review in one year with a view to withdrawing therapy
d) Lifelong therapy
e) Stop one month after resolution of symptoms

Answers

1: C
Nocturnal oxygen is not recommended for any severity of OSAS. CPAP is the recommended treatment for patients with moderate or greater OSAS if tolerated (20). Weight loss of >10% has been demonstrated to improve sleep patterns, apnoeas and daytime somnolence. Reduction of alcohol intake helps maintain the structural integrity of the airway at night. OSAS is linked to increased cardiovascular morbidity and mortality (21) and investigation and treatment of modifiable risk factors is advised.

2: A
The gold standard investigation for suspected OSAS is Polysomnography which involves overnight monitoring in a sleep centre with measurement of multiple variables including apnoeas, oxygen saturations, snoring, electroencephalogram and thoracic movements (22). A more available method is a limited sleep study measuring overnight desaturations which is often sufficient. History, examination and Epworth Sleepiness Scale are useful in grading daytime somnolence but are not diagnostic. Pulmonary function tests are not required for the diagnosis of OSAS.

3: D
It has been demonstrated that patients with OSAS are at a significantly increased risk of road traffic accidents (23). Current advice is that when OSAS is diagnosed the patient must inform the DVLA (24). A DVLA assessment will be made and if daytime somnolence is deemed significant enough to increase risk the patient is not to drive until they have received adequate treatment and have been re-assessed by the DVLA.

4: E
Patients with recurrent nocturnal hypoxaemia are at increased risk of all of the above and many other conditions including pulmonary hypertension and cardiac failure (5). Early recognition and diagnosis of OSAS is therefore essential as effective treatment is available.

5: D
In the majority of patients commenced on CPAP for OSAS the therapy is lifelong with rapid recurrence of symptoms on withdrawal (16). An exception is when risk factors have been reversed; for example tonsillectomy or significant weight loss.

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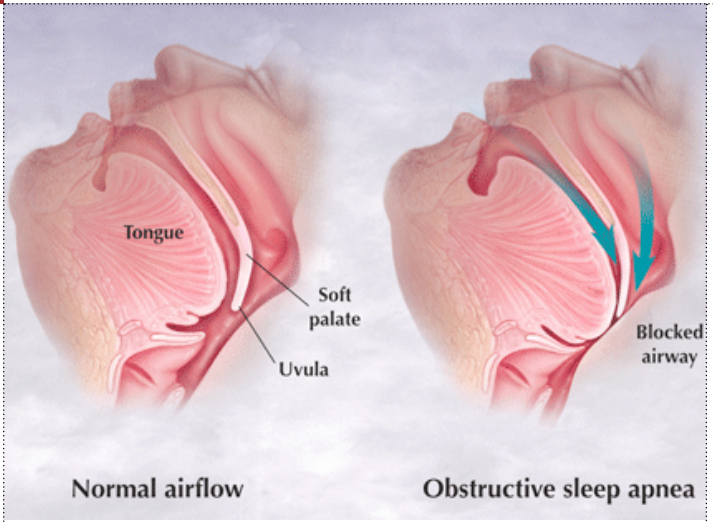

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HYPERSENSITIVITY PNEUMONITIS

H Quin, M Babores, S Iyer & R Trafford

Hypersensitivity Pneumonitis
Patient Management

Abstract

A 63 year old female with a previous radiological diagnosis of hypersensitivity pneumonitis (HP) presented to the Accident and Emergency Department for the third time in 8 years. No known allergen had been identified. She complained of progressive shortness of breath, a dry cough and a significant reduction in exercise tolerance.

Salient investigations included an arterial blood gas (ABG) which confirmed hypoxia and a high resolution CT (HRCT) scan of the chest revealing bilateral interstitial pulmonary infiltrates. A diagnosis of recurrent HP was made and the allergen identified as goose feather from household bedding products.

HP is a relatively uncommon, yet important cause of progressive breathlessness. It is caused by recurrent inhalation and sensitisation to certain allergens resulting in a hypersensitivity reaction. It is treated with oral corticosteroids. If left untreated it can progress to irreversible pulmonary fibrosis. Identifying the allergen to facilitate allergen avoidance is crucial to its management.

This case highlights the process of investigating and managing patients with HP, the challenges of identifying the responsible allergen and how this impacts patient prognosis.

Case history

A 63 year old lady presented to A&E with a four month history of progressive breathlessness and associated reduction in exercise tolerance, dry cough and lethargy. She had been treated for a lower respiratory tract infection by her GP with a two week course of antibiotics with little symptomatic benefit. She reported no haemoptysis, weight loss or chest pain. She is a lifelong non-smoker and a retired cleaner. She lives alone with no pets or birds and has no history of asbestos exposure or occupational chemical exposure.

Past medical history includes two episodes of HP (2006 and 2012), treated with a prolonged course of oral corticosteroids. Otherwise she has GORD for which she takes Lansoprazole.

Examination

On presentation to A&E, oxygen saturations were 87% on air, with a raised respiratory rate of 20 per minute. She was apyrexial and haemodynamically stable. Systemic examination revealed no evidence of finger clubbing, but bi-basal fine inspiratory crepitations on auscultation of the chest. Heart sounds were normal and there was no pedal oedema.

Investigations

Routine Investigations were organised in order to rule out other causes of breathlessness.

ABG showed a pO_2 of 8.3kPa and pCO_2 of 5.0kPa. Chest X-ray showed a subtle increase in interstitial shadowing bilaterally (Figure 1). Blood tests were unremarkable with a WCC of 7.4 x 109/L and CRP of 11mg/L.

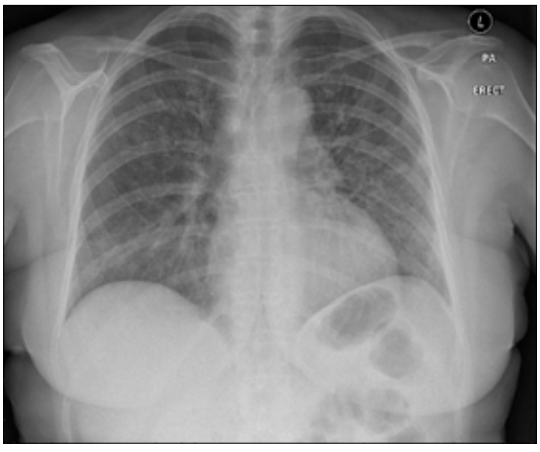

Figure 1

HYPERSENSITIVITY PNEUMONITIS

H Quin, M Babores, S Iyer & R Trafford

The differential diagnoses for hypoxia and bilateral chest x-ray changes are broad and include viral and atypical pneumonia, pulmonary oedema, idiopathic pulmonary fibrosis, Cryptogenic Organising Pneumonia (COP), pulmonary haemorrhage, eosinophilic pneumonia and drug induced lung disease. However, in the clinical context of the insidious onset of symptoms, previous HP and absence of infective symptoms/ biochemical changes, HP was felt to be the most likely diagnosis.

Specialised tests

With a presumptive diagnosis of recurrent HP having been made, it was prudent to then tailor the ongoing investigations in order to confirm this. This is vital in ensuring that all efforts are made to prevent long term damage developing in the form of irreversible pulmonary fibrosis as a consequence of untreated HP.

Imaging

High resolution CT scanning (HRCT) is considered pivotal for investigating interstitial lung disorders. The thinly sliced images HRCT produces allows a more accurate assessment of the interstitium: the alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues. The HRCT in this case showed 'diffuse interstitial infiltrates and groundglass shadowing in both lungs'. (Figure 2)

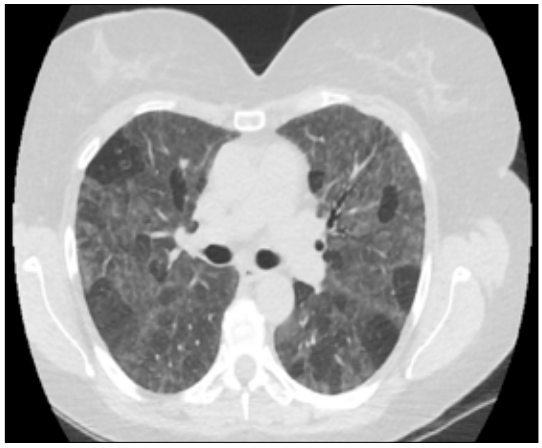

Figure 2: Pulmonary Function Tests.

Pulmonary function tests can aid diagnosis by characterising whether there is an obstructive or restrictive pattern of disease and whether this is causing impaired gas exchange within the lungs.

As expected the results in this case confirmed a restrictive deficit with a forced expiratory volume in 1 second/ forced vital capacity (FEV1/FVC) ratio of >70%. Gas exchange was markedly reduced with a transfer factor (TLCO) of 26% predicted. (Figure 3)

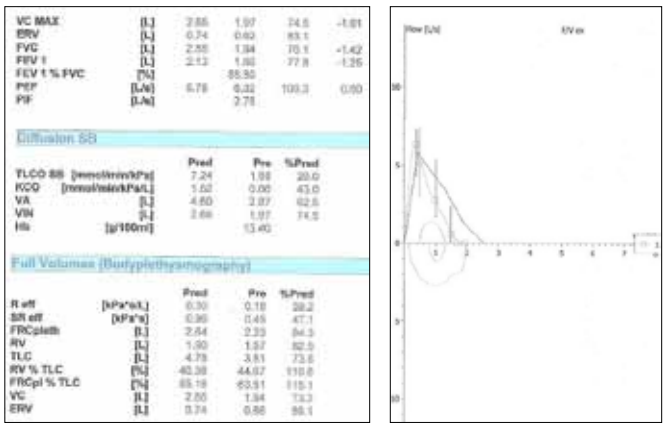

Figure 3: Bloods.

Serum precipitins can be sent which identifies levels of IgG antibodies against mycospora faeni (farmer's lung) and avian precipitans (bird fancier's lung). The presence of antibodies however may only indicate previous exposure and sensitisation in healthy individuals and conversely may not be detectable in those with HP. Despite this however, positive results and high titre levels can be useful in supporting the diagnostic process. (1-4)

Bronchoscopy

This can be performed to obtain a bronchial-alveolar lavage (BAL). The BAL can generate a differential cell count, with a lymphocytosis (20-50% of the white cell count) expected in HP. This is not however unique to HP. (1)

HYPERSENSITIVITY PNEUMONITIS

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Lung or transbronchial biopsy

This is generally not required to make the diagnosis of HP, however is useful when clinical doubt is present.

Our patient underwent a lung biopsy which confirmed the characteristic changes of HP: 'thickening of the interstitium with a mild chronic inflammatory cell infiltrate and mild fibrosis suggestive of HP'.

Treatment

The mainstay of treatment for HP is oral corticosteroids (prednisolone) and allergen avoidance. The corticosteroids are normally commenced at a high dose for a month (40-60mg dependent on symptom severity) and then weaned down over several months. Regular outpatient review is required during the period of weaning to ensure symptoms remain controlled on the reducing dose of corticosteroid.

Patients must be commenced on bone prophylaxis in the form of a bisphosphonate and a proton pump inhibitor to counteract the common side effects of osteoporosis and gastric reflux disease. Conventional corticosteroid information should be given in relation to corticosteroid cessation, increased infection rates and thin skin and easy bruising. The patient was commenced on 40mg of Prednisolone and noticed a rapid improvement in her symptoms.

Progress

Several months later our patient was seen in the outpatient clinic and had been successfully weaned off corticosteroids. On further questioning it transpired that prior to the first episode of HP in 2006 she had bought a new duvet made of goose feathers prior to her becoming unwell and had also bought new goose feather pillows prior to the latest flare of HP.

With allergen avoidance and steroid therapy her pulmonary function tests and HRCT appearances continue to improve. She remains well from a symptomatic perspective and remains under regular outpatient follow up.

Discussion

HP is a spectrum of immune mediated disorders causing diffuse inflammation of the terminal bronchioles, alveoli and interstitium. Inflammation is caused by prolonged or frequent exposure to an inhaled allergen, generally less than 5 µm in size to which a person becomes sensitised. The pathophysiology of HP is poorly understood and lies between a type IV (T-cell mediated) hypersensitivity reaction and a type III (antibody-antigen immune complex formation) hypersensitivity reaction.

Antigens can be divided into: organic dusts (dairy and grain products, animal dander and proteins, wood bark, water reservoir vaporisers, fungi), animal proteins (bird serum, faeces or feathers), and low-molecular-weight chemicals (isocyanates, zinc, and nickel). These most commonly manifest as farmer's lung, bird fancier's lung, and chemical worker's lung, respectively. (1, 2, 5-7).

HP appears to be more common in non-smokers and occurs in people in their 40s-60s. (8-9) Risk factors include pre-existing lung disease, bird keeping, regular use of hot tubs and occupational exposure eg. Farmers (2) At least 8% of budgerigar and pigeon keepers and 5% of farmers are known to have developed HP. (8) Exposure has been known to come from down related products rather than direct bird exposure, as described in the case study.

It can be divided into acute, sub-acute and chronic progressive forms which have varying symptoms and prognostic implications (Box 1). Acute HP reflects a short period of exposure to a high dose of the antigen, which usually responds well to corticosteroids. Subacute/ intermittent HP normally has an insidious onset of symptoms with frequent acute reactions. Chronic HP refers to a longer period of exposure to a lower dose of antigen and tends to be less responsive to treatment. (1, 10-11)

Acute
- *Onset within 8 hours of exposure to allergen*
- *Breathlessness, dry cough and flu-like symptoms*
- *Symptoms related to level of exposure*
- *May see a rise in inflammatory markers*

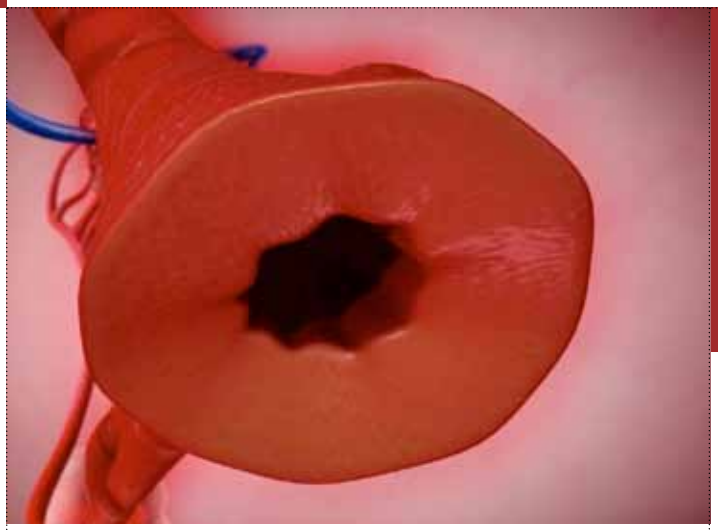
Sub-acute/Intermittent
- *Symptoms less severe than acute reaction*
- *More insidious onset*
- *Productive cough, breathlessness, fatigue and weight loss*
- *Acute flare ups may occur*
- *Symptoms resolve over weeks to months with treatment*

Chronic
- *Weight loss*
- *Reduced exercise tolerance due to breathlessness*
- *May have no identifiable acute episodes*
- *Can develop cor pulmonale and pulmonary fibrosis*
- *Less responsive to corticosteroid treament*

Box 1

HYPERSENSITIVITY PNEUMONITIS

H Quin, M Babores, S Iyer & R Trafford



As in the case study, the patient had recurrent exposure to high dose allergen and progressive symptoms. This is more suggestive of a sub-acute HP picture. It is felt that intermittent high dose allergen exposure is less likely to progress to chronic fibrosis than low dose chronic allergen exposure. This highlights the importance of identifying the allergen in treating patients with HP to improve their overall prognosis.

Summary

This case emphasises the importance of identifying the allergen early on in patients diagnosed with HP in order to prevent recurrent exposure and associated flare ups of the disease. It also highlights the value of history taking and to remember to ask about bedding products when seeing patients with HP. In view of the long list of potential triggers for HP the value of a thorough occupational and social history (including hobbies outside the home) should be stressed as part of the assessment of potential allergen triggers.

MCQ's

Test Yourself

1) A 60 year old farmer presents to respiratory clinic with an 8 week history of progressive dyspnoea and dry cough. Past medical history includes hypertension and ischaemic heart disease. He is a current smoker. He is diagnosed with 'Farmer's lung' what is the most likely causative organism? Choose ONE correct answer.

A. Micropolyspora faeni
B. Thermoactinomyces vulgaris
C. Aspergillus clavatus
D. Klebsiella pneumoniae
E. Streptococcus pneumoniae

Hypersensitivity Pneumonitis
Patient Management

Micropolyspora faeni bacterium is a Gram-positive rod commonly responsible for 'Farmer's Lung' after handling of mouldy hay or hay dust. Infection causes a type III hypersensitivity reaction and leads to the clinical picture of progressive breathlessness, dry cough and systemic symptoms such as weight loss, arthralgia and pyrexia. Up to 5% of farmers with exposure to hay may develop Farmer's Lung.

2) A 48 year old pigeon keeper is diagnosed with hypersensitivity pneumonitis and is commenced on corticosteroids after initial investigations have been performed. She is normally fit and well with no past medical history. She takes no regular medication and is a non-smoker with no passive exposure. Which ONE of the following is most likely to represent her initial pulmonary function testing prior to steroid treatment.

A. FEVÐ/ FVC 0.54,TLCO (transfer factor) 98%,TLC (total lung capacity) 111%
B. FEVÐ/FVC 0.54, TLCO 31%, TLC 111%
C. FEVÐ/FVC 0.80, TLCO 31%, TLC 73%
D. FEVÐ/FVC 0.80, TLCO 98%, TLC 73%
E. FEVÐ/FVC 0.54, TLCO 98%, TLC 111%

Hypersensitivity pneumonitis typically causes a restrictive deficit on pulmonary function testing with a FEVÐ/FVC ratio of greater than 0.70%. Obstructive lung disease such as chronic obstructive pulmonary disease (COPD) is characterised by a FEVÐ/FVC ratio of less than 0.70. Transfer factor (TLCO or DLCO) is a measure of how well oxygen from the alveoli is transferred into the blood.

In active hypersensitivity pneumonitis the gas transfer (TLCO) would typically be reduced due to active inflammation and impairment of gas exchange across the alveolar wall.

Many lung diseases can reduce the transfer factor including pulmonary embolism, COPD and pulmonary hypertension.

Due to the restrictive nature of the disease we may expect lung function to show a reduced total lung capacity but this is not always the case.

HYPERSENSITIVITY PNEUMONITIS

H Quin, M Babores, S Iyer & R Trafford

Answers

1. A

Micropolyspora faeni

2. C

FEVĐ/FVC 0.80, TLCO 31%, TLC 73%

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INVESTIGATIONS & MANAGEMENT OF LUNG CANCER

JA Kastelik, M Abeer & J Morjaria

Abstract

Lung cancer is the second most common cancer diagnosed in the UK. The investigations and management of patients with lung cancer remains complex. In the UK it involves a multidisciplinary team approach, which includes close working between respiratory physicians, oncologists, cardiothoracic surgeons, radiologists, histopathologists, palliative care team and specialist nurses. The investigations of patients with lung cancer have also become multifarious, as new technologies such as positron emission tomography scanning, endobronchial or endoscopic ultrasound have acquired wider use.

Moreover, the management of patients with lung cancer has become more complex as new chemotherapy and radiotherapy modalities have been developed. The understanding therefore of the modes of presentation of patients with lung cancer is pivotal as it may result in early detection. Moreover the awareness of investigational pathways and therapeutic options remains an important aspect of managing this devastating condition.

Introduction

Lung cancer is second most common cancer with over 40,000 people diagnosed each year with this neoplasm and around 35,000 people dying from this disease in the UK (1). Majority of patients with lung cancer present in more advanced stages of the disease with estimates from the Lung Cancer UK suggesting that only approximately 5% of lung cancer patients in the UK would be expected to survive 10 or more years (2).

Management of lung cancer has become more intricate over the years. In the UK, it involves a multidisciplinary team approach, which includes close working between respiratory physicians, oncologists, cardiothoracic surgeons, radiologists, histopathologists, palliative care specialists and specialist nurses (3).

In addition, multidisciplinary teams are supported by an administrative team managing the lung cancer pathway and co-ordinating patients' investigations and care. The investigations of patients with lung cancer have also become more complex as new technologies such as positron emission tomography (PET) scanning, endobronchial or endoscopic ultrasound (EBUS, EUS) have acquired wider use. In this review we will discuss the up to-date approach to investigations and management of patients with lung cancer.

Pathology of lung cancer

Smoking is the commonest cause of lung cancer with smokers having approximately ten fold increased risk of developing lung cancer compared with nonsmokers. Other contributing risk factors for lung cancer include exposure to passive smoking, asbestos and radiation. Therefore it is important to document any of the risk factors when assessing patients with lung cancer (3). In broad terms lung cancer can pathologically be divided into small cell (SCLC) and non-small (NSCLC) (4). In the UK approximately 12% of lung cancer cases are SCLC with the remaining being NSCLC. NSCLC could be further subdivided into adenocarcinoma (40%), squamous cell carcinoma (30%) and large cell (9%) (1,4).

Adenocarcinoma also includes a subtype that used to be called bronchoalveolar cell carcinoma (5). The diagnosis is made by a microscopic examination of the specimens, which may be sufficient in a proportion of cases to confirm the sub type of lung cancer. However, it is accepted practice that additional immunohistochemistry techniques be used to provide further information. Thus, the use of thyroid transcription factor (TTF)-1, p 63 or cytokeratin 5/6 can help to classify the type of cancer namely assisting in distinguishing between squamous cell and adenocarcinoma (4,5).

Besides the above mentioned subtypes less common cancers such as carcinoid can be diagnosed in the lungs6. NSCLC that is not of squamous cell type are now routinely analyzed for Epidermal Growth Factor (EGFR) and aplastic lymphoma kinase (ALK) gene mutations as the presence of these can help with directing specific types of chemotherapy (6,7). ALK genes encode for tyrosine kinase. EGFR belongs to family of transmembrane receptor tyrosine kinase. Mutations in exon 19 and 21 hyper activate the EGFR tyrosine kinase making cancer cell survival dependent on EGFR oncogenic pathways (6,7).Therefore if EGFR mutations are present within cancer, its inhibitor may be used.

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Staging of NSCLC is based on TNM system (Tumour size, Lymph node involvement, Metastasis), which subdivides cancer into stages 1 to 4 depending on the size of the lung lesion, involvement of the lymph nodes and spread to other organs (8). Thus lung cancer when there is no lymph node involvement (N0) and there is no evidence of distant metastases (M0) would be staged depending on the tumour size as T1 (T1a when the tumour is smaller than 2cm in size and T1b when the size is between 2 cm to 3 cm), T2 (T2a when the tumour is size between 3 cm to 5 cm and T2b when the tumour is size between 5 cm to 7 cm), T3 when the tumour is greater than 7 cm in size or there is more than one tumour nodule in the same lobe or the tumour invades the chest wall and T4 when the tumour invades the mediastinum, the hear, the great vessels, the trachea, spinal vertebrae or is present in more than one lobe of the same lung.

The nodal involvement is staged as N1 when the lymph nodes close to the lung are involved, N2 when the ipsilateral mediastinal lymph nodes are involved and N3 when the contralateral mediastinal or hilar lymph nodes or the cervical lymph nodes are affected. Distal metastases are defined as M1b by the presence of the tumour in the distant organs e.g. the liver, the adrenals, the bones or M1a when the neoplasm is present in both lungs or there is a presence of malignant pleural or pericardial effusion. In contrast SCLC is subdivided into limited and extensive stage although more recently the use of the TNM system has been recommended.

Clinical presentation

When assessing patients with a suspected lung cancer it is important to document a history of cigarette smoking, which is the main risk factor for developing lung cancer. However, it is also essential to be aware that the epidemiological studies showed that 10% to 15% of lung cancer cases may occur in patients who never smoked (3). Many symptoms of lung cancer unfortunately, occur when the disease is advanced and treatment options are limited (9).

Despite the advances in chemotherapy and radiotherapy techniques surgery remains the only potentially curative intervention in the context of lung cancer. Surgery can only be offered if lung cancer is diagnosed in the early stages. Therefore there are suggestions that patients at higher risk groups such as those aged 55 to 74 years with a 30 pack years history of smoking or up to 15 years ex smokers should undergo regular screening for lung cancer (10). Currently in the UK there is no lung cancer screening program.

Some of the common symptoms associated with lung cancer include cough, dyspnoea haemoptysis or localized chest pain (3). Many of these symptoms may be related to other disorders caused by cigarette smoking such as chronic obstructive pulmonary disease (COPD) or cardiac diseases. In the context of lung cancer, dyspnoea may be related to external compression by the neoplasm or endobronchial narrowing of lumen of the airways leading to segmental or lobar collapse. In advanced stages of lung cancer patients may present with a pleural effusion or lymphangitis carcinomatosa, which also can cause breathlessness.

In addition, lung cancer may affect the phrenic nerve leading to diaphragmatic paralysis culminating in dyspnoea. Hoarseness is another symptom due to cancer affecting left recurrent laryngeal nerve resulting in vocal cord palsy. When cancer compresses onto the superior vena cava (SVC) patients can present with facial and upper limbs swelling, distended chest veins, characteristic plethora and dizziness or headache so called SVC obstruction syndrome. Pancoast's or superior sulcus tumour can present with Horner's syndrome, wasting of the small muscles of the hand and shoulder pain due to invasion by the cancer of the brachial plexus, spine or ribs.

In advanced disease when cancer metastasizes to other organs such as bones, liver or brain, patients can present with symptoms such as bony pain, pathological fractures, cord compression, jaundice, headaches, seizures or localized neurological deficit. The presence of cord compression is a medical emergency and needs to be recognized early. Hence symptoms such as spinal pain, weakness, incontinence or sensory level should raise suspicion and urgent investigations including an MRI of the spine should be considered (11).

Paraneoplastic syndromes related to lung cancer include endocrine abnormalities such as hypercalcaemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing's syndrome, haematological abnormalities for example anaemia, thrombocytosis, hypercoagulation syndromes e.g. superficial thrombophlebitis, deep vein thrombosis (DVT), disseaminated intravascular coagulation (DIC), neurological disorders e.g. Lambert Eaton syndrome, peripheral neuropathy, cerebellar degeneration, limbic encephalitis, cutaneous and musculoskeletal disorders including hypertrophic osteoarthropathy, dermatomyositis or acanthosis nigricans (12).

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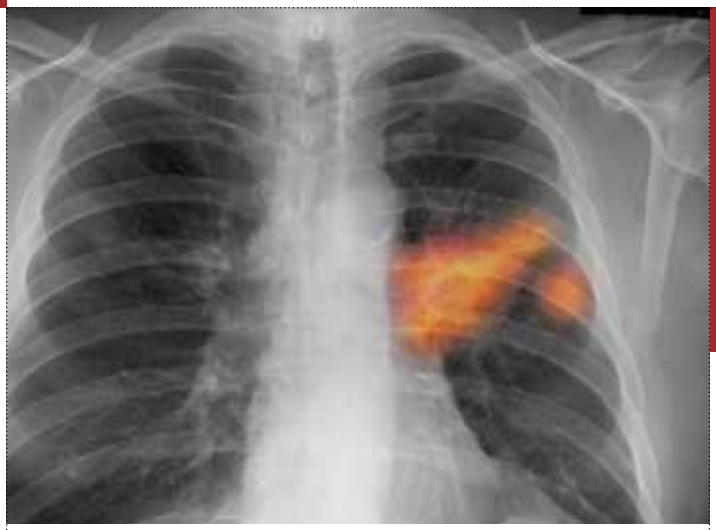

These syndromes can be confirmed through specific testing, for example hypercalcaemia in the context of lung cancer will reveal high serum calcium levels with low or normal serum levels of parathyroid hormone. SIADH can be confirmed by testing serum and urine osmolality and sodium levels. Some of the neurological paraneoplastic syndromes can be confirmed by the presence of specific antibodies such as anti Hu or anti Ri (13).

Clinical examination of patients with suspected lung cancer should involve examination of hands for presence of finger clubbing or small muscle wasting suggestive of a Pancoast's neoplasm; facial examination for presence of Horner's syndrome or facial swelling or plethora and distended chest wall veins suggestive of SVC obstruction. Additionally, examination of the neck should be undertaken to assess whether there is any cervical lymphadenopathy.

Clinical examination of the respiratory system may reveal a monophonic wheeze suggestive of possible endobronchial lesion or stridor, which would suggest a lesion within the trachea. Examination of the respiratory system may also suggest lobar collapse or presence of a pleural effusion, and an abdominal examination may reveal hepatomegaly suggestive of liver metastases. Neurological examination may show signs of cord compression or a localized neurological deficit suggesting a central nervous system involvement (13). Occasionally skin metastases can be detected as well as a rash of acanthosis nigricans or dermatomyosistis.

Investigations

Initial investigations of patients with suspected lung cancer include a chest radiograph, a simple spirometry to assess FEV1 and FVC and baseline full blood count and biochemical profile including liver function and calcium levels (14, 15). More importantly, patients would require a staging thoracic computed tomography (CT), which will also assess the major organs such as the liver, the adrenal glands, the kidneys and the pancreas.

In fact, in a proportion of patients lung cancer may be detected when a CT scan is performed for other reasons such as assessment for possible pulmonary embolism or unexplained weight loss (3). CT thorax allows for lung cancer staging, thus tumour size (T) can be determined, as well as the involvement of the lymph nodes (N) and the involvement of the distant organs or the presence of pleural effusion (M) (8).

For a definitive diagnosis of lung cancer, biopsy specimens for histological analysis are essential. Flexible fiber optic bronchoscopy allows for examination and sampling of the lung cancer from the bronchial tree and upper airways. Flexible fiberoptic bronchoscope is composed of glass fibers that allow for the image to be transferred from the bronchial tree to the screen. It also has a working channel that allows for sampling from the bronchial tree. Routinely in patients with suspected cancer samples are collected for cytology (bronchial wash and bronchial brushings) and bronchial biopsies for histological analysis (3).

Bronchial biopsies are performed by passing a small forceps through the working channel of the bronchoscope and taking samples from the suspected areas. Due to the size of the bronchoscope only the main, segmental and occasionally subsegmental bronchi can be sampled. Therefore, for the peripheral lesions other techniques such as CT-guided biopsies may be required. If patients have evidence of liver metastases, ultrasound-guided liver biopsy may be performed. Similarly, in patients with neck lymphadenopathy, ultrasound-guided lymph node fine needle aspiration (FNA) or true cut biopsies can be undertaken. In patients with skin metastases cutaneous FNA can provide a diagnosis.

PET scan can help to evaluate the mediastinal and cervical lymph node involvement as well as assess the presence of distal metastases (16). Currently most of the scans incorporate integrated CT and PET, which allows to provide both anatomic imaging of the neoplasm and its metabolic activity. PET scans, in the context of lung cancer use tracer 18-Fluoro 2-deoxyglucose (18-FDG), as neoplastic cells are more metabolically active and therefore would uptake more glucose and 18-FDG.

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Areas of infection or inflammation may also show avid 18-FDG uptake making differentiation from cancer difficult. PET scans help to provide more accurate staging of lung cancer as well as diagnosing distant metastases. It is of particular use in staging the mediastinal nodes involvement and is more accurate than CT alone with suggested sensitivity of 74% and specificity of 85% (16). There are also newer techniques that allow sampling of mediastinal lymph nodes such endoscopic ultrasound or endobronchial ultrasound (3).

These techniques use a scope with an ultrasound probe placed at the tip of it, which allows for visualization of mediastinal lymph nodes and sampling them. Using these endoscopic techniques samples may be obtained from subcarinal, paratracheal and mediastinal lymphnodes. The presence of cancer in these lymph nodes will usually prevent surgical resection of lung cancer. Some patients may require cervical mediastinoscopy or video assisted surgery (VATS) to sample paratracheal or mediastinal lymphnodes (3).

Surgery for lung cancer

When making a decision whether surgical resection for lung cancer is possible, firstly it is important to assess whether the patient is fit to undergo surgery. Co-morbidities such as presence of severe COPD and a significant cardiovascular disease may prevent patients from having surgery. It is accepted that patients with FEV1 below 2L and those with an FEV1 below 1.5L may not be fit to undergo pneumonectomy and lobectomy, respectively. Therefore full lung function testing may be required including lung volumes, transfer factor, six minutes or shuttle walk. In borderline cases cardiopulmonary exercise stress testing may be required as patients with VO2 max below 15ml/kg have increased risk of peri-operative complications (15,17).

The second aspect of the assessment for surgical resection includes staging of lung cancer. Thus patients with early stages of NSCLC e.g. stage I and stage II could be offered surgery. Presence of distal metastases, N2 and N3 lymph nodes involvement would usually mean that patients would not be offered surgery (3,15). There are different types of surgery for lung cancer such as lobectomy or pneumonectomy (15). In some patients with marginal lung function a sub lobar resection e.g. segmentectomy can be offered which may be performed using VATS. Lobectomy or bilobectomy carries mortality below 2%. For more central and larger neoplasm pneumonectomy may be required with higher operative mortality at around 5% or slightly higher for right sided pneumonectomy (15).

Radiotherapy

Patients with early stages of non small cell lung cancer who are not fit to undergo surgical resection should be considered for external beam radiotherapy (3). This form of therapy is called radical radiotherapy and involves delivery of between 45 and 66 Gy. The outcomes of radiotherapy in these settings are better than no treatment but much worse compared to surgery with expected 5-year survival of 20%.

An accelerated form of radiotherapy so called Continuous Hyperfractionated Accelerated Radiotherapy (CHART) which involves 12 days treatment of 54 Gy has also shown of benefits (19). More recently stereotactic body radiation therapy (SBRT) has been used especially for smaller peripheral lesions (20). This form of radiotherapy uses higher doses of radiotherapy in lower number of treatments, thus resulting in higher neoplasm killing effect. The studies have shown that overall survival at three years at around 53% (20). In a subgroup of patients with good performance status and locally advanced lung cancer, concomitant chemotherapy and radiotherapy have been shown the most beneficial treatment approach.

Chemotherapy

The SCLC is managed differently to the NSCLC, as although the TNM staging can be applied, an alternative classification is frequently used that classifies patients into limited and extensive stages (21). Limited disease is usually present when disease is within the ipsilateral lung and within a single radiation port. In a small proportion of SCLC patients, mainly those where an early lung cancer is resected without prior histological diagnosis, may undergo surgery (22). These patients have been shown to have better survival probably due to early stages of the disease. However in the majority of patients with SCLC chemotherapy is the main therapeutic option. Unfortunately, as SCLC is very aggressive, survival in untreated patients is limited usually to a few months.

Despite SCLC is being chemotherapy sensitive, the five-year survival is relatively poor with 10% and 2% for limited and extensive disease respectively (3). There are varied regimes of chemotherapy used most incorporating platinum-based agents and etoposide. Patients with limited stage of disease would be offered combination of chemotherapy and thoracic radiotherapy, as well as prophylactic cranial irradiation (3, 23).

Patients with extensive disease especially those who responded to chemotherapy, can also be considered for thoracic and cranial radiotherapy (3). In the context of NSCL chemotherapy can be offered to patients with good performance status who have inoperable disease (3). In a proportion of patients with NSCLC size of 4cm or greater a post operative chemotherapy can be offered as it has been shown to improve 5 year survival by 4% (3,24).

INVESTIGATIONS & MANAGEMENT OF LUNG CANCER

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Investigations & Management Of Lung Cancer
Patient Management

In recent times the management of lung cancer has become very complex involving close collaboration between a number of specialists forming a multidisciplinary team, which co-ordinates the investigations and decides on the potential therapies for each individual patient. The management pathways as well as involvement of multiple professionals would not only provide a smooth patient journey but also optimism if this condition is diagnosed at an early stage.

The patient journey

Most patients with suspected lung cancer in the UK consult their GP usually with symptoms such as cough, haemoptysis, breathlessness or weight loss. The GP would order an urgent chest radiograph and if this raises suspicion of lung cancer the patient will be referred urgently to a secondary care respiratory physician to undergo urgent investigations.

In the UK the Department of Health recommends that patients with lung cancer should receive treatment within 31 days from diagnosis, a maximum total of 62 days from their referral. Patients will have investigations such as CT or PET scan, a CT guided biopsy, bronchoscopy or EBUS/EUS25. In some patients ultrasound guided biopsy of the neck lymph nodes or liver biopsy may provide diagnosis.

Once diagnosis is confirmed each case will be discussed at a lung cancer multi disciplinary team (comprising of respiratory physician, oncologist, radiologist, thoracic surgeon and specialist nurses) meeting and decision with regards to the treatment will be made. During a patient's journey the MDT will support the patient and co-ordinate the investigations with the main aim being the provision of patient centered care based on good communication, timely investigations and treatment (3). The role of the Cancer Nurse Specialist is paramount here with regards to communication, information, support and co-ordination of investigations and patients' care (26).

Conclusions

The awareness of potential symptoms with which patients may present is pivotal as appropriate and rapid investigative pathways may result in early detection of this devastating condition and possible hope of a treatment to extend survival.

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INVESTIGATIONS & MANAGEMENT OF LUNG CANCER

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MANAGEMENT OF THE CYSTIC FIBROSIS PATIENT IN THE MEDICAL ASSESSMENT UNIT

L Guhaniyogi & J Duckers

Abstract

Cystic fibrosis (CF) is an autosomal recessive multi-system disease that can result in different presentations in the acute setting. Managing CF can be challenging and daunting for the foundation doctor. A stepwise approach, with input from the local CF team, can ensure that patients are managed as a whole. We will discuss the management of common presentations.

Case history

The patient is a 20 year old male presenting with hyperglycaemia, productive cough and abdominal pain.

He has a background of CF with a bilateral lung transplant 6 months ago. He is on Tacrolimus, Mycophenolate Mofetil and Prednisolone for immunosuppression. He has developed diabetes mellitus post transplant, which is managed with insulin. His appetite has been poor and he has not been using his insulin for 5 days. He is constipated and has severe generalised abdominal pain with vomiting.

On examination, the patient was clinically dry. There were audible crepitations at the lung bases. The patient's abdomen was distended and generally tender with no guarding. The patient has a Passport, a totally indwelling venous access device which non trained staff should not try to access, in his left arm. The Passport was clean and patent. He had a percutaneous endoscopic gastrostomy (PEG) tube in situ which looked clean.

His observations showed he was tachycardic, hypotensive and pyrexial. His blood glucose measurement was high.

Blood samples were sent for full blood count, urea and electrolytes, liver function tests and a venous blood gas, all of which were normal. Inflammatory markers were found to be raised. A urine dipstick was negative for ketones.

Management of the cystic fibrosis patient in the medical assessment unit
Patient Management

Abdominal and chest x-rays showed new consolidation and dilated loops of small bowel with faecal loading, suggesting distal intestinal obstruction syndrome. He was commenced on a sliding scale insulin infusion to manage his hyperglycaemia, IV fluids to rehydrate him and regular gastrografin via the patient's PEG to treat the obstruction.

Following a discussion with the CF team, he was commenced on IV tobramycin and meropenem due to previous colonisation with pseudomonas. His trough tacrolimus levels were sub-therapeutic. Oral immunosuppressants were converted to IV following discussion with the transplant registrar.

Within 2 days, his constipation had resolved, his glycaemic control had stabilised and his chest symptoms had improved. Gastrografin was stopped and he was re-established on oral immunosuppressants and a basal-bolus insulin regime. The patient was discharged after 14 days of treatment with follow up.

Discussion

The patient presented with multiple issues, which is a common scenario when patients with CF become acutely unwell.

Managing infective exacerbation of cystic fibrosis

In CF, combination of increased sodium and defective chloride absorption across the airway epithelium results in increased viscous secretions. (2) The accumulation of thick sticky mucus causes chronic infections and bronchiectasis. (2)

An infective exacerbation is defined as an increase in sputum production with a change in the consistency and colour of the sputum. Other symptoms include reduced exercise tolerance, reduced appetite, new chest signs or radiological changes. (1) The most common underlying pathogen is bacterial (2).

Nebulised mucolytics such as hypertonic saline and domase alfa aid mucous clearance. Physiotherapy techniques and positive pressure devices such as acappella are also useful in maintaining mucus clearance. These should be continued during an acute illness.

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Colonisation by bacteria can occur and the most common pathogen is pseudomonas aeruginosa. (1,2) Patients can also grow staphylococcus aureus and haemophilus influenzae. (1) Nebulised, inhaled and oral antibiotics are used to prevent exacerbations and attempt to eradicate the organisms. (1)

All patients should have blood tests for full blood count, urea and electrolytes, liver function tests, inflammatory markers and a blood glucose. A chest x-ray should be performed to identify any new changes. (1) Sputum samples should be sent for culture, sensitivities and acid fast bacilli.

When deciding antibiotic treatment, it is important to take into account the types of organisms previously grown by the patient, allergies, previous responses to antibiotics, current antibiotic regime and local guidelines. (1,2)

Combinations of antibiotics are used to cover multiple organisms and reduce resistance. Current guidelines suggest a combination of a beta-lactam and aminoglycoside (Ceftazidime and Tobramycin) in patients with pseudomonas colonisation. (1,2) Alternatives include Meropenem and Astreonam. (1) Patients with CF are considered to have chronic infection requiring a longer duration of treatment (10-14 days) and higher doses. (1,2)

Patients who have grown staphylococcus aureus recurrently require long term oral Flucloxacillin. (1) In the case of acute infection, the dose is usually increased to 1g four times a day. Patients are usually on a combination of regular inhaled or nebulised antibiotics.

To reduce the risk of toxicity before prescribing IV tobramycin it is important to weigh the patient, check their serum creatinine and stop any maintenance tobramycin. (1)

You should contact the local microbiology and CF team if there are any questions regarding antibiotic therapy.

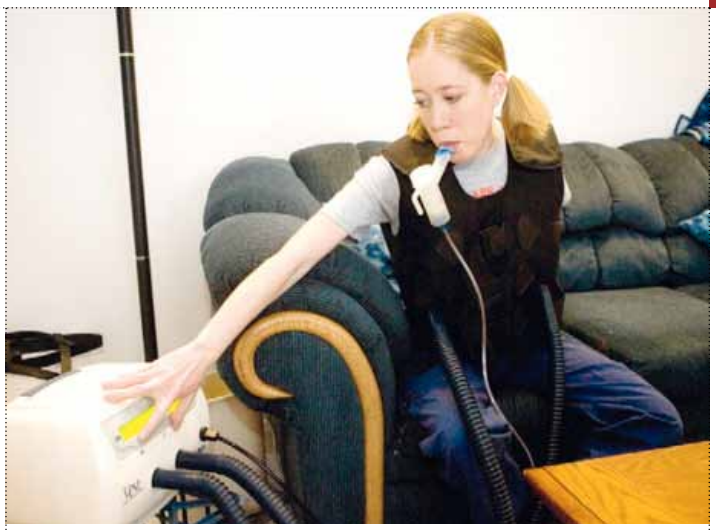
Due to the increased sputum volume and consistency, physiotherapy may be required acutely. If there are concerns, particularly with maintaining oxygen saturations, there will be an on call physiotherapist available out of hours.

Managing abdominal pain in patients with cystic fibrosis

Patients with CF commonly have pancreatic insufficiency. This can lead to malabsorption, constipation and distal intestinal obstruction syndrome (DIOS). (3)

Malabsorption is treated with pancreatic enzyme replacement and it is important to check compliance and bowel habit on admission. (3)

DIOS is unique to CF and is associated with episodes of partial or complete obstruction of the distal ileum and proximal large bowel. (3) This is caused by thickened faecal material that accumulates in the bowel, leading to obstructive symptoms. (3)



Presenting symptoms include intermittent abdominal pain, often localised to the right lower quadrant. (3) There can be vomiting, distension and a palpable mass may be present. (3) Patients may report constipation. (3) Blood tests should be performed to exclude an acute inflammatory process and assess hydration status. (3) An abdominal x-ray may demonstrate proximal faecal loading of the large bowel and small bowel dilatation. (3)

Management includes intravenous fluids for rehydration and laxatives to relieve the obstruction. (3) Gastrografin is effective in relieving the obstruction and polyethylene glycol solution has also been used. (3) Patients should receive their pancreatic enzyme replacement and be encouraged to mobilise. It is important to avoid opioid analgesia for pain as this can exacerbate the obstructive symptoms. (3)

Patients can present with acute appendicitis and pancreatitis so it is also important to assess CF patients as you would any patient with abdominal pain. (3)

Diabetic emergencies in cystic fibrosis

CF related diabetes is a distinct form of diabetes mellitus. It is a combination of impaired insulin secretion and a variable degree of insulin resistance. (4) The mainstay of treatment is with insulin therapy. (4) All patients with CF should have their blood glucose measured on admission. (5)

With increased survival, patients with CF related diabetes can present acutely with diabetic ketoacidosis or with symptoms suggestive of hyperosmoler non-ketotic coma. (5)

Potential underlying causes include infection, poor compliance with medications and poor oral intake with weight loss. (5)

Hyperglycaemia in patients with CF should be managed according to local hospital guidelines. Assessment for underlying ketoacidosis includes a urine dipstick for ketones and a blood gas to assess for acidosis. (5)

MANAGEMENT OF THE CYSTIC FIBROSIS PATIENT IN THE MEDICAL ASSESSMENT UNIT

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Those who present with hypoglycaemia should be managed according to local hospital guidelines. (5)

The transplanted patient

Patient who have undergone transplantation are on a combination of immunosuppressants including corticosteroids. (6,7) It is important to ask about the combination of immunosuppressants and the dosages. Levels should be taken for tacrolimus and ciclosporin on admission but may not fully indicate the degree of immunosuppression (9). Patients should continue on their current dose until a level is available.

It is important to discuss all patients with the transplant centre where the transplant was performed or the centre which cares for the patient. They will also need to be informed of the patient's condition during the admission to advise on monitoring and dosages of immunosuppression.

The dose of corticosteroid is not typically increased during an acute illness. If there are concerns regarding the patient's oral intake then conversion to the IV immunosuppression may be indicated. Local guidelines regarding IV immunosuppression should be available and this should be discussed with the respiratory consultant in charge of the patient's care and the local transplant centre.

Antibiotic treatment depends on previous sputum growths and should be discussed with the transplant centre. (8)

Conclusion

CF is a chronic multi-system disease that can lead to multiple presentations. It is important to fully assess the patient, mange the patient's acute problem and take into account other co-morbidities to ensure holistic management. Patients are often very knowledgeable about their condition and it is always advisable to liaise with the patient's own CF team for advice and for potential transfer, if required, to their local CF centre.

Management of the cystic fibrosis patient in the medical assessment unit
Patient Management

MCQ

1. What underlying genetic inheritance in cystic fibrosis?

a) Autosomal dominant
b) Autosomal Recessive
c) X-linked Recessive
d) X-Linked Dominant
e) Complex inheritance

2. What is the most common pathogen grown in sputum in patients with cystic fibrosis?

a) Staphylococcus aureus
b) Haemophilus influenzae
c) Pseudomonas aeruginosa
d) Klebsiella pneumoniae
e) Stenotrophamonas maltophilia

3. What is the first line antibiotic treatment for infective exacerbations in cystic fibrosis?

a) Ceftazidime and Tobramycin
b) Meropenem and Tobramycin
c) Meropenem and Gentamicin
d) Ceftazidime and Gentamicin
e) Tazocin and Gentamicin

4. What agent is used to relieve obstruction in distal intestinal obstruction syndrome (DIOS)?

a) Osmotic laxatives
b) Phosphate Enema
c) Bulking Laxatives
d) Stimulant Laxatives
e) Gastrografin

MANAGEMENT OF THE CYSTIC FIBROSIS PATIENT IN THE MEDICAL ASSESSMENT UNIT

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5. What is the mainstay of treatment for Cystic Fibrosis Related Diabetes Mellitus?

a) Subcutaneous Insulin
b) Diet Control
c) Metformin
d) Metformin and Subcutaneous Insulin
e) Metformin, Sulfonylurea and DPP-4 inhibitor

Answers

1. Answer: b
Cystic fibrosis is an autosomal recessive condition that leads to the mutation in both genes for the protein cystic fibrosis transmembrane conductance regulator. The gene is found on chromosome 7.

2. Answer: a
Due to the combined insulin resistance and reduced insulin secretion in Cystic fibrosis related diabetes mellitus, subcutaneous insulin is the mainstay of treatment.

3. Answer: c
The most common pathogen grown is pseudomonas aeruginosa. Patients can be colonised in childhood with stahylococcus aureus and haemophilus influenzae.

4. Answer: a
The current guidelines suggest the use of a combination of a beta lactam and aminoglycoside. Ceftazidime and Tobramycin is advised. It is important to take into account any available sputum cultures to guide antibiotic therapy.

5. Answer: e
Gastrografin has proven to be effective in relieving obstruction in DIOS. Patients also benefit from IV rehydration therapy in view of the thickened faecal matter leading to obstruction in DIOS. Mobilisation and pancreatic enzyme replacement compliancy should also be encouraged.

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THE IMPACT OF OBSTRUCTIVE SLEEP APNOEA IN PREGNANCY

A Ainley & HK Makker

The impact of obstructive sleep apnoea in pregnancy
Patient Management

Introduction

Obstructive sleep apnoea (OSA) is a condition of increasing prevalence worldwide. The number of patients affected is likely to continue rising, in keeping with the global epidemic of obesity, one of the conditions strongest risk factors. Over the last decade, there has been an increase in the work done to address the characterisation, investigation and management of patients with OSA as well as to identify the associated co-morbidities which lead to significant morbidity and mortality.

There is evidence linking OSA to an increased risk of hypertension, cardiovascular disease, stroke, pulmonary hypertension and type 2 diabetes mellitus, as well as a reduced quality of life, mood disturbance and increased incidence of road traffic accidents. More recently there has been growing evidence that these risks can be extrapolated to pregnant patients with links being demonstrated between maternal OSA and poor perinatal/pregnancy outcomes. This article will discuss with the use of an illustrative case the current evidence about the impact of OSA on pregnant patients.

Keywords
Obstructive sleep apnoea, pregnancy, consequences.

Abbreviations

Apnoea/hypopnoea index (AHI)
Continuous positive airway pressure (CPAP)
Epworth sleepiness core (ESS)
Function residual capacity (FRC)
Laser assisted uvulopalatoplasty LAUP)
Non-rapid eye movement (NREM)
Obstructive sleep apnoea (OSA)
Obstructive sleep apnoea/Hypopnoea syndrome (OSAHS)
Rapid eye movement (REM)
Polysomnography (PSG)
Uvulopalatopharyngoplasty (UPPP)

Clinical case

A 34 year old lady (KS) is referred to the sleep clinic by her GP. She is in her third trimester of pregnancy and has become concerned regarding the recurrence of disturbed sleep and wonders if her symptoms are due to sleep apnoea.

She was initially diagnosed with OSA at the age of 20. At the time of diagnosis she had been noted to snore and reported increased daytime sleepiness/somnolence. At that point her OSA had been confirmed by sleep studies and it was recommended that she have further intervention although the exact severity of her OSA at that point is not known.

She has never previously received continuous positive airway pressure (CPAP) but had been given advice regarding a reduction in associated lifestyle factors such as weight loss. She had also initially been given non-surgical interventions including a mandibular advancement device/splint and subsequently was referred for radiofrequency tongue base ablation, which she had on two occasions as her symptoms had recurred after the first course.

On assessment she has a BMI of 26.5, Neck size of 13.5 inchs/34.5cms and resting saturations of 98%. Her blood pressure is 122/67. Her Epworth sleepiness score (ESS) is 9. Both her adenoids and tonsils were removed as a child.

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Given her symptoms and previous diagnosis a formal sleep study was arranged and this demonstrated an apnoea/hypopnoea index (AHI) of 60 dips/hour and mean oxygen saturations were reported as being 93% (Figure 1).

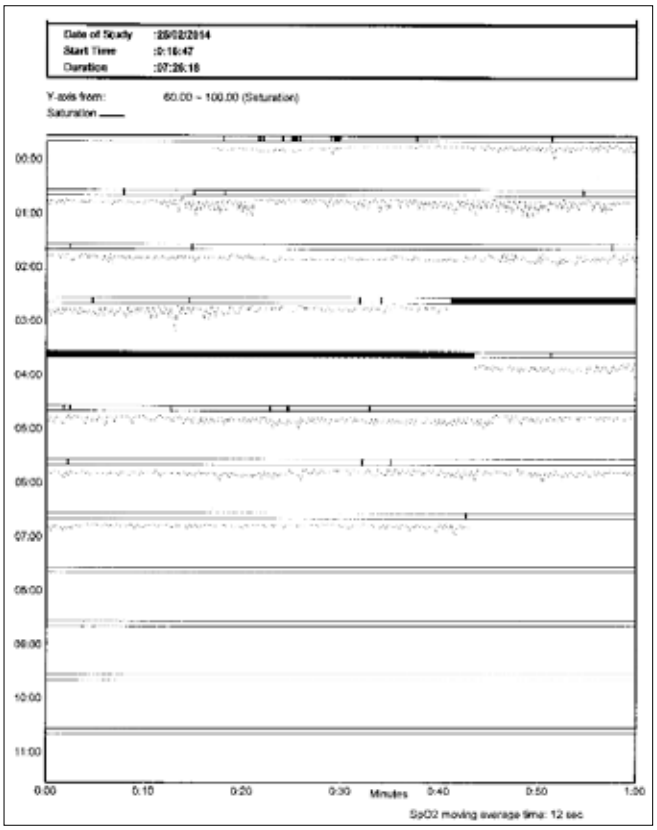

Figure 1: Pulse oximetry sleep study showing recurrent oxygen desaturation - saw-tooth pattern due to recurrent obstructive apnoeas.

Are this lady's clinical features characteristic of OSA?

In light of her investigations and presentation would she benefit from management of OSA and the use of continuous positive airway pressure (CPAP)?

Patient KS reflects some of the complexities in managing this group of patients. Her symptoms of daytime somnolence, snoring and her clinical phenotype are consistent with a diagnosis of OSA. Despite this her ESS does not correlate with significant daytime somnolence, a common finding during pregnancy that will be addressed below.

The limited effect of surgical and non-surgical interventions to control her symptoms and the exacerbation of her pre-existing OSA symptoms during pregnancy reflects current evidence. After diagnosis she went on to use Nasal CPAP which was well tolerated and she had a normal course of pregnancy using this. Her case highlights some of the difficulties faced when investigating and managing OSA in pregnancy. These shall be discussed further in this article and exemplify the need for prompt referral for further assessment in pregnant patients presenting with typical symptoms or common phenotypes.

Obstructive sleep apnoea basics

OSA is a more severe form of Sleep Disorder Breathing, a spectrum of conditions that vary in the degree of airway obstruction including 'simple snoring', upper airway resistance syndrome and obstructive sleep apnoea/hyponea syndrome. Around 1-2% of middle aged women in the UK are affected by OSA (1) and this increases up to 6% in women of reproductive age (2). Whilst being strongly correlated with obesity around 30% of those affected are not obese.

OSA is characterised by periods of complete or partial upper airway obstruction, defined as episodic apnoea (cessation in airflow of > 10 seconds) and/or hypopnoea (>50% reduction in airflow of >10 seconds) which is associated with oxygen desaturation resulting in arousal from and fragmented sleep (detected by electroencephalography). The term OSA is often interchangeable with obstructive sleep apnoea/Hypopnoea syndrome (OSAHS) due to the co-existence of both apnoea and hypopnoea. Episodes are most frequently noted during rapid eye movement sleep and at the beginning of the sleep cycle.

The diagnosis of OSA is made on the basis of commonly associated symptoms, physical characteristics and sleep studies (1). The most commonly reported symptoms include snoring, excessive daytime sleepiness (defined as an ESS>11), mood disturbance, impaired concentration/cognition and witnessed apnoeas. Recognised physical characteristics with increased risk of OSA are those associated with upper airway obstruction including obesity (BMI >30 kg/m^2), enlarged neck circumference (>17inches/43cm) and mallampati scores of grade 3-4 (a visual assessment of the uvula, tonsils and fauces to assess airway size).

Sleep studies are used to further evaluate for the presence of airway obstruction and its impact upon ventilation, oxygen saturations and sleep disturbance, as well as enabling a measurement of severity. Severity is determined by the frequency of apnoea/hypopnoea per hour calculated as the apnoea/hypopnoea index (AHI). Based upon this, OSA is determined to be either mild (AHI 5-14/hr), moderate (15-30/hr) or severe (>30/hr). It is upon this severity in combination with patient symptomology and choice that treatment strategies are decided.

THE IMPACT OF OBSTRUCTIVE SLEEP APNOEA IN PREGNANCY

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Treatment options range from lifestyle changes to non-surgical and surgical interventions and are often influenced by patient choice and tolerance. Lifestyle changes include weight loss, avoidance of sedative medications and alcohol, smoking cessation and are often sufficient in mild severity OSA. For those with Moderate or Severe OSA (AHI >15/Hr) CPAP therapy is recommended (3).

Alternatives include non-surgical interventions such as mandibular advancement devices which mechanically open the upper airway at the level of the pharynx but there is variable evidence about their effectiveness at reducing daytime somnolence or symptoms other than snoring. The evidence for the use of surgical interventions such as uvulopalatopharyngoplasty (UPPP), laser assisted uvulopalatoplasty (LAUP) and radiofrequency ablation is limited and these procedures have often been found to be ineffective with high likelihood of symptom recurrence.

Obstructive sleep apnoea in pregnancy

The exact prevalence of obstructive sleep apnoea in pregnancy is unknown, however 1-2% of middle aged women in the UK (1) and 6% of women of reproductive age (2) are affected by OSA. Existing data is often confounded by small study size, the use of self-reporting screening questionnaires and the limited use of sleep studies to confirm the presence of OSA. Although useful for gauging a patients (5) perception of sleepiness, screening questionnaires for sleep apnoea including the Berlin questionnaire and the ESS have been shown to have a poor sensitivity and specificity in women compared to men and poorly correlate with severity of OSA (1,4).

Despite this there is evidence that the incidence of symptoms such as snoring and daytime somnolence, as well as associated risk factor physical characteristics, are more commonly seen in pregnant women compared to non-pregnant patients suggesting an increased prevalence of OSA is likely. Whilst evidence about the overall prevalence of OSA in pregnancy is limited, there is evidence that patients with pre-existing OSA develop an increased severity during pregnancy as a result of the accompanying hormonal and physical changes of pregnancy.

The impact of obstructive sleep apnoea in pregnancy
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How does pregnancy increase the likelihood of OSA?

A number of physiological changes that occur during pregnancy have been attributed to the predisposition of pregnant women to either newly develop or exacerbate pre-existing OSA symptoms/severity.

1: Impact on upper airway obstruction

Neck circumference and upper airway patency are associated predictors of OSA. During pregnancy there is evident weight gain and it has been frequently demonstrated that there is a reduction in pharyngeal airway size with upper airway narrowing (6). This is most commonly noted in late gestation but it has been shown that this often improves post-delivery reflecting a temporary effect of pregnancy.

2: Impact upon ventilation and pulmonary function

Although OSA is strongly associated with obesity in non-pregnant patients the physiological changes that pregnant patients undergo have been shown to mimic the impact of obesity via an increase in intra-abdominal cavity dimensions that occurs to facilitate foetal growth and increases in visceral fat.

(a) **(b)**

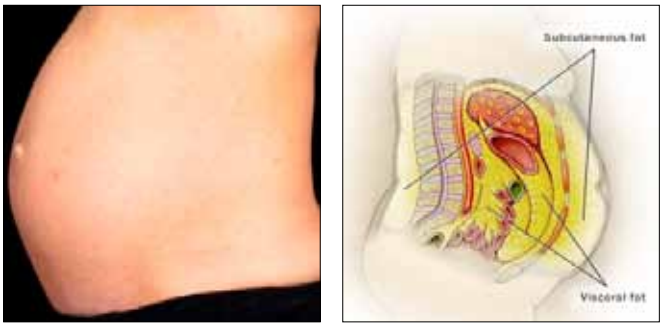

Figure 2: Abdominal distension due to an increase in intra-abdominal contents (a) pregnancy and (b) visceral obesity. (Source: (a) Ann Dermatol. 2011 Aug; 23(3): 265–275 (b) http://www.weightlossforall.com/fat-storage-visceral-fat-x.htm.

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These changes have been found to cause an elevation of the diaphragm and it has been demonstrated that this diaphragmatic elevation can lead to a 20% reduction in Function Residual Capacity (FRC) (6). This reduction is in excess to the fall in FRC which has been reported in non-pregnant patients during normal sleep. The excess reduction in FRC leads to a reduced maternal oxygenation via limited gas exchange and subsequent desaturation; this is exacerbated when lying in the supine position.

A reduction in lung volumes ultimately leads to a ventilation-perfusion mismatch and eventually a reduction in maternal oxygenation may in turn affect oxygenation of the placenta and foetus. This may further exacerbate a marked nocturnal hypoxia which has been noted in pregnant patients without OSA, particularly during sleep. It occurs most notably during the third trimester where studies have demonstrated mean saturations of <90% for more than 20% of the night (7).

3: Impact of hormonal changes seen in pregnancy

Whilst hormonal changes are necessary to help maintain a viable pregnancy, there is evidence that the accompanying increase in levels of oestrogen and progesterone can affect the respiratory drive. Progesterone has been shown to act upon the central chemoreceptors leading to an increased respiratory drive and subsequent hypocapnia and compensatory resting respiratory alkalosis (5). Although not conclusively proven during pregnancy, in non-pregnant individual's hypocapnia and compensatory alkalosis have been shown to cause central apnoeic episodes during non-rapid eye movement (NREM) sleep and it is likely that this also occurs during pregnancy.

A secondary effect of an increased respiratory drive is an increased diaphragm effort which is associated with greater negative inspiratory pressures at the upper airway (8). This has been shown to increase the risk of upper airway collapse and subsequent risk of apnoeic/hypopnoeic episodes.

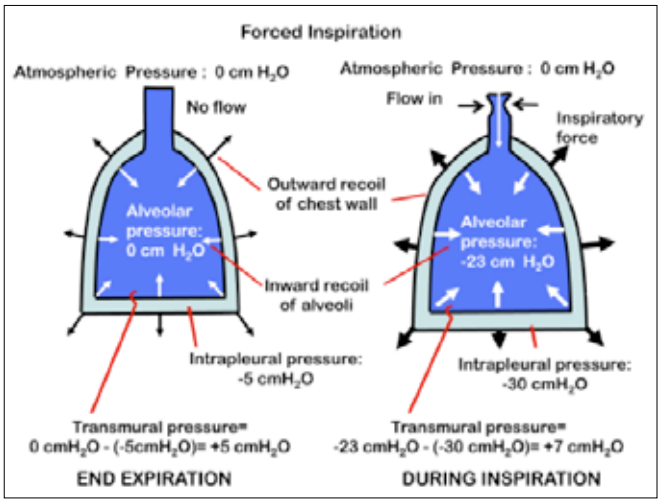

Figure 3: During normal inspiration upper airway narrows due to increased negative pressures. This negative pressure is increased in patients with OSA due to an increased diaphragmatic effort and can lead to an increased risk of upper airway collapse (9).

Nasal patency is an independent factor in developing OSA and both progesterone and oestrogen have been shown to affect this. Both hormones have been linked with the occurrence of nasal rhinitis and subsequent nasal congestion. This has been most commonly documented within the third trimester, where up to 42% of women have been shown to be affected (5). Oestrogen has also been associated with nasopharyngeal oedema leading to upper airway narrowing, increasing the risk of OSA.

4: Sleep disturbance

Due to multiple factors including hormonal and physical changes natural sleep patterns are also affected during pregnancy. This is most relevant during the third trimester during which a reduction in all areas of sleep is noted including both NREM and rapid eye movement (REM) sleep.

Increased symptoms

While up to 30% of middle age people in the UK snore many will have no evidence of airway obstruction. However, snoring is a commonly recognised symptom of OSA and has been shown to have an increased incidence during pregnancy of between 10-19% according to studies comparing pregnant patients to matched non-pregnant populations (11,12). It is thought that even these are conservation estimates as rates are based upon self-reported data and it has been shown that women often under report the symptom (13).

Does pregnancy protect against sleep apnoea?

Whilst there are many physical and hormonal changes that act to increase the likelihood of OSA in pregnant patients some changes are actually thought to be protective. Firstly, due to an increase in habitus pregnant patients often lie in a lateral position reducing the risk of upper airway closure. Most episodes of apnoea/hypopnoea also occur during REM sleep and there is evidence that this is reduced during pregnancy (14,15). Furthermore, whilst it has been demonstrated that there is an increased risk of nocturnal maternal hypoxia during pregnancy this is partly compensated for by a normal physiological response seen in pregnancy that leads to a right shift in the oxygen dissociation curve in order to improve foetal and maternal oxygen supply.

OSA and the impact on perinatal outcomes

The associated periods of hypoxia and altered sleep architecture noted in OSA are associated in non-pregnant patients with metabolic and endocrine disruption leading to increased cardiovascular risk, hypertension, diabetes mellitus and metabolic syndrome. Similar risk has been noted during pregnancy and associated with worsening perinatal outcomes.

1: Maternal hypertension and pre-eclampsia

In non-pregnant individuals hypertension is a recognised complication of OSA. During episodes of hypoxia levels of catecolamines are increased leading to an increase in sympathetic activation, altered baroreceptor activity and subsequent hypertensive episodes (16). Furthermore hypoxic stress has been associated with a pro-inflammatory response leading to neutrophil activation, the release of oxygen free radicals, subsequent endothelial dysfunction and eventually the development of atherosclerosis (17,18).

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Similarly in pregnancy there is evidence to suggest that OSA increases the risk of both pregnancy associated hypertension and pre-eclampsia via similar processes. However, it is important to note that risk factors for pre-eclampsia and OSA are similar e.g. Obesity and pre-eclampsia itself has been shown to increase upper airway obstruction via increased airway oedema which can lead to, or exacerbate pre-existing OSA (15).

An increased incidence of pre-eclampsia and hypertension has been noted in studies comparing snorers reporting daytime somnolence compared to non-pregnant and pregnant non-snorers (12). Studies have demonstrated that pre-eclampsia is more common in patients with OSA proven on polysomnography (PSG) (15). During PSG periods of increased systemic arterial blood pressure coincided with periods of partial upper airway obstruction. It has been demonstrated that the use of CPAP can reduce the presence of both, further suggesting an association (6).

2: Gestational diabetes and metabolic syndromes

Increased cortisol secretion occurs in patients with OSA leading to a disturbance in insulin and glucose metabolism (19) which has been associated with an increased risk of developing diabetes mellitus. This is further precipitated by an increased pro-inflammatory response to periods of hypoxia during which cytokines, especially interlukin-6 are released and are associated with developing insulin resistance (20).

The development of diabetes and insulin resistance in patients with OSA has been demonstrated in up to 40% of non-pregnant populations (21) and is independent of other associated risk factors such as obesity. Evidence is growing that the risk of developing gestational diabetes during pregnancy increases when OSA is present. Questionnaire based studies have demonstrated a higher likelihood of gestational diabetes in patients that snore or have symptoms of daytime somnolence (15) however there is a paucity in evidence and studies confirming OSA on PSG are still needed to clarify this risk further.

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3: OSA related foetal complications

One key feature of OSA is the associated hypoxia that accompanies periods of apnoea/hypopnoea. Maternal hypoxia in patients with OSA has been associated with foetal compromise secondary to reduced placental deliver, resulting in intrauterine growth restriction and lower APGAR scores at birth (10,11). This is further exacerbated by the effects of hypertension and peripheral vasoconstriction, both of which are associated with the presence of OSA. Evidence suggests that treating these patients with CPAP at diagnosis, if before the third trimester, can reduce this risk and lead to normal birth weights (22).

Investigating OSA in pregnancy

There are currently no clear guidelines outlining the appropriate investigation and treatment of pregnant patients at risk of OSA. As such a similar approach to that used in non-pregnant patients, considering symptoms, phenotypes and diagnostic investigations such as PSG showed be used.

The key factor is that clinicians have an increased awareness of the significant risk that this group of patients has for the development of OSA, with special attention paid to patients with gestational hypertension, diabetes and pre-eclampsia, all of which have been associated with OSA. Patients who have had pre-existing OSA or noted gestational OSA in previous pregnancies should also be evaluated (3,16).

Patients with symptoms associated with OSA should be referred for further investigation using the same methods used in non-pregnant patients. As discussed above ESS should be interpreted with caution but is still a useful screening tool. Evidence suggests that Sleep studies, in particular PSG can be successfully undertaken in these patients (5). However, it has been suggested that these might need to be interpreted with caution, especially in the last trimester during which patients more commonly lie on their side and as such may be protected from episodes of apnoea/hyponpnoa episode thus the degree of severity may be underestimated.

The treatment of OSA in pregnancy

Due to limited data there are no guidelines addressing the management of OSA specifically in pregnant patients and those for the general population are used. However, the physiological changes that occur during pregnancy pose unique challenges to the management of OSA during pregnancy.

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Conservative measures such as weight gain whilst recognised as an initial management step in non-pregnant patients are often more difficult during pregnancy due to increases in visceral fat, as outlined above. As such patients should be supported as much as possible with dietician and physiotherapy input.

Alternative management such as mandibular advancement devices which mechanically open the upper airway at the level of the pharynx are often not tolerated well in pregnant patients and compliance has been shown to be poor. Furthermore surgical interventions including vulopalatoplasty, laser assisted uvulopalatoplasty and radiofrequency ablation procedures are not preformed routinely due to the increased surgical risk during pregnancy.

The current evidence suggests that nasal CPAP should be recommended for pregnant patients with OSA. Nasal CPAP has been successfully used in pregnant patients leading to a reduction in OSA associated symptoms and has overall good compliance (15). Furthermore CPAP use has been associated with a reduction in the pro-inflammatory responses, interlukin 6 levels and CRP rises associated with the development of insulin resistance, atherosclerosis and hypertension.

CPAP has similar side effects in both pregnant and non-pregnant patients including discomfort, claustrophobia and dry mouth, nasal congestion and epistaxis. There is, however, little data assessing the frequency of these complications in non-pregnant patients. For patients who do not tolerate CPAP supplementary nocturnal oxygen can be offered to help reduce periodic desaturation but nasal CPAP remains the standard therapy.

Post-partum management

Evidence suggests that OSA precipitated or diagnosed during pregnancy may improve or resolve after delivery as a result of physiological and hormonal normalisation and associated weight loss. Continued improvements in AHI, measured desaturation and symptoms have been noted up to 6 months post-partum (5).

It is has been proposed that, in patients with mild-moderate OSA, CPAP, if started, may be withdrawn but follow up should be undertaken to ensure that symptoms have resolved and a repeat PSG should be undertaken if symptoms recur (23). In patients with newly diagnosed peri-partum severe OSA or pre-existing OSA, CPAP should be continued until their weight has returned to 10-15% of their baseline weight and a PSG repeated to re-assess ongoing need. Patients with gestational sleep apnoea should be reviewed again during subsequent pregnancies in case of recurrence.

Summary

The incidence of OSA overall is increasing, partly related to a growing epidemic in obesity and is likely to be reflected in pregnant individuals. It is already recognised that OSA is associated with significant morbidity and mortality secondary to the development of hypertension, cardiovascular disease, stroke and diabetes.

Although there is a paucity of data there is growing evidence that OSA in pregnancy can increase the risk of maternal hypertension, pre-eclampsia, gestational diabetes and impaired intra-uterine foetal growth, thus impacting upon perinatal outcomes. Whilst there are no clear guidelines, studies have demonstrated that the investigations and treatments used in non-pregnant patients are equally successful in the management of OSA during pregnancy and as such patients should be referred for further assessment.

Self assessment questions

1. Patients with OSA commonly have which of the following characteristic features?

a) Neck circumference of >17cm
b) ESS of 9
c) Mallampati grade 1-2
d) An apnoea/hypopnoea index (AHI) of >5
e) Obesity

2. Pregnancy is associated with which of the following changes in respiratory function?

a) An increased respiratory drive
b) A reduction in functional residual capacity
c) Nocturnal hypoxia
d) A left shift in the oxygen dissociation curve
e) Reduced diaphragmatic effort

3. Which of the following are associated with hormonal changes in pregnancy?

a) Reduced nasal patency
b) Improved gas exchange
c) Nasopharyngeal oedema
d) Increased duration of sleep
e) A reduced respiratory drive

4. OSA is associated with which of the following perinatal complications?

a) Hypertension
b) Gestational diabetes
c) Snoring
d) Pre-eclampsia
e) Liver dysfunction

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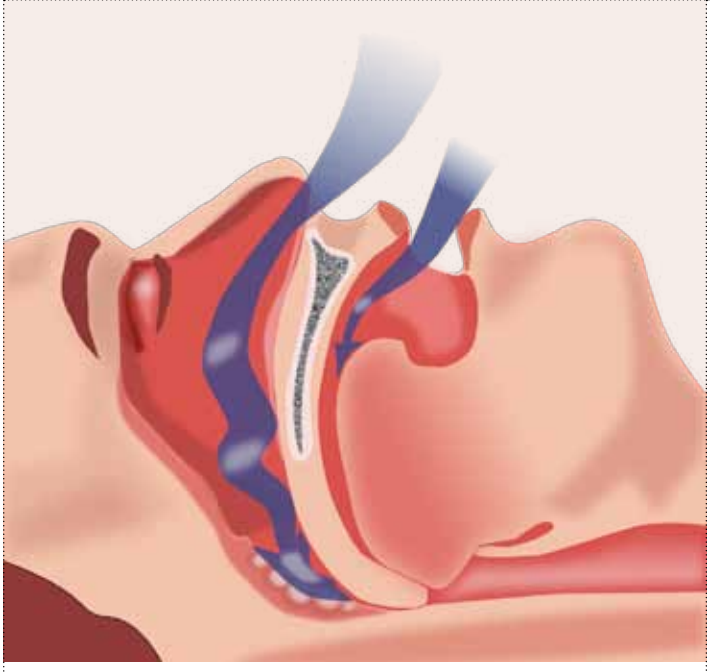

5. The treatment of OSA in pregnancy includes which of the following?

a) Weight loss
b) CPAPA
c) Palatophargyngoplasty
d) Sleeping in the lateral position
e) Radio frequency tongue ablation

Answers

1. A, E
2. B, C
3. A, C
4. A, B, C, D
5. A, B, D

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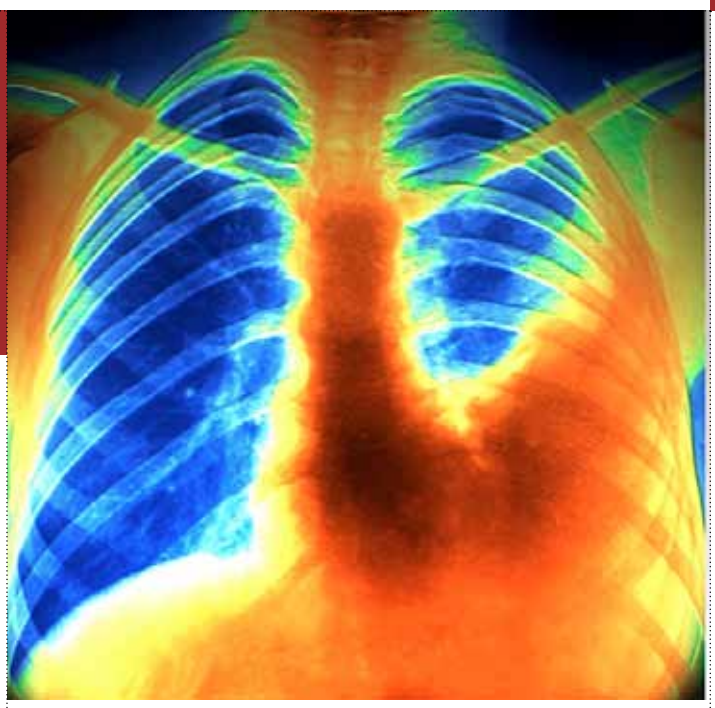
PULMONARY EMBOLISM: WHEN D-DIMER IS NOT A USEFUL TEST

D Salmon & G Hamza

Pulmonary embolism: When D-dimer is not a useful test
Patient Management



Abstract

D-dimer is a test commonly used to exclude pulmonary embolism (PE) due to its high negative predictive value. This case report describes a patient with new pulmonary embolism who was classified as 'moderate risk' according to the Well's score but had a negative d-dimer test. The diagnosis was confirmed with pulmonary angiography.

This case effectively illustrates the rationale behind current guidelines on the diagnosis of pulmonary embolism. Guidelines state that a negative d-dimer test can exclude PE in 'low risk' patients according to the Well's score, whilst d-dimer is not useful in 'high risk' patients as a significant proportion will still have PE. However, in 'moderate risk' patients clinical usefulness of the d-dimer test depends on the sensitivity of the assay used. In this hospital we use only a moderately sensitive assay which is unable to exclude PE in this patient group.

Case report

A 19 year old female was admitted with a history of sudden onset central chest pain and shortness of breath which had started at rest earlier that day. The chest pain was sharp and worse on inspiration. There was no history of haemoptysis, cough, sputum production or fevers. Her past medical history consisted of factor 5 Leiden and a previous pulmonary embolism (PE) just over 1 year previously. On this occasion she had been discharged on warfarin, which she had stopped recently after completing a one year course as prescribed.

She was otherwise well and independent. She took no medications (having stopped the oral contraceptive pill after her first PE) but continued to smoke approximately five cigarettes a day. The patient had an increased respiratory rate (24) on admission but oxygen saturations were 97% on room air; she was not tachycardic (rate 86/minute) with a stable blood pressure of 119/69. She was afebrile. Physical examination was otherwise unremarkable. Her ECG showed some T wave inversion (figure 1) but had not changed from her previous ECG a year previously. Chest X-ray showed no changes (figure 2).

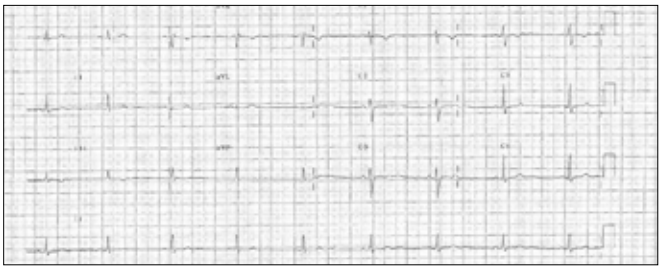


Figure 1: ECG findings.

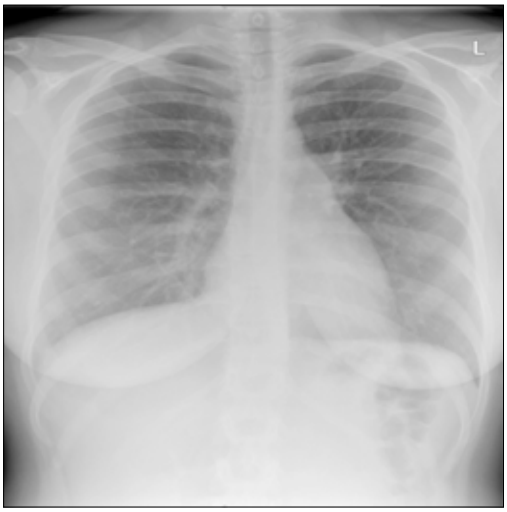


Figure 2: Chest X-ray showing clear lung fields bilaterally with no evidence of infarction or effusion.

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An ABG showed mild hypoxia with a low-normal pCO_2 (pH 7.44, pO_2 9.8 kPa; pCO_2 4.5 kPa on room air). A D-dimer was performed on two occasions and was negative (0.22). However, given the patients history and examination findings, a second PE was suspected and she had a Well's score of 4.5, equating to an 'intermediate risk'.

Wells score		
Variable	**Points**	**Patient's score**
Previous DVT/PE	1.5	1.5
Recent surgery/immobilisation	1.5	0
Cancer	1	0
Haemoptysis	1	0
HR>100	1.5	0
Clinical signs DVT	3	0
Alternative diagnosis less likely than PE	3	3
Original 3 level scoring system:	Total:	Patient's total:
High clinical probability	**>=7**	
Intermediate clinical probability	**2-6**	**4.5 (Intermediate)**
Low clinical probability	**0-1**	

Figure 3: The Well's score, used to assess the clinical risk of pulmonary embolism.

Therefore, despite a negative d-dimer a CTPA was performed, confirming a PE in one of the main branches to the left lower lobe. She was subsequently recommenced on warfarin and low molecular weight heparin (LMWH) until her INR was therapeutic. She was discharged 3 days after admission.

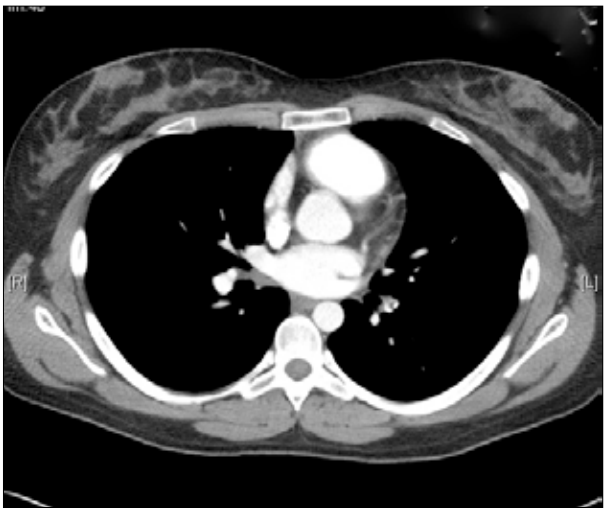

Figure 4: CT pulmonary angiogram image showing a filling defect in one of the main pulmonary artery branches to the left lower lobe suggestive of pulmonary embolism.

Discussion

The index of suspicion for pulmonary embolism (PE) has increased considerably over the past few years. Tools for the diagnosis of PE include clinical scoring tools such as the Wells score (figure 3), blood d-dimer measurement and imaging techniques such as ventilation-perfusion scanning or pulmonary angiography. The Wells score was originally designed for the diagnosis of deep vein thrombosis (1) but has been adapted for PE (2). This score defines a patient as low, intermediate or high risk for PE based on symptoms, risk factors, examination findings and clinical judgement.

D-dimer is a degradation product of cross-linked fibrin. It can be raised in PE, DVT and a number of other conditions, most commonly infection, malignancy and in the post-operative period. It has long been taught in medical schools that a raised d-dimer test is highly sensitive for pulmonary embolism but not very specific – in other words a negative d-dimer has a high negative predictive value and, in many cases, can be used to exclude PE.

Despite this, the case of a pulmonary embolism with a negative d-dimer test is not uncommon. Whilst a negative d-dimer in 'low risk' patients (according to the Well's score) effectively excludes PE, 'high risk' patients who have a negative d-dimer still have a post-test probability of PE greater than 3% (3). Therefore in high risk patients d-dimer is not a useful test and should not preclude appropriate diagnostic imaging.

This patient had a 'moderate risk' of PE, where the role of d-dimer is less clear. Firstly, it important to understand the limitations of the D-dimer test. Sensitivity and specificity of the D-dimer test for PE varies depending on the assay used. ELISA-derived assays (eg. VIDAS) have a sensitivity of over 95% (3,4,6) and in combination with a 'low' or 'moderate' clinical probability score can safely exclude PE without the need for further imaging.

For example, in a recent systematic review (5) using the VIDAS d-dimer assay, outpatients with an "low probability" of PE according to the Wells score and a negative d-dimer test had a 3 month thromboembolic risk of only 0.14% (CI 0.05-0.41%). In comparison, Latex-derived assays like the one used in this hospital have a lower sensitivity of 85-90% (3,4,6) and are only safe for excluding PE in patients with 'low risk' according to the Wells score – they have not been validated in moderate risk patients such as the case discussed here.

Due to the lower sensitivity assay used in this hospital it was correct in this case to disregard the negative d-dimer result and perform diagnostic imaging anyway. This is in keeping with most recent European Society of Cardiology guidelines (6) on PE diagnosis. This case therefore emphasizes the responsibility of the clinician to know the sensitivity of the d-dimer assay used in their hospital laboratory as it may influence patient management.

PULMONARY EMBOLISM: WHEN D-DIMER IS NOT A USEFUL TEST

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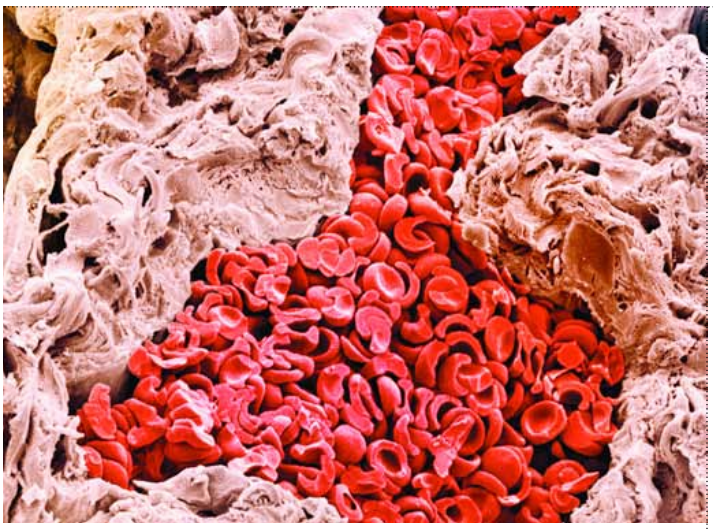

Conclusions

1) D-dimer is not a useful tool for excluding pulmonary embolism if clinical suspicion is high.

2) D-dimer should not be performed in cases where clinical suspicion of pulmonary embolism is high as it will be negative in a significant number of PE positive patients.

3) In moderate risk patients, whether or not a negative d-dimer assay is useful for excluding PE without further imaging depends on the sensitivity of the assay used.

4) It is the clinician's responsibility to know the assay used in their local laboratory as it will affect patient management.

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COPD & RESPIRATORY FAILURE

S Ghani, DPS Dosanjh & SA Fyyaz

Abstract

Chronic obstructive pulmonary disease (COPD) is a world leading cause of mortality and morbidity, and a common cause of hospital admission accounting for 10% of all medical admissions (1).

Patients with COPD are prone to respiratory failure, and it is noted between one fifth and one third of admissions with hypercapnoeic respiratory failure will die in hospital despite mechanical ventilation (2, 3).

As the junior doctor you will frequently clerk such admissions and your involvement, understanding and escalation can help dictate patient outcome.

Definitions

Respiratory failure is defined as inadequacy of gas exchange relating to either absorption of oxygen or elimination of carbon dioxide. Respiratory failure can be categorised into two types: **Type 1** is defined as PaO_2 of <8kPa with normal or low $PaCO_2$ and **Type 2** respiratory failure is defined PaO_2 <8kPa with $PaCO_2$ >6kPa. There is a further sub-classification of Type 2 respiratory failure with three categories: acute, acute-on-chronic, and chronic respiratory failure.

Acute	Acute-on-Chronic	Chronic
High $PaCO_2$	High $PaCO_2$	High $PaCO_2$
Low pH	Low pH	Normal pH
Normal HCO_3	High HCO_3	High HCO_3

Table 1: Sub-classification of type 2 respiratory failure.

Non-invasive ventilation (NIV) refers to the provision of ventilator support through means of mask or similar device. It is distinct from invasive mechanical ventilation in which the upper airway is bypassed with tracheal tube, laryngeal mask or tracheostomy for example.

COPD & Respiratory Failure
Teaching & Training

Non-invasive ventilation can refer to either of the following:

- *Bilevel positive airway pressure: involves the use of two pressures above ambient pressure which is comprised of: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP).*

- *Continuous positive airway pressure (CPAP) conversely maintains a steady pressure over the ambient pressure into the lungs in both expiratory and inspiratory phases of breathing.*

The aim is to reduce the work of breathing, increase tidal volume and decrease respiratory rate.

CPAP is indicated for type 1 respiratory failure (hypoxaemic) or cardiogenic pulmonary oedema, whereas for acute type 2 respiratory failure.

Bilevel ventilation has been shown to be beneficial in randomised control trials in reducing intubation and mortality rates in patients with COPD and decompensated respiratory acidosis (2-5).

Reference ranges

pH	7.35 - 7.45
PaO2	11 – 13 kPa
PaCO2	4.7 – 6 kPa
HCO3	22 – 26 mEq/L
Base Excess	-2 to +2 mmols/l

Arterial blood gas

An arterial blood gas is integral to the diagnosis of respiratory failure and a good understanding is crucial to its management. There are four main disorders of acid-base disturbance, metabolic acidosis or alkalosis and respiratory acidosis or alkalosis. The body can compensate for such disturbances, though this is rarely complete, and the degree of compensation depends on the chronicity of the disorder.

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Normal body pH is between 7.35 and 7.45 which is achieved by regulation of lungs, kidneys and intra and extracellular buffers. The lungs can regulate the partial pressure of CO_2 within the blood, and the kidneys can adjust excretion of carbonic acid or re-absorption of bicarbonate.

A simple guide to interpreting an ABG can be broken down into 5 steps.

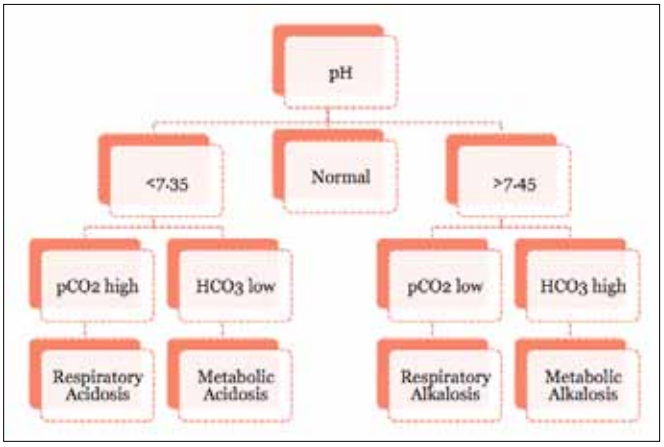

Table 2: ABG Interpretation.

1) Review the pH for evidence of acidosis, alkalosis or if it is normal

2) Ascertain if the abnormality is respiratory or metabolic in origin

a. pH <7.35 + raised pCO_2 = respiratory acidosis
b. pH <7.35 + low HCO_3 = metabolic acidosis
c. pH >7.45 + low pCO_2 = respiratory alkalosis
d. pH >7.45 + raised HCO_3 = metabolic alkalosis

3) Calculate anion gap (if metabolic acidosis) to identify cause.

a. Anion gap is calculated as: $Na+ - (HCO_3^- + Cl^-)$
b. Raised (>16mmol/L) think KULT = ketones, uraemia, lactic acid, toxins (including salicylates)
c. Normal (8-12mmol/L) – GI losses, renal tubular acidosis.

4) Assess for compensation

a. Respiratory – occurs within minutes (low pCO_2 with a metabolic acidosis)
b. Renal – can take up to 1 week. (raised HCO_3 with a respiratory acidosis)

5) Assess the alveolar arterial gradient (informs us about gas exchange)

a. $PAO¬_2 – PaO_2$ (alveolar minus arterial oxygen partial pressures)
b. Where PAO_2 (Alveolar) = $FiO¬_2 – PaCO¬_2 \times 1._2$
i. $FiO¬_2$ – fraction of inspired oxygen

c. Normal gradient is between 1.5 – 3.0 kPa (varies with age), if raised then differentials include:

i. Shunt – congestive cardiac failure, ARDS, lobar pneumonia
ii. V/Q mismatch – Pulmonary embolism, atelectasis, pneumonia, pneumothorax.

d. NB this is not routinely useful in assessment of type 2 respiratory failure.

Non-invasive ventilation

Patient Selection

Bilevel NIV is considered for all patients with persistent respiratory acidosis after 1 hour of maximal medical therapy with a diagnosis of COPD. This consists of:

- *Controlled oxygen targeting saturations of 88-92%*
- *Nebulised salbutamol 2.5 to 5mg*
- *Nebulised ipratropium bromide 500µg*
- *Steroids*
- *Antibiotics if indicated*

Other indications for NIV include (6):

- *Cardiogenic pulmonary oedema – requires CPAP*
- *Chest wall deformity / neuromuscular disease with acute hypercapnoeic respiratory failire*
- *Decompensated obstructive sleep apnoea*
- *Wean following invasive ventilation*
- *A trial of NIV could be undertaken in those with acute exacerbations of bronchiectasis with pH <7.35 and pCO_2 >6, however the excess of secretions limits the utility of NIV (6).*

Clear contraindications include:

- *confusion, agitation or severe cognitive impairment*
- *severe co-morbidity*
- *undrained pneumothorax*
- *facial burns, trauma, recent upper airway surgery*
- *excess of respiratory secretions*
- *high risk of aspiration (e.g. if they are vomiting)*

Patients should be stratified into 5 possible groups by severity of acid-base disturbance, pre-morbid state, reversibility, relative contraindications and the patients' wishes:

- *Immediate intubation and ventilation*
- *NIV and suitable candidate for intubation and ventilation*
- *NIV but not suitable candidate for further escalation*
- *Maximal medical therapy only.*
- *Palliation only.*

COPD & RESPIRATORY FAILURE

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It is important to note predictors of success such as lower APACHE score, younger age, better co-operation and tolerance, and improvements in gas exchange and observations within the first two hours (7).

Bilevel NIV settings

Initial settings should aim for an inspiratory positive airway pressure (IPAP) of 10cms H_2O to titrate up to 20cms H_2O as tolerated in small increments in ten minute intervals. The expiratory positive airway pressure (EPAP) is recommended to start at 5cms H_2O.

Monitoring

Monitoring patients is critical with NIV and can offer predictors of success as previously outlined (8). It is therefore important to review the following routinely.

- *Observations of pulse, RR and ABG at baseline*
- *Observations at 15 minute intervals for 1 hour,*

30 minutes for 4 hours, hourly for 4-12 hours.

- *ABG at 0, 1 and 4 hours*
- *Compliance, synchrony and regular checks*

to ensure no air leak are key to outcome.

Escalation

Ideally, a plan should be made at the outset regarding further escalation, and the decision for intubation and ventilation should be made within 4 hours of starting NIV.

Treatment duration

Patients who have responded to treatment, should normally receive NIV for as long as possible within the first 24 hours and should continue until the acute cause has resolved. Each NHS Trust will have a local weaning protocol.

Weaning

NIV should normally be weaned from daytime hours, particularly around meal times or for physiotherapy input and nebulisers. Broadly speaking a gradual reduction may follow:

- *Day 1: Maximise treatment duration on NIV*
- *Day 2: 16 hours on NIV*
- *Day 3: 12 hours on NIV (with 8 hours night NIV)*
- *Day 4: Aim to discontinue*

Clinical cases

Case 1

A 60 year old gentleman current smoker (50 pack years) with green productive cough presents to ED complaining of shortness of breath. ABCDE assessment, confirms patient airway is patent and he is able to speak in short sentences. Breathing: He is visibly dyspnoeic, RR 40, using accessory muscles of breathing and is sitting in a tripod position. His saturations are 72% on air. He has globally reduced breath sounds with expiratory wheeze. He has a stable blood pressure of 110/65 and pulse rate 63 beats per minute.

Investigations

ABG on room air: pH 7.37 pCO_2 7.6kPa pO_2 5.6kPa HCO_3 31 Lactate 1.5
CXR: hyper expanded lung fields

ABG Interpretation

This ABG shows a type 2 respiratory failure with metabolic compensation indicating that this gentleman has an element of chronic type 2 respiratory failure.

The pH is normal, however the pO_2 is low and the pCO_2 is raised. If this were all acute, you would expect the pH to be low due to an acute respiratory acidosis. We can see however that the pH is normal. If we look at the HCO_3 value, this is raised, indicating that there has been renal compensation for the respiratory acidosis suggesting a chronicity to his respiratory failure.

Options

1. Would you

a) Administer oxygen targeting saturations of 88-92%
b) Administer antibiotics, steroids and nebulisers
c) Administer oxygen targeting saturations 88-92%
and commence steroids, antibiotics and nebulisers
d) Commence BiLevel NIV, steroids, antibiotics and nebulisers.
e) Commence CPAP, steroids, antibiotics and nebulisers.

You are then bleeped back by the nurse some time later, the patient has become very drowsy and is no longer speaking and requires an urgent review. When you arrive you see the patient slumped down and is taking slow, shallow breaths. His GCS is 13/15. You do an ABG and the results are as follows:

ABG on 6litres oxygen: pH 7.26 pCO_2 10.6kPa pO_2 15.2kPa HCO_3 31.3 Lactate 1.2

ABG Interpretation

The patient has developed acute on chronic type 2 respiratory failure secondary to over oxygenation.

You reduce the oxygen immediately and administer further nebulisers. His ABG after 30 minute is repeated which shows minimal improvement. You decide he needs to be commenced on NIV and discuss this with the medical registrar who is in agreement and asks you to set it up as he is busy with another emergency.

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Options

2. What settings would you commence this patient on?

a) Bilevel ventilation: IPAP 10cms H_2O with EPAP 5cms H_2O
b) Bilevel ventilation: IPAP 20cms H_2O with EPAP 5cms H_2O
c) Bilevel ventilation: IPAP 20cms H_2O with EPAP 10cms $H2_2O$
d) CPAP: 5cms H_2O
e) CPAP: 10cms H_2O

Answers

1. Answer: C

It is likely this patient is having an exacerbation of his COPD. The patient is needs controlled oxygen to correct the hypoxia. Furthermore, he would benefit from nebulisers, steroids, and antibiotics. There is no indication for Bilevel NIV at this point as he has a chronic type 2 respiratory failure which is well compensated.

2. Answer: A

This patient would be commenced on bilevel ventilation for his acute hypercapnoeic respiratory failure, with guidance suggesting you start with an IPAP of 10cms H_2O with EPAP 5cms H_2O, up-titrating the IPAP every 10 minutes as tolerated up to 20cms $H¬_2O$. CPAP is not indicated in this scenario.

Further Comments

An ABG is repeated after 60 minutes: ABG on NIV:
pH 7.30 pCO_2 9.2kPa pO_2 12.4kPa HCO_3 31.6 Lactate 1.4

The patient is tolerating NIV well and the ABG shows evidence of improvement, with an increased pH and decreased CO_2. However in context of persistent respiratory acidosis, and given that he is tolerating NIV well, you could further optimise the settings.

In general terms, if hypoxia is a problem, you should increase the EPAP and if the pCO_2 is raised and the patient is acidotic, then you should increase the IPAP. In this case the patient is not hypoxic and so the EPAP is adequate. His IPAP should be increased.

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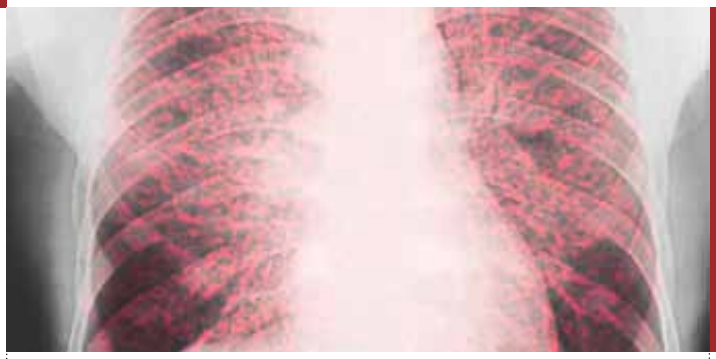
THE MANY FACES OF SARCOIDOSIS

R Rupesinghe, M Trawinska & SP Hart



Abstract

Sarcoidosis is a multisystem inflammatory disease of unknown aetiology. Its incidence is difficult to determine due to significant heterogeneity in disease presentation and severity among different ethnic and racial groups and geographical variation. We present a case that illustrates biochemical, radiological, and pathological abnormalities in sarcoidosis. We discuss complications and evidence for treatment in sarcoidosis.

Case history

A 46-year-old Caucasian man presented with a six month history of worsening shortness of breath. He had been previously fit and well, a non-smoker with no asbestos exposure. He was an office worker and kept a pet rabbit at home. On examination, his chest was clear to auscultation. His chest radiograph showed bilateral interstitial changes and mediastinal lymphadenopathy (figure 1).

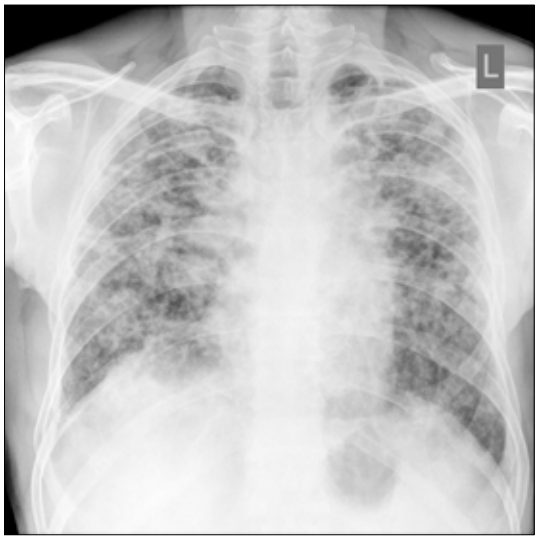


Figure 1: Chest radiograph demonstrating bilateral pulmonary interstitial changes.

To assess these changes in more detail a computed tomography (CT) scan was performed which showed wide-spread ill-defined opacities in both lungs (figure 2).

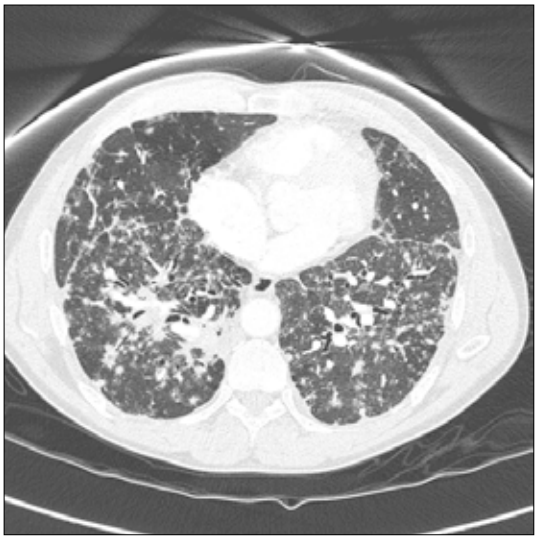


Figure 2: CT scan of thorax demonstrating multiple ill-defined nodular opacities in both lungs.

The serum angiotensin-converting enzyme (ACE) activity level was raised. He went on to have a transbronchial biopsy (TBB) which showed non-caseating epithelioid cell granulomata (figure 3).

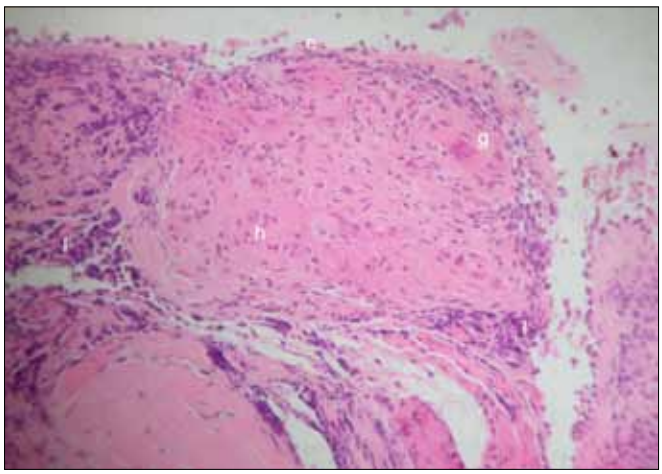


Figure 3: Transbronchial biopsy demonstrating non-caseating granulomatous inflammation. e, bronchial epithelium; g, giant cell; h, histiocytes (macrophages); l, lymphocytes.

THE MANY FACES OF SARCOIDOSIS

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An initial watch-and-wait approach was adopted, but three months later in August 2013 he was admitted with hypercalcaemia (serum calcium 3.78 mmol/L (reference range 2.2-2.6)). He was successfully treated with rehydration and a short course of oral prednisolone, and the serum calcium level rapidly returned to within the normal range. The patient preferred not to continue corticosteroids, so he discontinued treatment after one week followed by conservative management with attention to daily fluid intake and avoidance of sun exposure. He remained well for a year, but was admitted again with hypercalcaemia in the summer of 2014 (figure 4) and on this occasion he was prescribed maintenance low-dose corticosteroid therapy following discharge.

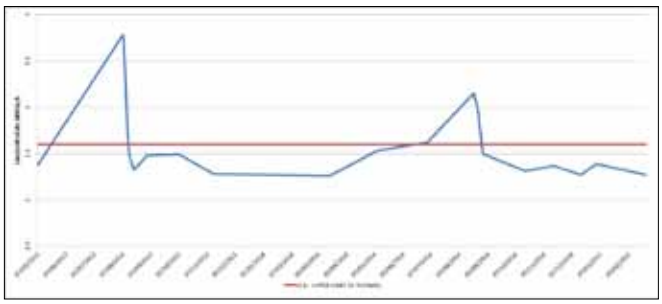

Figure 4: Serial serum calcium measurements.

While his serum 1,25-dihydroxycholecalciferol concentration was raised, his total cholecalciferol level was low, indicating vitamin D deficiency. He was referred to the endocrinology team and subsequently commenced on weekly bisphosphonate therapy. His lung disease remained stable (table 1), although he continued to report limited exercise tolerance and low energy levels.

	September 2013	June 2014
FEV_1(L)	1.61 (47% predicted)	1.43 (46% predicted)
FVC (L)	2.07 (54%)	1.95 (52%)
TL_{CO}(mmol/min/kPa)	3.34 (37%)	2.94 (33%)
K_{CO}(mmol/min/kPa/L)	1.05 (69%)	1.06 (70%)

Table 1: Serial pulmonary function measurements. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLCO, diffusing capacity for carbon monoxide; KCO, diffusing capacity for carbon monoxide adjusted for lung volume.

Discussion

Presentation

Sarcoidosis commonly affects the lungs, with frequent extra-pulmonary sites being the skin, lymph nodes, liver and eyes (1). Extra-pulmonary manifestations can occur before, coincidentally or after respiratory symptoms. Like our patient, it has been estimated that 50% of cases of sarcoidosis present with respiratory complaints, commonly breathlessness on exertion or cough.

Many patients report only systemic symptoms such as lethargy, fever and anorexia, whilst some are asymptomatic and detected incidentally, for example through chest imaging. Physical examination of the chest is usually normal in sarcoidosis, even when radiological changes are extensive.

Sarcoidosis is more common in African-American populations, and patients with this ethnic background also experience more severe disease (2). The male-to-female ratio is approximately 1:2. Morbidity, mortality and extra-pulmonary involvement are all higher in females (3), though the overall mortality rate in untreated patients is low at 5%, with deaths resulting from the complications of end-stage lung disease caused by progressive fibrosis.

Investigations

Serum ACE levels may be raised in sarcoidosis, but sensitivity is quoted as 60% with an even poorer specificity (1). Hypercalcaemia occurs in approximately 5% of patients with sarcoidosis and is related to elevated levels of 1, 25-dihydroxycholecalciferol [$1,25(OH)_2D3$], the metabolically active form of vitamin D3 (4). This happens because 1-alpha-hydroxylation occurs both in the kidney and granuloma macrophages but, while the former is regulated by feedback loops, the latter is not. 1,25(OH)2D3 serves to increase gastrointestinal absorption of calcium and phosphate, and possibly to increase bone resorption (4).

Prescription of further vitamin D may only serve to worsen hypercalcaemia and should be avoided. Similarly, increased synthesis of vitamin D3 from sunlight exposure is the reason why disease can flare in the summer months (4). This explains why our patient presented with hypercalcaemia in August on two consecutive years. Hypercalciuria has a prevalence of 40-62% and can be measured on 24-hour urine collection (4).

It is important to test for hypercalciuria, as it can lead to renal calculi and eventually renal insufficiency. Parathyroid hormone levels will be suppressed due to the hypercalcaemia, although concomitant hyperparathyroidism and sarcoidosis have been described (4).

Radiographic findings can be variable, leading to staging criteria in pulmonary disease (table 2).

Stage	*Chest Radiographic Findings*
0	Normal
I	Bilateral hilar lymphadenopathy
II	Bilateral hilar lymphadenopathy and lung infiltrates
III	Lung infiltrates alone
IV	Fibrosis

Table 2: Chest radiographic staging in sarcoidosis (after Scadding 1961).

THE MANY FACES OF SARCOIDOSIS

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The many faces of sarcoidosis
Patient Management

An important differential diagnosis is tuberculosis and, particularly when lymphadenopathy is present, lymphoma needs to be excluded. For these reasons, histological diagnosis is desirable. In the absence of more easily accessible extra-pulmonary disease, bronchoscopy allows for several different sampling methods. Washings or bronchoalveolar lavage can be sent for microbiology and cytology.

If there is hilar lymphadenopathy, endobronchial ultrasound sampling can be performed while TBB can be adopted for more diffuse parenchymal disease. It is advisable that CT imaging is performed prior to these more invasive investigations in order to decide which sampling method is most appropriate and from where samples should be obtained.

Pulmonary function testing (PFT) typically reveals a restrictive ventilatory defect, where both total lung capacity (TLC) and vital capacity (VC) are reduced, although airway obstruction may also occur.

Treatment

Historically, sarcoidosis has been treated with corticosteroids. Steroids work by suppressing pro-inflammatory mediators involved in granuloma formation, but control rather than cure the disease (5). Important side-effects that can result from prolonged use of corticosteroids include osteoporosis, diabetes mellitus, infection, adrenal insufficiency and Cushing's syndrome. This is why in many cases of sarcoidosis the risks associated with this treatment outweigh any benefits. It is essential that patients are aware of these potential complications, and have been counselled with regards to the risk of abruptly discontinuing treatment and precipitating an Addisonian crisis.

While oral corticosteroids are often prescribed for treatment of extra-pulmonary disease and hypercalcaemia, this practice is based mainly on observational data, as no randomised controlled trials have been carried out in these patient groups.

Nearly 40% of patients in the multicentre British Thoracic Society Sarcoidosis Study showed spontaneous radiographic improvement over a six-month period (6). In patients with progressive stage II or III pulmonary disease, oral corticosteroid therapy was associated with improvement in radiological findings as well as lung function over a period of six to 24 months.

The evidence for inhaled corticosteroid treatment in pulmonary sarcoidosis was appraised in a systematic review (7). The authors found two small studies using inhaled corticosteroid therapy, neither of which showed any improvement in radiological findings or any consistent lung function changes (7). However, there was a suggestion that inhaled corticosteroids helped patients who had cough (1).

Based on the evidence, guidelines state that treatment should be considered in patients with deteriorating lung function (as measured over three- to six-month intervals), deteriorating radiological changes, and significant symptoms (figure 5). Treatment is not recommended in asymptomatic stage I and stage II disease, or stage III disease which is stable (1).

Caution is warranted when considering steroid therapy, because a retrospective study suggested that corticosteroid therapy was associated with delayed disease resolution and a prolongation of the clinical course of sarcoidosis by increasing relapse rates (8).

Figure 5: Flowchart indicating a pathway for investigation and treatment of sarcoidosis.

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No randomised controlled trials have been carried out to identify an optimum corticosteroid dose, but prednisolone is usually started at 30-40mg daily and subsequently titrated down according to response. Therapy should be continued for a period of six to 24 months (1). Hypercalcaemia in sarcoidosis is particularly responsive to corticosteroids as they are potent inhibitors of 1-alpha-hydroxylase in macrophages, but treatment can worsen hypercalciuria (4). Again, there are no good studies looking into dose or duration of corticosteroid therapy for hypercalcaemia.

A variety of other immunomodulatory drugs have been proposed for treating sarcoidosis, including azathioprine, hydroxychloroquine, methotrexate, and mycophenolate. Whilst these agents may be steroid-sparing, none have been subjected to placebo-controlled randomised controlled trials (9). A limited number of studies have examined anti-cytokine biologic agents. Evidence for tumour necrosis factor-aplha inhibitor treatment can be found in individual case reports and small case series.

A phase two trial of infliximab in patients with pulmonary sarcoidosis was disappointing, reporting a 2.5% improvement in FVC at 24 weeks. Patients had also been taking prednisolone or other immunosuppressants, and the clinical relevance of this change is unclear (10). There have also been several reports of sarcoidosis apparently induced by TNF-alpha blockers.

Due to the lack of evidence, cautious use may be considered only in cases where disease is progressing and there are no suitable alternatives (1). In end-stage pulmonary sarcoidosis lung transplantation is an option (1). Survival and complication rates are similar to those of patients undergoing transplantation for other indications, though recurrence rates are high (11).

Conclusion

Sarcoidosis can affect a multitude of organs and therefore may present in different ways and to different specialities. The lungs are a commonly affected site and chest radiography is important in suspected cases, whether respiratory symptoms are present or not.

Patients with asymptomatic or mildly symptomatic pulmonary involvement do not require treatment, but should instead be monitored for signs of disease progression, with outpatient follow-up, serial PFTs and repeat chest radiography. Dysregulated calcium metabolism, including osteoporosis secondary to corticosteroid therapy, is well-recognised in sarcoidosis and can be difficult to manage, so advice from an endocrinologist is helpful. Evidence regarding treatment is limited, but supports the use of corticosteroids in patients with advanced or progressive disease.

Test yourself

1. Lofgren's syndrome is the combination of which three findings?

A. Bilateral hilar lymphadenopathy, arthritis/arthralgia, and erythema nodosum
B. Bilateral hilar lymphadenopathy, arthritis/arthralgia, and uveitis
C. Fever, parotid swelling, and uveitis
D. Fever, parotid swelling, and erythema nodosum
E. Shortness of breath, uveitis, and arthralgia

2. Which of the following would you expect to see in a patient with sarcoidosis and stage III pulmonary disease?

A. Fibrosis
B. Bilateral hilar lymphadenopathy with lung infiltrates
C. Lung infiltrates only
D. Bilateral hilar lymphadenopathy only
E. Pleural effusion

Answers

1. Answer A

Lofgren's syndrome tends to occur in acute sarcoidosis. The combination of fever, parotid swelling, uveitis and, sometimes, facial palsy is referred to as Heerfordt's syndrome.

2. Answer C

Based on the radiographic staging of sarcoidosis, in stage III disease you would find pulmonary infiltrates only. It is important to obtain repeat imaging and monitor for any progression of the changes, as well as assessing for worsening of symptoms or pulmonary

Acknowledgements
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The many faces of sarcoidosis
Patient Management

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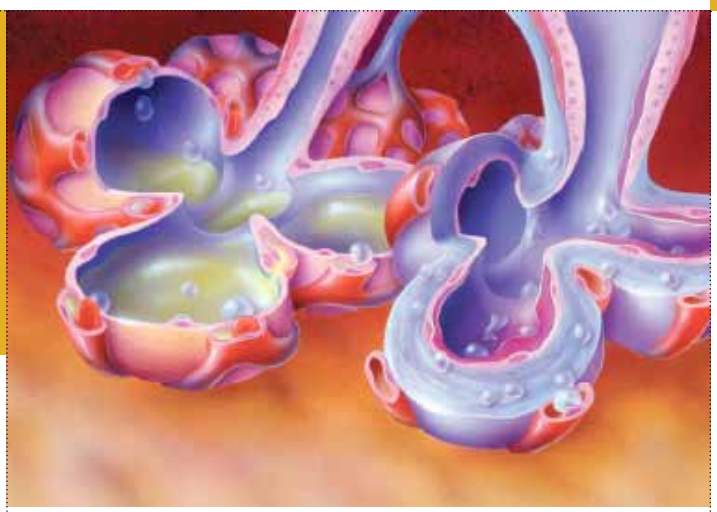
THE EFFECT OF NITRIC OXIDE ON THE PULMONARY CIRCULATION & ITS ROLE IN THE TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

C Karunaratne, D Karunaratne, D Chhabra & A Kumar

The effect of nitric oxide on the pulmonary circulation and its role in the treatment of acute respiratory distress syndrome (ARDS)
Good Clinical Care



Abstract

Acute respiratory distress syndrome (ARDS) is a disorder associated with high morbidity and mortality. In its pathophysiology, hypoxic pulmonary vasoconstriction results in ventilation perfusion (V/Q) mismatch, leading to life threatening hypoxaemia. Theoretically, reversal of pulmonary vasoconstriction could improve V/Q mismatch and thereby improve oxygenation. An agent that can accomplish this would be a suitable pharmacotherapy in the treatment of ARDS.

Nitric oxide is a vasodilator produced by the vascular endothelium and studies indicate that it can reverse pulmonary vasoconstriction. Therefore, nitric oxide may be a potential candidate in the treatment of ARDS. However, many studies show that nitric oxide does not significantly decrease the morbidity and mortality associated with ARDS. Despite appearing to be a promising therapy, nitric oxide is thus concluded to be unsuitable in the treatment of ARDS until further clinical evaluation.

Acute respiratory distress syndrome

The first description of acute respiratory distress syndrome (ARDS) was documented over thirty years ago. Though its causes are broad and many, the underlying pathophysiology is the same: there is an increased permeability of the pulmonary vasculature due to generalised inflammatory damage to the pulmonary capillary endothelium, leading to accumulation of fluid in the alveoli - causing non cardiogenic pulmonary oedema.

The clinical picture is of tachypnoea, hypoxia, decreased lung compliance, radiological appearances of diffuse pulmonary infiltrates and respiratory failure. The estimated incidence of ARDS in the UK is 4.5/100,000 (1). Despite this low incidence, the problem with ARDS is its high mortality which is estimated to be between 40-60% (2) and its morbidity, with survivors having a persistent functional limitation a year after discharge (3).

The normal response to hypoxia in the systemic circulation is vasodilatation, whilst the pulmonary vasculature responds to hypoxia with vasoconstriction. This phenomenon is beneficial in localised hypoxia so as to divert blood to better oxygenated areas of the lung and reduce V/Q mismatch. This physiological response is detrimental in ARDS as widespread lung inflammation leads to generalised hypoxia which then causes generalised hypoxic pulmonary vasoconstriction – rapidly worsening V/Q mismatch.

Current management strategies for ARDS therefore seek to improve V/Q mismatch. Hence the mainstay of current ARDS management is mechanical ventilation whilst also increasing the fraction of inspired oxygen (FIO2) to improve arterial oxygenation and applying positive end expiratory pressure (PEEP) to recruit more alveoli and increase the functional residual capacity (FRC).

Mechanical ventilation is not without its complications, with barotrauma being a noteworthy problem. However, current practice is to allow respiration to stabilise using mechanical ventilation in order to buy time for treatment of the underlying cause of ARDS. Surprisingly, there is no efficacious pharmacological treatment for ARDS and this highlights a longstanding need to develop a pharmacotherapy.

Endothelial nitric oxide is a free radical and the major paracrine vasodilator produced and released by vascular endothelial cells. Endothelial nitric oxide synthase (eNOS) is the main enzyme isoform responsible for nitric oxide production, using the substrate L-arginine. eNOS is activated by mediators such as bradykinin, histamine and serotonin. Shear forces can also activate eNOS and cause basal nitric oxide release with local blood flow. Once released from the endothelium, nitric oxide diffuses into the vascular smooth muscle and activates guanylyl cyclase and increases levels of cGMP, causing vascular smooth muscle relaxation.

In principle, nitric oxide administration could reverse hypoxic pulmonary vasoconstriction in ARDS, but could this theory hold true in practice? The present review discusses the effect of nitric oxide on the pulmonary circulation, specific to reversal of hypoxic pulmonary vasoconstriction and also discusses the role of nitric oxide as a pharmacological intervention in the treatment of ARDS, drawing on experimental and clinical literature.

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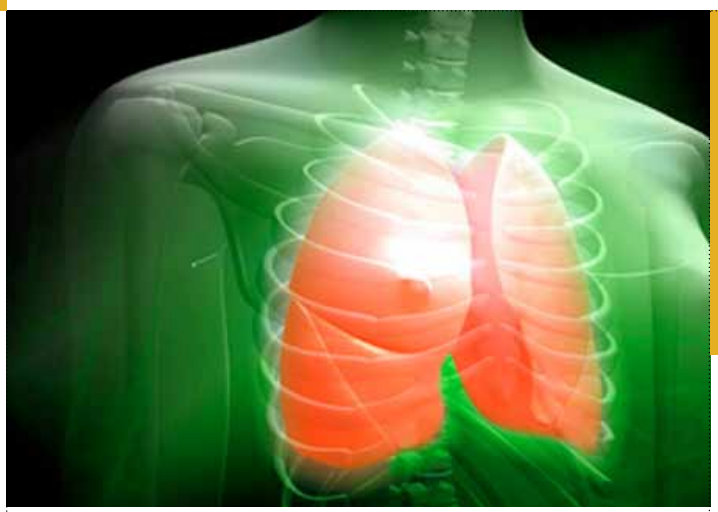

The effect of nitric oxide on the pulmonary circulation was investigated in a study (4) using human pulmonary arteries. It was found that synthesis of nitric oxide was inhibited by pre-treatment by a non-selective NOS inhibitor, as is expected. The NOS inhibitor inhibited acetylcholine induced vascular relaxation dose dependently and infusion of L-arginine (the substrate for nitric oxide) was able to reverse this inhibition dose dependently.

The NOS inhibitor had no effect on the vascular relaxation caused by administration of sodium nitroprusside (a nitric oxide donor), showing that the site of action of the NOS inhibitor was at the level of the endothelium only. The study concluded that nitric oxide produced by the pulmonary vascular endothelium is likely used to maintain basal pulmonary vascular tone in humans and similar conclusions were drawn from other studies (5). These papers led to a hypothesis that if nitric oxide causes pulmonary vasodilatation, reduction of nitric oxide production could be linked to the pulmonary vasoconstriction response to hypoxia.

So could a decrease in nitric oxide production be the mechanism behind hypoxic pulmonary vasoconstriction? Guanylyl cylase inhibitors are inhibitors of the downstream vasodilator effects of nitric oxide. A study using a guanylyl cyclase inhibitor on rat lungs found that in normoxic conditions, there was no difference in pulmonary perfusion pressure in rat lungs given the guanylyl cyclase inhibitor and control lungs (6).

However, administration of the guanylyl cylase inhibitor potentiated the hypoxic vasopressor response by four fold when injected just before or during alveolar hypoxia. This observation led to the suggestion that that nitric oxide activity must actually be increased in hypoxia. Contrary to the idea that nitric oxide reduction may cause vasoconstriction, it appeared that hypoxic pulmonary vasoconstriction occurs by a different mechanism and nitric oxide production is actually increased as a brake mechanism against vasoconstriction being excessive. A similar study drew the same conclusions (7).

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Although nitric oxide production in pulmonary arteries appears to be increased in acute hypoxia, this relationship may not hold true in situations of chronic hypoxia, as what happens in ARDS. A study (8) on the pulmonary arteries of humans with cystic fibrosis and control patients, found that pulmonary artery segments from the cystic fibrosis patients showed less vasodilation in response to acetylcholine, in comparison to the controls ($p<0.001$). Similarly, there was less of a vasodilator response from the cystic fibrosis patients' pulmonary arteries to the vasodilator ADP, in comparison to the controls ($p<0.01$).

This relationship has been mirrored in a similar study using COPD patients (9), which additionally discovered a normal vasodilator response of the pulmonary arteries when administered sodium nitroprusside (a nitric oxide donor). These results suggested that in chronic hypoxia, vascular smooth muscle is functional but that the endothelium is dysfunctional, the latter which leads to a lack of nitric oxide production, and impairs endothelium dependent relaxation and causes pulmonary vasoconstriction. Therefore, pulmonary vascular remodelling may be the mechanism by which pulmonary vasoconstriction persists in chronic hypoxia.

It has now been theorised that hypoxic pulmonary vasoconstriction occurs by a mechanism that is unrelated to nitric oxide, involving intracellular calcium release and calcium sensitisation (10, 11). Therefore, the theory that nitric oxide production increases to brake against hypoxic pulmonary vasoconstriction and that, in chronic hypoxia, endothelial dysfunction leads to an impaired relaxation response are feasible. It corresponds that in a chronic hypoxic situation such as ARDS; administration of nitric oxide should cause generalised pulmonary vasodilatation and improve pulmonary function of patients. But does the existing body of literature support this?

A trial using inhaled nitric oxide on normal lambs and those with acute pulmonary hypertension due to hypoxia or thromboxane administration, found that inhaling nitric oxide at 40 parts per million (ppm) or more reversed pulmonary vasoconstriction (12). In addition, vasoconstriction resumed within three to six minutes of stopping nitric oxide inhalation, indicating that nitric oxide was likely responsible for the initial improvements.

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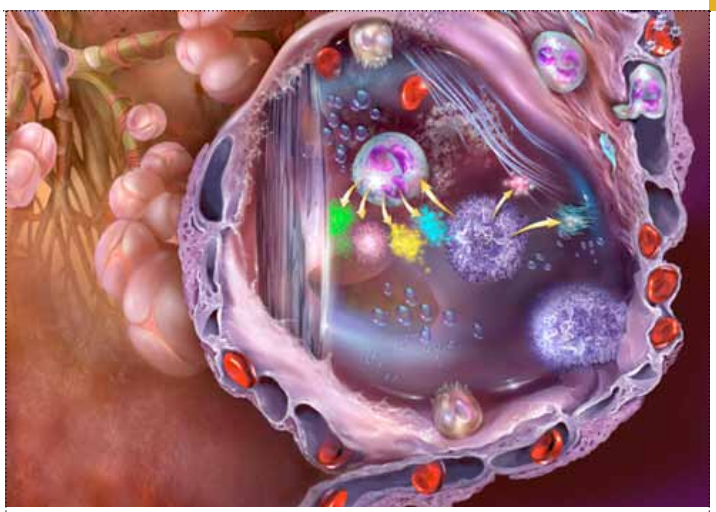
In the normal control lambs, important cardiovascular parameters such as pulmonary vascular resistance, systemic vascular resistance, cardiac output, left atrial pressure and central venous pressure were not altered, indicating a lack of systemic side effects. This type of trial has been replicated in healthy human volunteers (13) to achieve reversed pulmonary vasoconstriction and normalisation of mean pulmonary arterial pressure on inhalation of 40 parts per million (ppm) nitric oxide, without significant alteration of systemic vascular resistance or mean arterial blood pressure. However, the major limitation of both trials is that they were undertaken on healthy subjects and in induced acute hypoxia scenarios, so although nitric oxide appears beneficial in reversing acute pulmonary hypoxic vasoconstriction, this may not be true in chronically hypoxic ARDS patients.

A study on nitric oxide therapy in ARDS used nine patients without previous history of lung disease and with severe ARDS to compare haemodynamic variables, gas exchange and V/Q mismatch when given nebulised nitric oxide versus prostacyclin, a vasodilator (14). It was found that the use of nitric oxide reduced the mean pulmonary arterial pressure and decreased intrapulmonary shunting, both significant statistically and clinically. It also increased the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FIO_2), which indicates improved arterial oxygenation.

Prostacyclin was associated with decreased pulmonary arterial pressure, but increased intrapulmonary shunting and reduced PaO_2/FIO_2. This study pointed towards nitric oxide being the more feasible treatment for ARDS. These findings are reiterated in another study (15) that found arterial oxygenation to be increased with nitric oxide delivery and the redevelopment of pulmonary hypertension on cessation of nitric oxide delivery. The major limitation of these studies is that only the short-term effects of nitric oxide therapy were evaluated and the longer term effects may be very different.

Some studies have evaluated the long-term effects of nitric oxide therapy, finding that nitric oxide use for up to twenty seven days reduced mean pulmonary arterial pressure and improved systemic oxygenation (16). Patients that received nitric oxide also had significantly better measures of pulmonary function (e.g. increased total lung capacity) six months post treatment in comparison to controls (17). In addition to this, there was evidence that nitric oxide can improve cardiac function, with improvements in right ventricular ejection fraction in ARDS patients (18, 19). This suggested that nitric oxide therapy may be useful in reduction of respiratory and cardiovascular morbidities.

Although the above mentioned literature appears to point to a clear benefit in the use nitric oxide in improvement of pulmonary haemodynamics, there is little emphasis on how long-term survival changes after nitric oxide therapy. As mortality due to ARDS is high, it is arguably the most important parameter to measure. The idea that nitric oxide does not improve long-term survival in ARDS was put forward by early studies (20). Randomised control trial evidence (21) found that the mortality rate of the nitric oxide group and the control group was not significantly different and this lack of improvement in mortality is echoed in further, more recent studies (22-24).



Another limitation of the supportive literature is the difference in doses used and lack of agreement on the most efficacious dose. From the previously quoted studies, efficacious doses varied from 40 parts per million (13) to 60 parts per billion (15), with contrasting or no explanations of how these doses were calculated.

Moreover, there is evidence to suggest that of people given nitric oxide, 60-69% may not respond to any dose at all (25, 26), that increasing nitric oxide dose further and further may paradoxically worsen oxygenation (25, 27) and that of patients that did initially respond to nitric oxide, there was no improvement or benefit after twenty four hours (21). Finally, a phase III randomised control trial (28) found that ARDS is associated with poor survival, high costs of care and the need for resources even after discharge, and that inhaled nitric oxide made no significant change to any of these parameters.

Nitric oxide was thus deemed to be inappropriate in the treatment of ARDS and further discredited in the ARDS management recommendation by the Cleveland Clinic (29). There is a marked lack of literature on nitric oxide therapy in ARDS from the years 2009-2013. The few that have been published recently (23) discredit the use of nitric oxide further, casting this once hopeful therapeutic modality into deeper disrepute.

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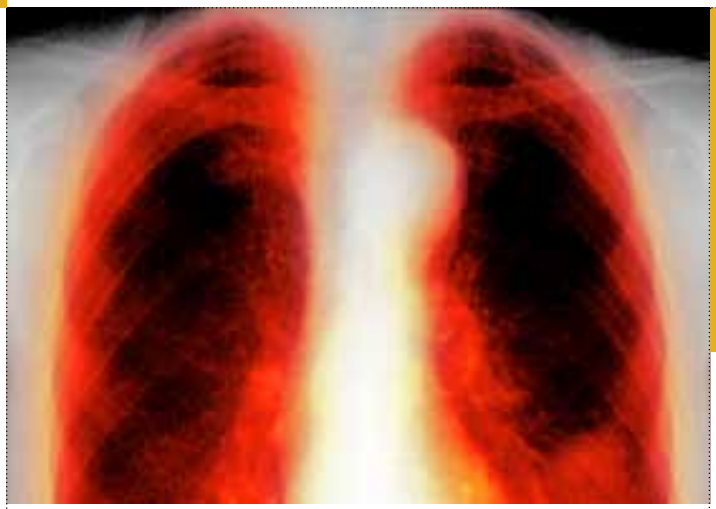

Nitric oxide administration was theorised to be able to reverse hypoxic pulmonary vasoconstriction and therefore be a treatment for ARDS. Clinical and experimental literature have shown that it is able to reverse pulmonary vasoconstriction, as well as improve arterial oxygenation without significant systemic haemodynamic side effects in both healthy humans and ARDS patients.

Despite it appearing a promising pharmacological therapy in ARDS, there are many studies which discredit its use. Interestingly, many of the conflicting studies, in and out of favour of the use of nitric oxide, were undertaken around the same time period which indicates a large scale debate and mixed conclusions regarding its usefulness as a treatment in ARDS.

The biggest problem identified is that although nitric oxide does improve pulmonary haemodynamics and arterial oxygenation, mortality between control and intervention groups remains unchanged. Further to this, it appears as though a greater percentage of patients do not respond to nitric oxide than do and it is unsuitable to use a therapeutic modality that is only suitable in a minority.

The lack of recent literature on nitric oxide and ARDS only worsens the inconclusive debate and it is in danger of being discarded too quickly as a therapeutic strategy. It has many desirable traits such as its greater affinity for haemoglobin than oxygen, binding to pulmonary venous blood on inhalation and thus leaving its effects confined to the pulmonary vasculature.

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The short half-life of nitric oxide in the presence of haemoglobin (30) prevents it from having systemic effects when inhaled. These are desirable traits in a drug that is targeted to a specific tissue. The existing body of literature is subject to selection bias as many did not use randomised selection methods for the patients and the total number of patients was too small for any differences in outcomes measured to be very significant. There are differences between the studies in the treatment protocol and method of nitric oxide delivery, all of which can affect the end conclusion.

The recommendation from this review is that the best method by which to evaluate the use of nitric oxide in ARDS is to undertake a multicentre study, perhaps UK based or worldwide, using the same quality control measures and experimental technique. This is the best way by which to allow valid comparisons, assess reproducibility and draw sound conclusions. Until such a study is done, the role of nitric oxide in the treatment of ARDS cannot be discarded fully.

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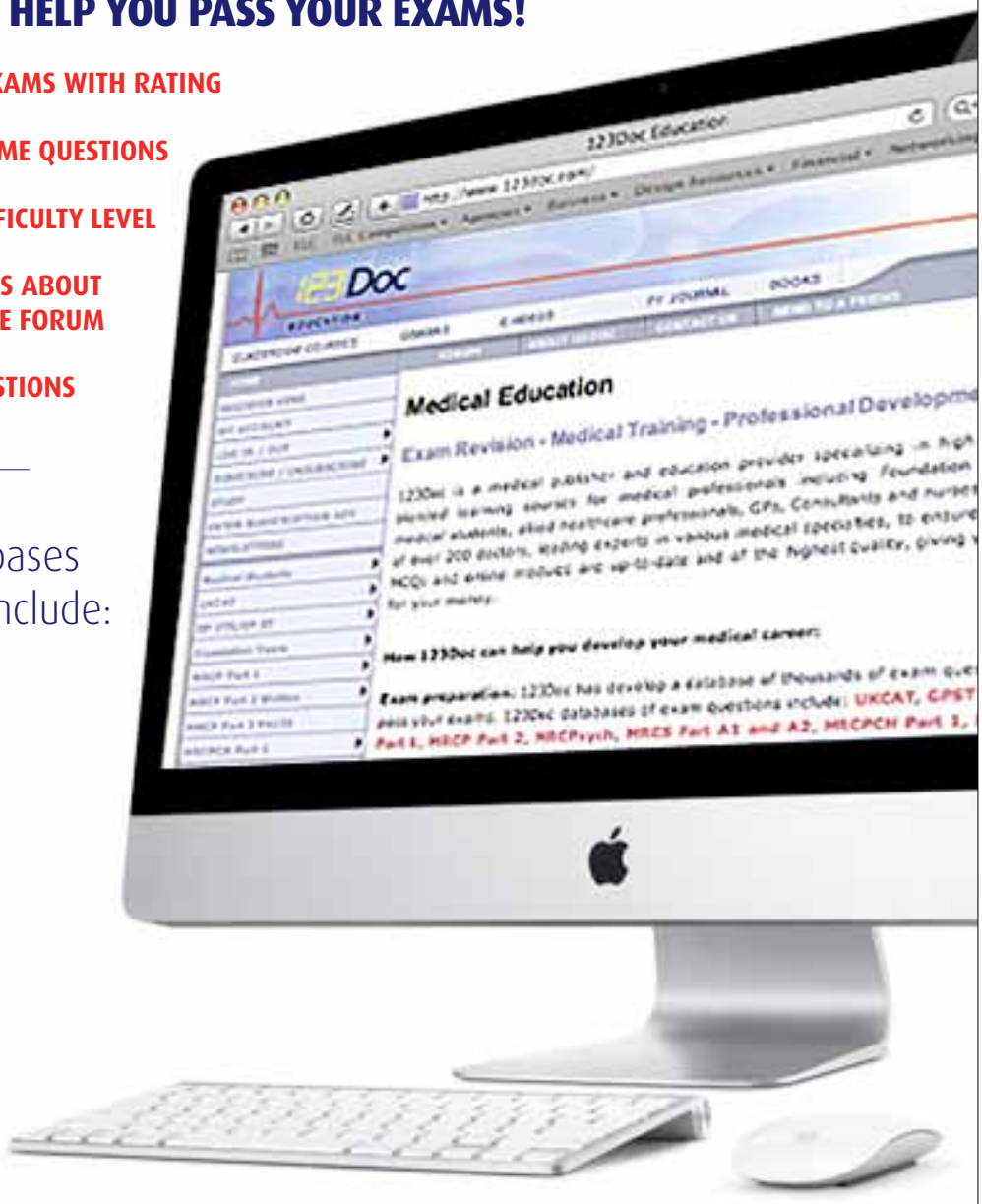

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