

6 GENERAL INVESTIGATIONS

6.1 What general investigations should be done in the community?

Recommendations

- **General investigations, including a chest x-ray, are not necessary for the majority of patients managed in the community.**

6.2 What general investigations should be done on all adults referred to hospital?

6.2.1 Radiology

In acute uncomplicated influenza the chest X-ray is usually normal. When primary viral pneumonia occurs as a complication, particularly in elderly adults the chest X-ray often shows multiple infiltrates or consolidation. Cavitations or pleural changes suggest bacterial superinfection. In combined viral-bacterial pneumonia, the clinical features typically appear later than primary viral pneumonia and the chest X-ray often shows cavitation or pleural effusions. Secondary bacterial pneumonia usually occurs after apparent improvement from the viral infection; the chest -ray may show consolidation.

Recommendations

- **A chest x-ray should be obtained during assessment of a suspected case of influenza seen in the hospital setting (accident and emergency department or acute admissions ward).**
- **In those patients who are subsequently followed up in a hospital outpatient clinic or by a general practitioner a repeat chest X-ray should be obtained at around 6 weeks if respiratory symptoms or signs persist or where there is a higher risk of underlying malignancy (especially smokers and those over 50 years of age).**
- **Further investigations including a CT thoracic scan and bronchoscopy should be considered if the chest X-ray remains abnormal at follow up (ref BTS CAP guidelines).**

6.2.2 Blood tests

In those patients severe enough to present to secondary care then the following tests may be useful.

- Full blood count: a leucocytosis with left shift may occur in those with primary viral pneumonia, mixed viral-bacterial pneumonia or secondary bacterial pneumonia. Lymphopenia has been noted in human cases of severe avian H5N1 influenza.
- Urea and electrolytes may reveal evidence of hypo or hypernatraemia or renal impairment.
- Liver function tests are usually normal.
- Creatine kinase (CK) may be elevated in those with severe myalgia.

C reactive protein (CRP) is unlikely to be helpful except where superimposed bacterial infection is suspected(59). However the diagnostic value of CRP in lower respiratory tract infections remains controversial.(60)

Recommendations

- The following blood tests should be obtained in patients admitted to hospital:
 - a. Full blood count
 - b. Urea, creatinine and electrolytes
 - c. Liver function tests
 - d. Creatine kinase (if myositis is suspected)
- In patients with suspected secondary bacterial infection, the C-reactive protein (CRP) level may aid diagnosis.

6.2.3 *Other tests*

Recommendations

- Pulse oximetry should be carried out in all patients presenting to secondary care.
- If the oxygen saturation is below 92% then arterial blood gases should be obtained.
- An electrocardiogram (ECG) should be obtained in all patients with cardiac or respiratory complications.

6.2.4 *Lung function tests*

In acute uncomplicated influenza larger airway function remains normal. However there is often an increase in bronchial reactivity which may persist for many weeks after resolution of the infection.(61) Lung function tests are unnecessary in most patients.

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7 MICROBIOLOGICAL INVESTIGATIONS

7.1 Introduction

The guidelines provided below are based on the assumption that when cases are first occurring in the UK as part of a global pandemic, it will be possible to perform full microbiological investigations in all new cases of influenza-like illness and influenza-related pneumonia. As case numbers rise, possibly to pandemic levels, full or indeed any microbiological investigation will become increasingly difficult. Thus, data on the relative frequency of different bacterial causes of influenza-related pneumonia and their antimicrobial susceptibilities amongst investigated cases gathered earlier in the pandemic should be available to guide and refine empirical antimicrobial therapy choices for cases occurring later in the pandemic.

The most likely pathogens implicated in influenza-related pneumonia are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and to a lesser extent beta-haemolytic streptococci (see Section 3.3). In the early phases (UK Alert Levels 1, 2 and 3 – see Appendix 1) of a pandemic microbiological diagnostic approaches should focus on confirming influenza as the primary illness, defining bacterial causes of influenza-related pneumonia and optimizing both specific (for individual patients) and general (for populations) antimicrobial treatment recommendations. In later pandemic phases (UK Alert Level 4) with the much higher caseloads anticipated, microbiological investigation should be focused on patients with severe influenza-related pneumonia unresponsive to empirical antimicrobial therapy. Actual and practical local level transition to less intense microbiological investigation may occur at UK Alert Level 3 in some regions as the number of local cases is likely to vary between regions.

PRIMARY CARE

7.2 What microbiological investigations should be undertaken for patients in the community?

The aim of microbiological investigations early in a pandemic (UK Alert Levels 1, 2 and 3) will be to confirm that Influenza A is circulating in the local community. Once a pandemic is established (UK Alert Level 4), microbiological investigations are not recommended routinely or likely to be available readily. Routine testing for bacterial pathogens is not recommended at any stage.

Recommendations

- Where possible, early in a pandemic (UK Alert Levels 1, 2 and 3), nose and throat swabs in virus transport medium should be collected from patients and submitted to the local laboratory.
- Once a pandemic is established (UK Alert Level 4), microbiological investigations are not recommended.

IN HOSPITAL

7.3 Early in a pandemic (UK Alert Levels 1, 2 and 3), what microbiological investigations should be undertaken for hospitalised patients?

It will be necessary to perform full microbiological investigations on all hospitalised cases, including patients with severe and non-severe influenza-related pneumonia, in order to;

- confirm influenza as the primary infection,
- optimize treatment options for the patients investigated and
- define the most common bacterial causes of influenza-related pneumonia and their antimicrobial susceptibility patterns.

The latter data will help to inform empirical antimicrobial therapy of subsequent cases for which microbiological investigation may not be undertaken fully, or at all.

7.3.1 Virology

In influenza, rapid virological tests, viral culture and PCR of respiratory samples will yield positive results between 1 and 7 days after illness onset. However, if presentation is more than 7 days after the onset of influenza-like illness then such sampling and testing is unhelpful. Instead, serum samples for serological testing for evidence of recent influenza infection is recommended.

Specific detailed microbiological guidance for taking and handling specimens from individuals at risk of avian influenza prepared by Prof Maria Zambon of Health Protection Agency (HPA) Centre for Infections is available at;
http://www.hpa.org.uk/infections/topics_az/avianinfluenza/guidance/microbiological_guidance.htm

7.3.1 Bacteriology

Bacteriological investigations are only recommended in patients with influenza-related pneumonia. *Legionella pneumophila* infection is not normally associated with influenza-related pneumonia, despite this *Legionella* urine antigen tests should be performed on severe CAP cases in the early stages of an outbreak/incident in order to confirm *Legionella* infection is not the reason for a local increase in pneumonia admissions. These recommendations are modified from those contained in the British Thoracic Society Community Acquired Pneumonia (BTS-CAP) Guidelines 2001 Thorax 2001;56 (suppl iv) see Sections 5.7, 5.8 and 5.9 (pp iv23-iv28) and the 2004 Update (see pages 4-5) both available at; http://www.brit-thoracic.org.uk/iqs/bts_guidelines_pneumonia.html

Sputum investigative efforts must be focused on quality samples (i.e. those from patients who are able to expectorate purulent samples, *and* have not received prior antibiotic treatment) and not dissipated on large numbers of poor quality samples. It is important to acknowledge that the criteria for quality samples may only be met for a minority of admissions. Laboratories should offer a reliable Sputum Gram stain for appropriate samples, as on occasions this can give immediate indication of likely pathogens. The most likely influenza-related pneumonia pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* all of which may present a characteristic appearance on Gram stain of purulent sputum. Laboratories performing sputum Gram stains should adhere to strict and locally agreed criteria for interpretation and reporting of results.

Recommendations (Early in a pandemic: UK Alert Levels 1,2 and 3)

A. VIROLOGY – ALL PATIENTS

- Nose and throat swabs in virus transport medium should be collected from all patients and submitted to the local laboratory. The relevant laboratory should be notified of the suspected diagnosis and there should be close liaison over sample collection, handling and transport.
- Rapid testing by direct immunofluorescence or rapid EIA test, virus culture and/or PCR should be undertaken according to local availability and/or referred to an appropriate laboratory
- If presentation is more than 7 days after onset of illness, an 'acute' serum (5-10mLs clotted blood) should be collected and a 'convalescent' sample (5-10mLs clotted blood) obtained after an interval of not less than 7days. The two sera should be examined serologically for evidence of recent influenza infection.

B. BACTERIOLOGY – PATIENTS WITH INFLUENZA-RELATED PNEUMONIA

- The following bacteriological tests should be performed:
 1. Blood culture (preferably before antibiotic treatment is commenced)
 2. Pneumococcal urine antigen (20 mls urine sample)
 3. Legionella urine antigen (20 mls urine sample)
 4. Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from patients who:
 - a. are able to expectorate purulent samples, *and*
 - b. have not received prior antibiotic treatment.

Sputum samples should be transported rapidly to the laboratory.
 5. Paired serological examination for influenza/other agents. Acute serum should be collected and a 'convalescent' sample obtained after an interval not less than 7days (both 5-10mLs clotted blood) and the two sera stored for subsequent testing.

7.4 Once a pandemic is established (UK Alert Level 4), what microbiological investigations should be undertaken for hospitalised patients?

In a pandemic situation, virological investigations are not recommended routinely and in a pandemic situation may not be available readily. The diagnosis of influenza will be based on clinical findings. If influenza-related pneumonia is present, the degree of microbiological investigation will be directed by disease severity and the presence of co-morbidities.

In influenza-related pneumonia, examination of sputum should be considered for patients who do not respond to empirical antibiotic therapy. This will be particularly relevant if *Staph aureus* is identified as a common influenza-related pneumonia pathogen during the early phase of the pandemic as, in contrast to *S pneumoniae* and *H influenzae*, antimicrobial susceptibilities of this organism are less predictable and empirical choices more speculative.

Recommendations (Once a pandemic is established: UK Alert Level 4)

- A. VIROLOGY – Not routinely recommended.**
- B. BACTERIOLOGY - PATIENTS WITH INFLUENZA-RELATED PNEUMONIA**

(I) Non-severe pneumonia (CURB-65 Score 0,1 or 2)

- Sputum samples should be sent for Gram stain culture and antimicrobial susceptibility tests in patients who do not respond to empirical antibiotic therapy.

(II) Severe pneumonia (CURB-65 Score 3, 4 or 5)

- Specific investigations should include:
 1. Blood culture, preferably before antibiotic treatment is commenced
 2. Pneumococcal urine antigen (20mls urine)
 3. Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from patients who:
 - a. are able to expectorate purulent samples, and
 - b. have not received prior antibiotic treatment.

Sputum specimens should be transported rapidly to the laboratory.

4. Paired serological examination for influenza/other agents. 'Acute' serum should be collected and a 'convalescent' sample obtained after an interval not less than 7 days (both 5-10mLs clotted blood) and the two sera stored for subsequent testing.
5. Tracheal or endotracheal aspirate samples, if available, should be sent for Gram stain, culture and antimicrobial susceptibility testing.

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