Investigating the patient with recurrent pneumonia

Each month we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Recurrent pneumonia is pneumonia occurring at least twice in 12 months or three times during a lifetime. There is nearly always an underlying cause for recurrent pneumonia.

What is pneumonia?

Pneumonia is defined as the clinical and radiological consolidation of the lungs. It is usually due to infective causes but can be due to chemical or physical factors that cause pneumonitis, which may also be complicated by secondary infection.

The causes of pneumonia are often classified according to the aetiological agent. However, in about 50% of the cases of pneumonia treated in hospital the causative agent is not identified. The commonest causes identified are *Streptococcus pneumoniae* (also known as pneumococcus), *Haemophilus influenzae* and the atypical agents *Mycoplasma*, *Chlamydia* and *Legionella*. Viruses, rickettsia, fungi, drugs, aspiration of upper airway or gastric secretions and radiotherapy are other causes. Pneumonia is often classified as community acquired pneumonia or nosocomial pneumonia (pneumonia acquired during a hospital admission); the causative organisms are often different.

'Pneumonia and influenza' was the seventh commonest cause of mortality in Australia in 2000 and caused 2.3% of total deaths that year.[1] There are no data available on the incidence of recurrent pneumonia in Australia, although a retrospective analysis of pneumonia in a paediatric hospital estimated 8% of childhood pneumonia was recurrent.[2]

Causes of recurrent pneumonia

Recurrent pneumonia can affect all ages and the underlying causes differ according to age (Table 1). Recurrent infection in the same site should raise suspicions of a localised bronchopulmonary abnormality while recurrent infection in different sites may reflect a generalised underlying lung disease, an immunodeficiency state or neuromuscular or oesophageal dysfunction. The causes are discussed further in the box on page 63.

Clinical presentation

The main clinical features of pneumonia are fever and productive cough. Patients may also have pleuritic chest pain and dyspnoea. In the geriatric age group the features are often nonspecific, with delirium being the major manifestation.

IN SUMMARY

- **Recurrent pneumonia is pneumonia occurring at least twice in 12 months or three times during a lifetime.**
- **It can affect all ages but the underlying causes differ according to age.**
- **Investigation involves assessment of the current episode so it can be managed properly and a search for the underlying cause of the pneumonia.**
- **Appropriate investigations include a chest x-ray, thoracic CT scan, identification of the causative organism and, as indicated, bronchoscopy and tests of swallowing, immune and cilial functions.**
- **Specialist assistance is usually required for the management of recurrent pneumonia.**

Table 1. Underlying causes of recurrent pneumonia

Children
- Oropharyngeal inco-ordination
- Aspiration
- Immunodeficiency states
- Respiratory tract anomalies
- Cystic fibrosis

Young adult
- Cystic fibrosis
- Pulmonary tumours
- Immunodeficiency states
- Ciliary dysfunction

Adult
- Bronchiectasis
- Acquired immunosuppression
- AIDS
- Lung cancer
- Immunosuppression associated with cancer chemotherapy, organ transplant
- Ciliary dysfunction

Elderly
- Multiple pathology
- CNS diseases such as stroke and motor neurone disease
- Primary or secondary malignancy

Clinical signs include tachypnoea (this can be a sensitive sign in the elderly), crackles or bronchial breath sounds. Wheeze may indicate sputum in the airway, a fixed localised obstruction or the co-occurrence of airways obstruction. Other signs may occur as a result of complications associated with pneumonia.

Diagnosis

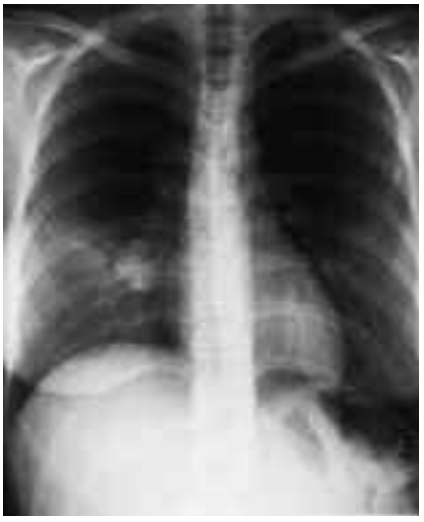
Diagnosis of pneumonia is based on clinical signs on physical examination and consolidation or other typical signs on chest x-ray. Investigations should be directed at assessment of the current episode to guide management and a search for the cause of recurrent episodes (Tables 2 and 3).

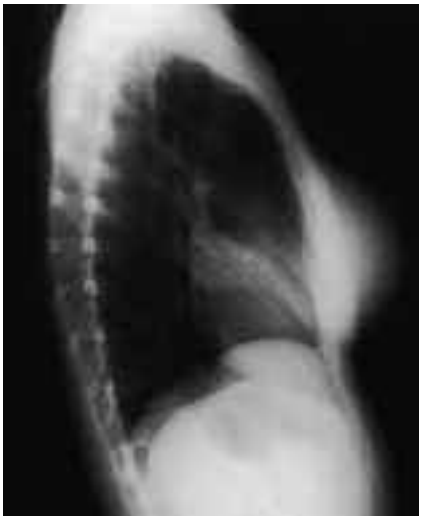
Investigating the current episode

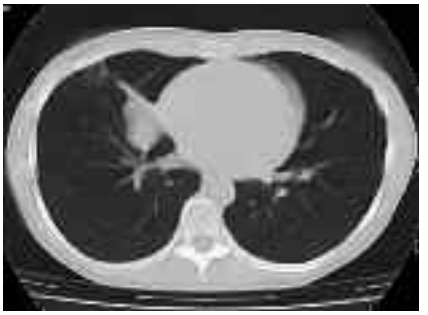
For very mild episodes the diagnosis of pneumonia may be made clinically and empirical treatment then started. A chest x-ray, however, is needed to make a definite diagnosis or if the response to treatment is inadequate. The classical appearance on x-ray is lobar consolidation with an air bronchogram, but the appearance may range from a patchy to confluent opacity with involvement of one or more lobes and one or both lungs. Poor prognostic features on x-ray include multilobar involvement, cavitation, pleural effusion and rapid extension.

An x-ray may suggest an underlying cause or demonstrate coexistent abnormalities, such as apical lesions suggesting tuberculosis, lobar pneumonia due to *S. pneumoniae* or cavitation due to *Staphylococcus aureus* or Gram-negative organisms. Aspiration occurs in the supine position so the apical segments of either or both lower lobes or posterior segments of the upper lobes are most often affected. Acidity can result in pulmonary oedema and acute respiratory distress syndrome, while occasionally food can physically obstruct a bronchus. Oximetry, full blood count and electrolytes, urea and creatinine will help determine patients at risk (O_2 saturation <85%; haemoglobin <90 g/L; white cell count $<4x10^9$/L or $>30x10^9$/L; creatinine >110 µmol/L; blood urea nitrogen >7.0 mmol/L) who may warrant hospitalisation.

Although it is ideal to treat according to causative agent this is often not possible for the following reasons:
- in over 50% of pneumonia cases in hospital the causative agent is not identified
- delay in initiating antibiotic (more than eight hours after hospital presentation) is associated with poorer outcome
- co-infection may occur in about 10%







Figures 1a to c. Chest x-rays and CT scan of a 24-year-old woman with recurrent episodes of right middle lobe broncho-pneumonia. The x-rays and CT scan showed a right infrahilar mass. This was resected and found to be a carcinoid tumour.

Specific causes of recurrent pneumonia

Aspiration

Pneumonia caused by aspiration of upper airway or gastric secretions, or both, generally results from impaired protection of the airway or increased reflux. The cause may be chemical, bacterial or both. Gastric secretions cause a chemical pneumonitis because of their acidity. Occasionally, aspirated food may obstruct an airway and cause distal atelectasis or infection.

Small amounts of saliva are aspirated into the lungs during sleep in 45% of healthy patients and 75% of patients with a depressed level of consciousness. The organisms causing infection generally reflect the oral population and include the anaerobes *Bacteroides*, *Fusibacterium* and *Peptostreptococcus*. The likelihood of pneumonia developing after aspiration is influenced by the quantity, bacterial content and pH of the fluid aspirated and the patient's defence mechanisms.

Aspiration probably causes about 3 to 6% of all cases of community acquired pneumonia. It occurs in particular risk groups, including patients with:

- a suppressed cough reflex, e.g. caused by alcohol, sedative drug overdose, general anaesthesia
- neurological conditions, e.g. cerebrovascular events, spinal cord injury, epilepsy and bulbar palsy
- oesophageal obstruction, e.g. achalasia, pharyngeal pouch and tracheo-oesophageal fistula
- dysfunction of the upper and lower oesophageal sphincters or oesophageal muscle
- respiratory conditions causing tachypnoea – patients may have difficulty maintaining apnoea during swallowing and also can be at risk of aspirating if their cough reflex is compromised
- end stage lung disease, such as chronic airflow limitation.

Bronchiectasis

A common cause of bronchiectasis is cystic fibrosis, which is best dealt with by specialised paediatric and adult respiratory units. Other forms of bronchiectasis are most often due to pulmonary infections and localised obstruction. It may also be due to developmental abnormalities.

Primary or secondary cilial dysfunction

Primary cilial motility disorders, now renamed immotile syndrome or dyskinetic cilia syndrome, are due to ultrastructural anomalies in respiratory cilia causing dysfunction and hence inadequate clearing of the airways and increased risk of infection. The frequent reduction in cilial function caused by cigarette exposure, pollutants, infection and drugs can also contribute to ongoing infection.

If cilial dysfunction is suspected or proven, physical aids to pulmonary drainage, i.e. physiotherapy, should be used aggressively.

Immune deficiencies

Infections may be associated with a wide range of inflammatory or immunological response defects and immunodeficiency states, e.g.:

- primary immunodeficiencies involving impaired T and B cell dysfunction – e.g. severe combined immunodeficiency and congenital (X-linked) hypogammaglobulinaemia
- secondary or acquired immunodeficiencies – e.g. HIV, malnutrition, malignancy and chemotherapy
- splenectomy – increases risk of bacterial infection
- neutropenia – especially acute in onset and involving neutrophil function abnormalities, such as chemotaxis (leucocyte adhesion deficiency, Job's syndrome, Chediak–Higashi syndrome) and microcidal defect (chronic granulomatous disease)
- impaired cellular phagocytosis – e.g. in systemic lupus erythematosus, chronic myeloid leukaemia and megaloblastic anaemia
- complement deficiencies, which impair the ability to opsonise bacteria – deficiencies in complement can result in immune complex syndromes and recurrent pyogenic infections.

Immunodeficiency states occur in less than 10% of adult cases of recurrent pneumonia. Humoral immunodeficiencies include congenital (X-linked) hypogammaglobulinaemia and acquired common variable hypogammaglobulinaemia. The latter is more common and presents at any age but more often in childhood and adolescence. Immunoglobulin replacement may prevent progressive lung damage.

Selective IgA deficiency is quite common (1 per 600 recurrent pneumonia cases) but leads to recurrent infection in very few patients. Bronchiectasis, therefore, is not usually associated with isolated IgA or IgM deficiencies but is more likely if these occur with a selective IgG subclass deficiency. Isolated selective IgG subclass deficiencies are also described in bronchiectasis.

IgE deficiency is not associated with recurrent infection but hyperimmunoglobulinaemia E syndrome (Job's syndrome) is associated with recurrent sinopulmonary infections.

Impaired immunity with secondary hypogammaglobulinaemia may also result from coexisting disease, especially lymphoma, chronic lymphocytic leukaemia, myeloma and diseases with heavy protein loss such as nephrotic syndrome and protein losing enteropathies.

Anatomical abnormalities

Pneumonia due to abnormalities in anatomy is more likely in young patients. Recurrent pneumonia involving the same site should raise suspicion of such a localised abnormality or malignancy (see below).

Malignancy

A primary lung malignancy can cause airway obstruction with distal pneumonia that is likely to recur unless the obstruction is removed. Metastatic malignancy is more often intrapulmonary but can cause external airway compression with the same consequences as an endobronchial tumour. Patients with other malignancies may be at increased risk of recurrent pneumonia due to immunosuppression associated with the primary tumour or chemotherapy. Protein and calorie malnutrition may also increase the risk.

Asthma

Asthmatics are generally not at increased risk for developing pneumonia but can develop recurrent atelectasis due to allergic bronchopulmonary aspergillosis or mucoid impaction. This process needs to be differentiated from recurrent bronchopneumonia. Oral steroids may cause immunosuppression and increased risk of infection.

Elderly patients

The increased risk of recurrent pneumonia in the elderly relates to many factors, including frequent use of antibiotics, pre-existing chronic disease, silent aspiration, crowded institutional care and ageing of immune and physical defences (leading to, for example, reduced cough reflex).

of cases of community acquired and 50% of nosocomial pneumonia.

For these reasons a variety of empirically based regimens are used; these are described elsewhere.[3,4]

Hospital admission is required for severe pneumonia, allowing a greater effort in identifying the causative organism. The usefulness of these investigations is described below.

Table 2. Investigating a current pneumonia episode

- Physical examination for clinical signs consistent with pneumonia
  - crackles
  - bronchial breath sounds
- Chest x-ray to show consolidation and other changes consistent with pneumonia
- For severe pneumonia, identification of causative organism by:
  - blood culture
  - respiratory serology
  - bronchoscopy (in at-risk patients)

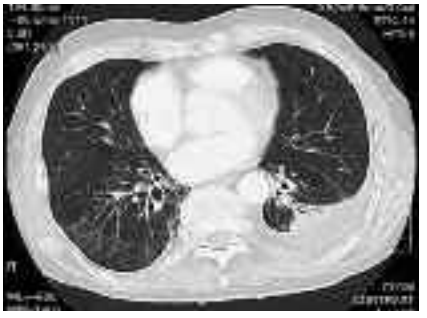


Figure 2. A 71-year-old man with Parkinson's disease, SLE and Sjögren's syndrome, bronchiectasis and recurrent lung infections. A right-sided empyema had been drained 12 years previously. He is on long term oral corticosteroid therapy. He has had three episodes of broncho-pneumonia in the last 12 months. CT scan shows basal fibrosis and atelectasis, traction bronchiectasis, air bronchogram in left lower lobe and left pleural effusion.

Investigating recurrent episodes

Investigation and management of recurrent pneumonia usually requires specialist assistance. Often the patient's presentation or underlying medical problems suggest a predisposing cause and careful clinical assessment will lead to selection of some of the investigations listed below.

CT scan

As mentioned earlier, recurrent infection in the same site should raise suspicions of a localised obstruction, while recurrent infection in different sites may reflect generalised underlying lung disease or immunodeficiency. A CT scan should be performed in all cases of recurrent pneumonia to exclude anatomical abnormalities, tumours and bronchiectasis (Figures 1 and 2). Contrast should be used when tumours are suspected.

High resolution CT is required to diagnose bronchiectasis because chest x-rays are less than 50% sensitive for diagnosis. High resolution CT uses thin (1 to 2 mm) cuts at 10 mm intervals and is 82 to 97% sensitive when compared to the previous gold standard of bronchography.

Microbiology assays

Microbiological assays are best used with the advice of the local microbiology laboratory with regard to the speed, specificity and sensitivity of each test.

Sputum culture and sensitivity

There is a lot of controversy as to the overall usefulness of sputum culture. Treatment should not be delayed until a causative agent is identified. Problems with sputum testing include:

- inadequate samples
- contamination of the sample, which may prevent identification of the causative pathogen
- bacterial colonisation, which can result in the identification of a nonrelevant pathogen
- prior use of antibiotics preventing bacterial growth.

If the patient's initial response to treatment is poor then it is important to assess carefully the results of sputum culture and sensitivity. Specific stains may be diagnostic for certain pathogens – for example, *Mycobacterium, Nocardia, Legionella, Pneumocystis carinii* and fungi, although with fungi it has to be decided whether the isolate is clinically relevant. Identification of a Gram-negative organism on repeated cultures may suggest an underlying lung disease such as bronchiectasis. Identifying a pathogen may lead to an alteration in management.

If aspiration pneumonia is suspected, the Gram stain may be expected to show various Gram-positive cocci and Gram-negative rods in a purulent sample with a negative culture result. Under these circumstances, noncontaminated samples should be obtained (blood culture, sheathed bronchial brush, pleural aspiration) and then cultured under anaerobic conditions.

Sputum sensitivity results may also guide antibiotic usage in specific instances, such as partially resistant *S. pneumoniae.* The antibiotic sensitivities of Gram-negative bacteria may change over time, especially in patients receiving repeated courses of antibiotics, and should be checked. It is mandatory to obtain sensitivity results in the management of tuberculosis.

Antigen detection

Tests for antigens using monoclonal antibody or polymerase chain reaction techniques (PCR) on sputum or serum samples are available for *Mycobacterium tuberculosis, M. avium* and *M. intercellulare, Pneumocystis, Mycoplasma, Chlamydia, Bordetella pertussis* and cytomegalovirus. In some cases, such as pertussis, PCR results are superior to culture. *H. influenzae* PCR will become available in the future. PCR tests can give both false positive and false negative results so liaison with the microbiology laboratory is recommended.

Legionella pneumophila urinary antigen is a good test for early detection of disease and can be detected in the urine of more than 80% of patients with *L. pneumophila* serogroup 1 infection. It can be a useful epidemiological tool.

Serology

Serology is usually requested as:

- viral respiratory screen – for influenza A and B viruses, adenovirus, herpes zoster)
- atypical serology – for *Chlamydia, Legionella* and *Mycoplasma*.

Blood cultures

Blood cultures are less likely to be contaminated than sputum cultures so the results are more significant. Two sets of blood cultures should be taken, preferably before the initiation of antibiotic therapy. The overall yield in patients with pneumonia is about 11%, with *S. pneumoniae* being the most common isolate. About 70% of adults with a positive blood culture for *S. pneumoniae* have pneumonia as a focus of their infection. In nonindigenous and indigenous children under 15 years, this figure is 27% and 58%, respectively.[5]

Bronchoscopy

Bronchoscopy may be undertaken to obtain a bronchoalveolar lavage or bronchial brush sample for culture and sensitivity testing (the latter can be made free of contamination by using a sheathed brush). The usefulness of this procedure is limited because generally by the time it is initiated antibiotic therapy has already been started. The yield in ventilated community acquired pneumonia is 13 to 48%. The sensitivity of bronchoalveolar lavage in detection of AIDS-related pneumocystis pneumonia is high (86 to 97%). Bronchoalveolar lavage is also useful for diagnosis of cytomegalovirus pneumonia and invasive pulmonary aspergillosis.

Bronchoscopy is also undertaken to look for a bronchial abnormality as a cause of the recurrent pneumonia and as a therapeutic process to remove obstructions such as food or mucous plugs.

Investigating pneumonia due to specific causes

Aspiration pneumonia

Assessment of the cough reflex

Getting patients to cough provides a quick assessment of the strength of their cough, which is an intrinsic component of the ability to clear airway secretions. A nonexplosive or bovine cough is associated with recurrent laryngeal nerve palsy. Patients often suppress coughing because of pain caused by, for example, a rib fracture or pleurisy. Analgesia should help.

Table 3. Investigating causes of recurrent pneumonia

General investigations

- CT scan – to exclude anatomical abnormalities, tumours and bronchiestasis
- High resolution CT scan – to diagnose bronchiectasis
- Microbiological assays – to identify causative organisms
  - sputum and blood cultures and sensitivities
  - monoclonal antibody and polymerase chain reaction tests, for antigen detection (*Mycobacterium, Pneumocystis, Mycoplasma, Chlamydia, Bordetella pertussis* and cytomegalovirus)
  - serology tests, for respiratory viruses and atypical causative organisms
- Bronchoscopy
  - culture and sensitivity
  - bronchial abnormalities
  - obstruction (food or mucous plugs)

Assessment of suspected aspiration pneumonia

- Cough reflex
- CNS assessment
  - consciousness level and cranial nerve function
  - gag reflex
  - swallowing mechanism
- Gastrointestinal tract assessment
  - radiology, motility and manometry studies
  - oesophageal pH
  - endoscopy

Investigation of immunodeficiency-related pneumonia

- Full blood count
- Immune system testing
  - immune response
  - serum electrophoresis
  - delayed hypersensitivity skin tests and proliferative responses
  - complement levels
  - neutrophil and macrophage function

Investigations for suspected cilial abnormalities

- Saccharin test, for cilial function
- Light microscopy, for nasal cilia beat frequency
- Electron microscopy, for ultrastructural abnormalities

CNS assessment

The level of consciousness, the function of the 7th, 9th, 10th and 12th cranial nerves (which play a part in protection of the upper airway) and the ability to swallow should be assessed. A reduced gag reflex indicates reduced sensory function, which can predispose to aspiration.

The swallowing mechanism can be assessed by stimulating a swallow (for example, by applying pressure at the back of the tongue) or by watching the patient swallow a bolus of food. Absent or sluggish swallowing indicates a risk for aspiration. Silent aspiration cannot be detected clinically. However, if it is suspected, a modified barium swallow (videofluoroscopy) can detect abnormalities such as pooling of fluid, pharyngeal spills, sluggish swallowing, anatomical deformities and silent aspiration. Upper airway endoscopy to watch part of the swallow, using food stained with blue food dyes, can also show abnormalities. These techniques require the skills of a speech therapist and an ENT surgeon.

Gastrointestinal assessment

Investigations used to assess the gastro - intestinal tract include radiology (barium swallow with fluoroscopy), motility and manometry studies, oesophageal pH and endoscopy of the oesophagus and stomach.

Immunodeficiency-related pneumonia

Investigation of the immune system requires evaluation of humoral immunity (B cells), cell-mediated immunity (T cells), neutrophils, macrophages and complement. Investigations include:

- full blood count – to detect neutropenia and lymphocytopenia (CD4 counts are useful prognostically to determine the likelihood of *Pneumocystis carinii* pneumonia in HIV-positive patients, counts under 0.2 x 10^9/L indicating high risk)
- IgG, IgM, IgA and IgG levels – these may be low in primary and acquired immunoglobulin deficiency states
- immune response to *S. pneumoniae* or *H. influenzae* postvaccination – functional immunoglobulin deficiencies are detected by failure of a serological response to pneumococcus and tetanus toxoid (one prospective study showed that pneumonia recurrence was more likely if there was a low antibody response to pneumococcal vaccine)[4]
- serum electrophoresis (EPG and IEPG) – to look for monoclonal bands present in multiple myeloma
- delayed hypersensitivity skin tests and proliferative responses to mitogens and allogeneic cells, cytokine production – to evaluate T cell function
- complement tests (C3, C4, CH50) – to look for complement deficiencies
- tests of neutrophil and macrophage function – these are performed by specialist units.

Other tests are only relevant if indicated, such as testing for autoantibodies if scleroderma, Wegener's granulomatosis or rheumatoid arthritis is suspected.

Pneumonia and cilial abnormalities

The simplest test of cilial function is the saccharin test, in which saccharin is placed on either inferior nasal turbinate and normal cilial function results in tasting the saccharin within 30 minutes. Another investigation is determining the beat frequency of nasal cilia. This can be done by light microscopy of a sample of nasal cilia obtained using a nasal brush (12 to 14 beats per second is normal).

Electron microscopy is required to make a specific diagnosis of individual cilial structural defects. Radionuclide scans show promise in defining the rate of particle clearance from the airways but are still only used as a research tool.

Conclusion

Investigation of a patient with recurrent episodes of pneumonia involves assessment of the current episode so it can be managed properly and a search for the underlying cause of the pneumonia. Investigations will include a chest x-ray, thoracic CT scan, identification of the causative agent and, as indicated, bronchoscopy and tests of swallowing, immune and cilial functions. MT

References

1. Australian Bureau of Statistics. Causes of death, Australia 2000. (www.abs.gov.au)
2. Owayed AF, Campbell DM, Wang EE. Underlying causes of recurrent pneumonia in children. Arch Pediatr Adolesc Med 2000; 154: 190-194.
3. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2001; 163: 1730-1754.
4. Therapeutic Guidelines: Antibiotic 11th edition 2000. Melbourne: Therapeutic Guidelines Ltd, 2000: 143-157.
5. McIntyre PB, Gilmour RE, Gilbert GL, et al. Epidemiology of invasive pneumococcal disease in urban New South Wales, 1997-1999. Med J Aust 2000; 173: S22-26.