

EASILY MISSED?

Lung cancer

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Hamden, professor of primary care, Department of Primary Care Health Sciences, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at practice@bmj.com.

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Previous articles in this series

- ▶ Nasal septal haematoma (*BMJ* 2014;349:g6075)
- ▶ Perthes' disease (*BMJ* 2014;349:g5584)
- ▶ Kawasaki disease (*BMJ* 2014;349:g5336)
- ▶ Postnatal depression (*BMJ* 2014;349:g4500)
- ▶ Motor neurone disease (*BMJ* 2014;349:g4052)

A 65 year old recent ex-smoker with a 20 pack year history and chronic obstructive pulmonary disease (COPD) consults his general practitioner because of worse chest symptoms over the past three weeks, with increasing breathlessness and production of green sputum, and a feeling of being “off colour.” Similar previous spells have been treated with antibiotics and steroids to good effect. On examination his temperature is normal, his heart rate is 88 beats/min, respiratory rate is 16 breaths/min, and oxygen saturation is 94% on air. He has tobacco stained fingers but no clubbing or evidence of weight loss. Scattered crackles and wheezes are found on auscultation of the lungs. After treatment with antibiotics and steroids he feels no better, and after two further consultations he is referred for chest radiography, which is reported as showing a lesion suspicious of lung cancer.

Lung cancer

Lung cancer refers to primary tumours of the lung and is initially classified histologically as small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) because these two types behave very differently. The main forms of NSCLC are squamous, adenocarcinoma, and neuroendocrine large cell cancers. This subdivision has become more important with the advent of tailored chemotherapy for advanced disease based on the subtype of NSCLC and biological drugs for some adenocarcinomas. These include tyrosine kinase inhibitors in tumours with sensitising mutations in the epidermal growth factor receptor and, even more recently, anaplastic lymphoma kinase inhibitors.

Why is it missed?

Lung cancer is harder to diagnose than most other cancers so the diagnosis is often delayed. There is evidence from recent well conducted cohort studies that:

- A third of patients consulted their GP about the health problem caused by cancer three or more times before referral (third highest of the 18 cancers reported)³

HOW COMMON IS IT?

- In 2011, there were 43 463 new cases of lung cancer in the United Kingdom, making it the second most common cancer and representing 13% of all new cancers¹
- The crude incidence rate is 77 cancer cases per 100 000 men in the UK, and 61 per 100 000 women
- In most cases there is a history of smoking, and incidence increases with age
- Patients with chronic obstructive pulmonary disease are about four times more likely to develop lung cancer than those without (1% risk/year)²
- Lung cancer accounts for 22% of deaths from cancer in the UK. An average GP will see about one new diagnosis of lung cancer each year

- The median diagnostic interval (time from first presentation to diagnosis) is 112 days (interquartile range 45-251)—the second highest of the 15 cancers reported⁴
- The median primary care interval (time from first presentation to referral) is 14 days (3-40) (only myeloma is higher) and increases with increasing numbers of pre-referral consultations³
- Thirty nine per cent of lung cancers present as an emergency (a marker for poor outcomes)—only cancers of the brain and pancreas are higher.⁵

The diagnosis may be initially missed because of lack of a clear “symptom signature,”⁶ symptomatic “noise” resulting from COPD and other comorbidities,⁷⁻⁸ chest radiographs being reported as normal or benign findings,⁹ presentation with non-respiratory or atypical symptoms, or patient mediated factors (such as delay in re-presenting or declining earlier referral).

Why does this matter?

Overall, lung cancer has a poor prognosis. Longer diagnostic intervals are associated with increased mortality,¹⁰ with fewer patients being amenable to curative treatments. There may also be morbidity and quality of life benefits from more timely diagnosis, although this has not been proved. Certainly, late diagnosis creates enormous challenges for patients and their families in coming to terms with the diagnosis, planning for their changed circumstances, and resolving their affairs. It is not unusual for patients to present for the first time as a medical emergency and then to die in hospital.⁵

How is it diagnosed?

Chest radiography is the main investigation that leads to diagnosis. In about 10% of patients subsequently diagnosed with lung cancer, the initial radiograph is reported as normal, and indeterminate abnormalities are found in a further 13%.⁹ Computed tomography is used largely in specialist practice, either when the radiograph is

THE BOTTOM LINE

- Suspect lung cancer in all at-risk patients (age, smoking, chronic obstructive pulmonary disease) with a new respiratory symptom, or atypical non-respiratory symptom, even if they appear otherwise well
- Consider lung cancer in non-smokers with suspicious symptoms, especially haemoptysis and multiple symptoms
- Chest radiography is cheap, easy, widely available, and relatively harm free, but can be falsely negative. Have a low threshold for repeating or referring for specialist opinion (or considering computed tomography if available) if there are diagnostic suspicions
- Aim to diagnose patients as quickly as possible to optimise the chance of cure and active anti-cancer treatment

negative but cancer is still suspected or when the radiograph shows an abnormality. Further invasive tests are then undertaken to provide a tissue diagnosis. Thus, identification in primary care, where most patients initially present,¹¹ generally hinges on identifying features that prompt a chest radiograph or that require specialist investigation even if the radiograph is normal, such as persistent haemoptysis in an older smoker. Thus, we concentrate on features that may prompt a request for chest radiography.

A recent systematic review collated five primary care reports of lung cancer symptoms.⁶ Positive predictive values (PPVs, which express the risk of cancer numerically) of symptoms were: cough 0.4% in two studies, weight loss 1.1% and 6.1% in two studies, and appetite loss 0.9% and 4.7% in two studies. The classic feature of lung cancer—haemoptysis—had a PPV of 2.4–7.5%. However, only a minority of primary care patients with lung cancer report haemoptysis.¹¹ PPVs increase with age, current smoking, and multiple or persistent symptoms.^{11–13}

Three algorithms for the diagnosis of lung cancer have been created: the simplest, a risk assessment tool, offers PPVs for pairs of symptoms or for repeated symptoms, stratified into smokers and non-smokers. In a before and after study, use of the tool was accompanied by increased requests for chest radiography and lung cancer diagnosis, including early stage cancers.¹⁴ Q-cancer and a second algorithm are multivariable equations that incorporate data on risk factors as well as symptoms.^{12–13} Their theoretical performance is good, but no reports of actual performance are available. Risk assessment tools and Q-cancer have been incorporated into all UK based primary care clinical software systems and can be programmed to prompt the GP once a lung cancer risk above an agreed threshold has been estimated.

Patients who present with symptoms recommended by the National Institute for Health and Care Excellence (NICE) for investigation have shorter times to diagnosis compared with those without these symptoms.^{4–15} This reflects possible alternative diagnoses for the “low risk but not no risk” symptoms, such as cough, plus the atypical presentations, especially with metastases.

How is it managed?

Treatment in the United Kingdom is based on NICE guidance and depends on histological type, disease stage, fitness, performance status, and patient preference.¹⁶ Tissue diagnosis is commonly achieved at bronchoscopy, sometimes using endobronchial ultrasound, or imaging guided needle biopsy. In NSCLC, if the tumour appears localised on the diagnostic computed tomogram, staging positron emission tomography-computed tomography is needed to establish eligibility for curative treatment. When the disease is localised and the patient has adequate physiological reserve, surgery is the treatment of choice. If the tumour is unresectable, radiotherapy is an alternative radical option, provided the disease can be encompassed in a treatment volume. Stereotactic ablative radiotherapy is increasingly available as a curative option in patients with peripheral tumours and borderline fitness. Multimodality treatment may increase cure rates

and should be considered in fitter patients. When radical treatment is not possible in NSCLC and functional status is good, chemotherapy can improve life expectancy and symptom control. Highly effective biological agents are now available for the minority of adenocarcinomas that carry specific sensitising mutations.

For localised SCLC, chemoradiotherapy can be given with curative intent, and chemotherapy has prognostic and palliative value in the remaining patients, provided they are fit enough. The substantial majority of patients who present with advanced disease of whatever histological type can benefit from palliative treatments, including radiotherapy and specialist palliative care. However, resection rates are improving,¹⁷ and there are encouraging signs that early diagnostic initiatives, such as the use of risk assessment tools, may have benefit¹⁴—particularly in reducing the number of emergency admissions.

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GUIDELINES

Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance

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Community acquired pneumonia is a common condition that causes considerable morbidity and has a mortality rate of approximately 20% for patients admitted to hospital in the United Kingdom.¹ It is diagnosed in 5-12% of adults who present to general practitioners with symptoms of lower respiratory tract infection,^{2 3} and 22-42% are subsequently admitted to hospital.^{3 4} Adherence to previous guidelines has been poor, and this variation in practice can lead to suboptimal outcomes such as increased mortality and longer stay in hospital.⁵⁻⁷ Hospital acquired pneumonia (excluding ventilator associated pneumonia) has a point prevalence of approximately 1% of hospital inpatients, is estimated to lengthen hospital admission by an average of eight days, and has a high mortality rate.^{8 9} This article summarises the most recent recommendations for the management of both types of pneumonia from the National Institute for Health and Care Excellence (NICE).¹⁰

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on thebmj.com.

Presentation with lower respiratory tract infection

Of people who present to general practitioners with symptoms of lower respiratory tract infection, only a small proportion have community acquired pneumonia. In those who do not have a clinical diagnosis of pneumonia, the decision whether to prescribe antibiotics can be difficult, with a tendency towards over-prescription. Performing a point of care C reactive protein test can help to identify patients with lower respiratory tract infections who will, and will not, benefit from antibiotics.

- For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C reactive protein test if after clinical assessment a diagnosis of pneumonia has not been

Box 1 | CRB65 score for mortality risk assessment in primary care¹¹

CRB65 score is calculated by giving 1 point for each of the following prognostic features:

- Confusion (abbreviated mental test score 8 or less or new disorientation in person, place, or time)*
- Raised respiratory rate (30 breaths per minute or more)
- Low blood pressure (diastolic 60 mm Hg or less, or systolic less than 90 mm Hg)
- Age 65 years or more

Patients are stratified for risk of death as follows:

- 0=low risk (less than 1% mortality risk)
- 1 or 2=intermediate risk (1 to 10% mortality risk)
- 3 or 4=high risk (more than 10% mortality risk)

*For guidance on delirium, please refer to National Institute for Health and Care Excellence. Delirium: diagnosis, prevention and management (NICE clinical guideline 103). 2010. www.nice.org.uk/guidance/cg103

made and it is not clear whether antibiotics should be prescribed. Use the results of the C reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows:

- Do not routinely offer antibiotic therapy if the C reactive protein concentration is less than 20 mg/L
- Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C reactive protein concentration is between 20 mg/L and 100 mg/L
- Offer antibiotic therapy if the C reactive protein concentration is greater than 100 mg/L.

Community acquired pneumonia

Assessment of severity in community acquired pneumonia is important, as it helps to guide subsequent aspects of management such as place of care and choice of antibiotic therapy.

Severity assessment in primary care

- When a clinical diagnosis of community acquired pneumonia is made in primary care, determine whether patients are at low, intermediate, or high risk of death by using the CRB65 score (see box 1).

Box 2 | CURB65 score for mortality risk assessment in hospital¹¹

CURB65 score is calculated by giving 1 point for each of the following prognostic features:

- Confusion (abbreviated mental test score 8 or less or new disorientation in person, place, or time)*
- Raised blood urea nitrogen (over 7 mmol/L)
- Raised respiratory rate (30 breaths per minute or more)
- Low blood pressure (diastolic 60 mm Hg or less, or systolic less than 90 mm Hg)
- Age 65 years or more

Patients are stratified for risk of death as follows:

- 0 or 1=low risk (less than 3% mortality risk)
- 2=intermediate risk (3 to 15% mortality risk)
- 3 to 5=high risk (more than 15% mortality risk)

*For guidance on delirium, please refer to National Institute for Health and Care Excellence. Delirium: diagnosis, prevention and management (NICE clinical guideline 103). 2010. www.nice.org.uk/guidance/cg103

- Use clinical judgment in conjunction with the CRB65 score to inform decisions about whether patients need hospital assessment as follows:
 - Consider home based care for patients with a CRB65 score of 0
 - Consider hospital assessment for all other patients, particularly those with a CRB65 score of 2 or more.

Severity assessment in hospital

- When a diagnosis of community acquired pneumonia is made at presentation to hospital, determine whether patients are at low, intermediate, or high risk of death by using the CURB65 score (see box 2).
- Use clinical judgment in conjunction with the CURB65 score to guide the management of community acquired pneumonia, as follows:
 - Consider home based care for patients with a CURB65 score of 0 or 1
 - Consider hospital based care for patients with a CURB65 score of 2 or more
 - Consider intensive care assessment for patients with a CURB65 score of 3 or more.
- Stratify patients presenting with community acquired pneumonia into those with low, moderate, or high severity disease. The grade of severity will usually correspond to the risk of death.

Microbiological tests

- Do not routinely offer microbiological tests to patients with low severity community acquired pneumonia.
- For patients with moderate or high severity community acquired pneumonia:
 - Take blood and sputum cultures *and*
 - Consider pneumococcal and legionella urinary antigen tests.

Timely diagnosis and treatment

Early administration of antibiotics to patients admitted with community acquired pneumonia improves

outcomes, but this must be linked to swift, accurate diagnosis to avoid inappropriate, potentially harmful, administration of antibiotics to those who prove to have a different diagnosis (for example, heart failure).

- Put in place processes to allow diagnosis (including x rays) and treatment of community acquired pneumonia within four hours of presentation to hospital.
- Offer antibiotic therapy as soon as possible after diagnosis, and certainly within four hours to all patients with community acquired pneumonia who are admitted to hospital.

Antibiotic therapy

Antibiotic therapy is the cornerstone of management of community acquired pneumonia, but overuse may be harmful. Careful tailoring of antibiotic type and duration to severity of pneumonia is therefore important. The recommendation for a five day course of antibiotics in low severity community acquired pneumonia is shorter than in previous guidance, with the safety net of advising patients to seek further medical advice if they are not improving and clinicians to consider extending the course as a possible management strategy when improvement is inadequate. Routine use of longer antibiotic courses and dual antibiotic therapy should be reserved for patients with moderate or high severity community acquired pneumonia.

Low severity community acquired pneumonia:

- Offer a five day course of a single antibiotic to patients with low severity community acquired pneumonia.
- Consider amoxicillin in preference to a macrolide or a tetracycline. Consider a macrolide or a tetracycline for patients who are allergic to penicillin.
- Consider extending the course of the antibiotic for longer than five days as a possible management strategy for patients whose symptoms do not improve as expected after three days.
- Explain to patients treated in the community, and, when appropriate, to their families or carers, that they should seek further medical advice if their symptoms do not begin to improve within three days of starting the antibiotic, or earlier if their symptoms are worsening.
- Do not routinely offer:
 - A fluoroquinolone
 - Dual antibiotic therapy.

Moderate and high severity community acquired pneumonia:

- Consider a seven to 10 day course of antibiotic therapy for patients with moderate or high severity community acquired pneumonia.
- Consider dual antibiotic therapy with amoxicillin and a macrolide for patients with moderate severity community acquired pneumonia.
- Consider dual antibiotic therapy with a β lactamase stable β lactam and a macrolide for patients with high severity community acquired pneumonia. Available β lactamase stable β lactams include co-amoxiclav, cefotaxime, ceftriaxone, cefuroxime, and piperacillin with tazobactam.

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Previous articles in this series

▶ Diagnosis and management of gallstone disease
(*BMJ* 2014;349:g6241)

▶ Diagnosing and managing acute heart failure in adults
(*BMJ* 2014;349:g5695)

▶ Multiple sclerosis
(*BMJ* 2014;349:g5701)

▶ Assessment and management of bipolar disorder
(*BMJ* 2014;349:g5673)

▶ Diagnosis and management of drug allergy in adults, children and young people
(*BMJ* 2014;349:g4852)

Glucocorticosteroid treatment

- Do not routinely offer a glucocorticosteroid to patients with community acquired pneumonia unless they have other conditions for which glucocorticosteroid treatment is indicated.

Monitoring in hospital

Measuring C reactive protein concentration in patients in hospital with community acquired pneumonia can help to identify patients who are not responding to treatment and need their management to be reassessed.

- Consider measuring a baseline C reactive protein concentration in patients with community acquired pneumonia on admission to hospital and repeat the test if clinical progress is uncertain after 48 to 72 hours.

Safe discharge from hospital

Reducing length of stay has been a common goal in an over-stretched NHS in the United Kingdom. However, discharge of patients who are not yet sufficiently stable can result in increased mortality and higher readmission rates.

- Do not routinely discharge patients with community acquired pneumonia if in the previous 24 hours they have had two or more of the following findings:
 - Temperature higher than 37.5°C
 - Respiratory rate 24 breaths per minute or more
 - Heart rate more than 100 beats per minute
 - Systolic blood pressure 90 mm Hg or less
 - Oxygen saturation less than 90% on room air
 - Abnormal mental status
 - Inability to eat without assistance.
- Consider delaying discharge if their temperature is higher than 37.5°C.

Patient information

Many patients are unaware of what to expect when recovering from community acquired pneumonia. Knowing the timeline of a “normal” recovery can help to reduce anxiety, while also highlighting the need to seek further advice if they are not improving as expected.

- Explain to patients with community acquired pneumonia that after they start treatment their symptoms should steadily improve, although the rate of improvement will vary with the severity of the pneumonia, and most people can expect that by:
 - 1 week—fever should have resolved
 - 4 weeks—chest pain and sputum production should have substantially reduced
 - 6 weeks—cough and breathlessness should have substantially reduced
 - 3 months—most symptoms should have resolved, but fatigue may still be present
 - 6 months—most people will feel back to normal.
- Advise patients with community acquired pneumonia to consult their healthcare professional if they feel that their condition is deteriorating or not improving as expected.

Hospital acquired pneumonia (excluding ventilator associated pneumonia)

Unfortunately, the evidence base for hospital acquired pneumonia was sparse. As a result, the Guideline Development Group was not able to make specific recommendations on many of the topics examined.

Antibiotic therapy

- Offer antibiotic therapy as soon as possible after diagnosis, and certainly within four hours, to patients with hospital acquired pneumonia.
- Choose antibiotic therapy in accordance with local hospital policy (which should take into account knowledge of local microbial pathogens) and clinical circumstances.
- Consider a five to 10 day course of antibiotic therapy.

Overcoming barriers

Many patients expect to receive antibiotics whenever they feel unwell with a productive cough, and two aspects of this new guidance will run contrary to these expectations. Both are important because overuse of antibiotics can be detrimental to individual patients (owing to adverse effects of drugs and complications such as *Clostridium difficile* infection) and to the population in general (by promoting increased antibiotic resistance). Consideration of the use of a point of care C reactive protein test in primary care is a new recommendation that will require some initial, and ongoing, cost outlay and education. However, incorporating the result of the test into discussions with patients should help to reassure them when antibiotics are not indicated (most cases). Many people who have received antibiotics go on to receive a second course because their symptoms have not completely resolved. The evidence on the expected natural resolution of symptoms suggests that most of these courses are probably unnecessary, and education on this point should also reduce the misplaced use of antibiotics.

Other areas of the guideline focus on the importance of early but accurate diagnosis of pneumonia and on the use of validated severity assessment to guide the prompt and appropriate use of antibiotics when these are indicated. We hope that this guideline will not only remind clinicians of the importance of antibiotic stewardship but also encourage prompt and correct use of antibiotics once it is clear that these are required.

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