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ACUTE RESPIRATORY INFECTIONS.

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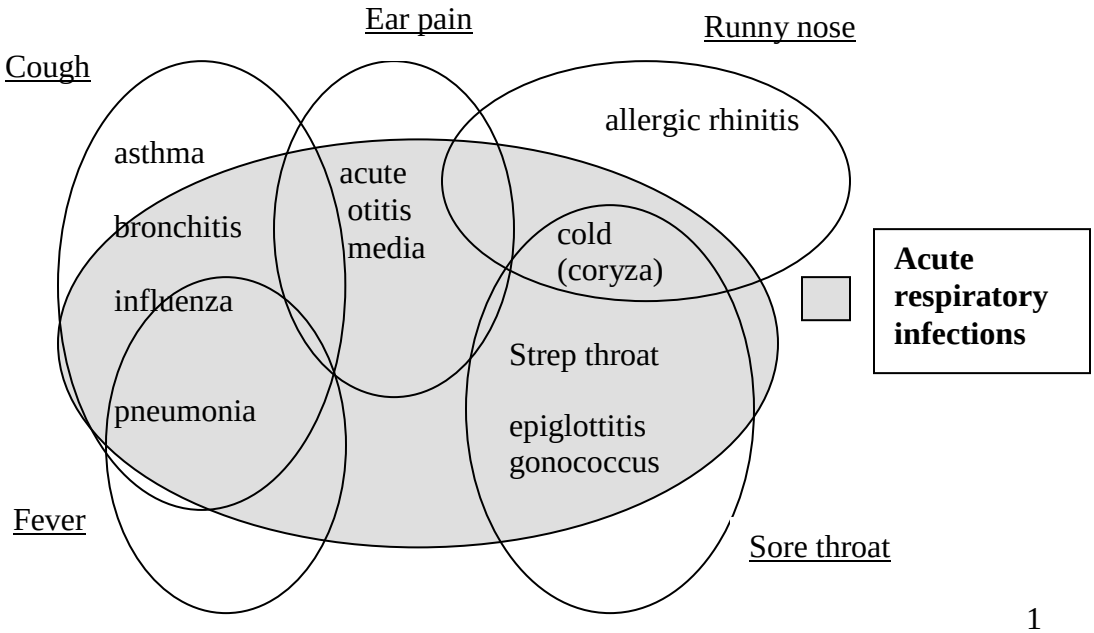
Introduction

Acute respiratory infections may be classified in several different ways: by their symptoms (fever, sore throat, cough, ear pain, runny nose); by their clinical manifestations (coryza, pharyngitis, tonsillitis, epiglottitis, otitis media, influenza, bronchitis, pneumonia); or by causative organism. Furthermore, their symptoms and sometimes the whole clinical picture may be shared by conditions that are not infections (asthma, allergic rhinitis). Some of this complexity is shown in Figure 1.

Figure 1. The way we classify acute respiratory infections is overlapping and confusing.



Elucidating the exact location or responsible organism is usually clinically unhelpful. In this section we focus on diagnostic questions that have the greatest impact on the patient with an acute respiratory infection. Sometimes the question is important because it affects the management of the illness (for example *Does this patient have pneumonia? Is this asthma or acute bronchitis?*); sometimes it is because the infection can have important sequelae (*streptococcal infection*); and finally there is the potentially extremely important question of *identifying possible cases of avian influenza*.

Does this patient have pneumonia?

Summary

- The reason for identifying patients with pneumonia is to identify those patients who may benefit from an antibiotic.
- None of the clinical symptoms and signs is able to rule in or rule out the diagnosis. Traditional signs, e.g. dullness to percussion and crackles, increase the probability of pneumonia only slightly and reduce it even less if absent.
- Even the global assessment after the history and examination is at best only moderately good at ruling pneumonia in or out.
- Laboratory values, such as ESR, CRP and full blood count contribute only modestly to the diagnosis.
- Investigating, with a CXR, only those patients who have a reasonable probability of pneumonia is a question of finding a balance between the risk of missing some pneumonias against that of over-investigation.
- Diagnosing community acquired pneumonia may not be necessary anyway.

Pre-test probability of pneumonia

The prevalence of pneumonia in a patient population can vary enormously. A review of data from the US National Ambulatory Medical Care Survey from 1980 to 1994 showed that 5% of patients who presented to a primary care provider with an acute cough were diagnosed with pneumonia.[1] Similarly, in a study of previously well patients presenting to a general practitioner in the UK with acute cough, 6% met CXR criteria for pneumonia.[2] These two studies suggest that over a longer time period and wide patient population, the prevalence of pneumonia in patients with acute cough stays fairly constant at about 5%, but the time of year, the mix of patients and many other factors can cause large variations around this level.

The diagnostic accuracy of symptoms and signs

The problem of the lack of a 'gold standard'. Establishing the clinical features that identify patients with pneumonia is difficult because of the lack of a reference test (a 'gold standard') that clearly differentiates patients with pneumonia from patients that do not have pneumonia. Pathological organisms cannot be identified in up to 50% of those with pneumonia, even with extensive diagnostic testing.[3] Because of this, CXR changes are the most common reference standard in diagnostic accuracy studies, although the way these changes are defined varies between studies and there are also questions about the

accuracy of even this test.[4] Nevertheless the CXR reference standard is the best we have, so we use it to study published estimates for the positive and negative likelihood ratios of clinical symptoms and signs for the presence of pneumonia in adults and children (Tables 1 and 2).

Table 1: Range of positive and negative likelihood ratios reported for symptoms and signs of pneumonia in adults using X-ray changes as the gold standard

Symptom or sign	LR+ (range)	LR- (range)
History		
Fever [5-7]	1.0 – 2.1	0.6 – 1.0
Dry cough [8]	1.7 ns	0.8 ns
Confusion [8]	4.0 ns	0.9 ns
Nausea [8]	2.3	0.8 ns
Diarrhoea [8]	3.0	0.9 ns
Chills [5-8]	1.3 – 1.7	0.6 – 0.9
Vital Signs		
Tachycardia (> 100 or 120/bpm) [5-7 9]	1.6 – 2.3	0.5 – 0.9
Tachypnea (> 25 breaths/m) [5-7 9]	1.2 – 3.4	0.7 – 0.8
Temperature (> 37.8^{o} C [5-7 9] or >38^{o} C [8]	1.4 – 4.6	0.3 – 0.8
Any abnormal vital sign [5]	1.2	0.2
Chest signs		
Asymmetric respiration [6]	Infinity	1.0
Aegophony [5-7]	2.0 – 8.6	0.8 – 1.0
Dullness to percussion [5-7]	2.2 - 7.1 ns	0.8 – 1.0
Crackles [5-7 9]	1.6 - 2.7	0.6 – 0.9
Decreased breath sounds [5 7]	2.3 – 2.5	0.6 - 0.8
Overall impression of disease		
General impression: moderate/ severe illness [8]	2.0	0.7 ns
Physicians judgment of pneumonia based on history and examination [10]	4.6	0.3

Aegophony is the high pitched sound of breath sounds heard with a stethoscope through consolidated lung.
ns: confidence interval of likelihood ratio not statistically significant
bpm: beats per minute

- The clinical studies suggest that no single sign or symptom can be used to rule-in or rule-out the diagnosis of pneumonia in adults. A recent study using a reference standard of biological evidence of bacterial lower respiratory tract infection also

showed that no single sign or symptom was able to predict the presence of a bacterial infection.[11]

- Combinations of clinical features may be more clinically useful. However, even the doctor's global judgment after the full history and examination was, at best, only moderately useful at ruling out the diagnosis in one study (LR- 0.3, 95% CI 0.1-0.7),[10] and was poor in another (LR- 0.9 (0.8 to 1.1).[8] If, after the history and clinical examination, the overall impression is that the patient does *not* have pneumonia, assuming a pre-test probability of 5%, the probability of pneumonia falls to <2%.[10] No decision rule has been developed that improves this value.[1] If the overall clinical history and examination suggest that the patient *does* have pneumonia, the probability of pneumonia increases to 13%.
- Several signs (in particular, dyspnoea, tachypnoea, thoracic pain, dullness to percussion, and 'crepitations' [crackles]), once thought to be clinically important, have been shown not to be so useful on testing. The contribution of some important clinical signs to the diagnosis of pneumonia in adults is shown in Figure 2.

Figure 2. Revised pneumonia probabilities based on history and physical examination findings in adults.[1] The effects of history and physical examination findings separately and in combination were examined in the ambulatory care setting, where the baseline prevalence of community-acquired pneumonia is 5%.

Insert Figure 2 here

'*Normal vital signs*' means pulse ≤100/min; temperature ≤37.8 °C; and respiratory rate ≤20 breaths/min.

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Clinical diagnosis of pneumonia in children

Some signs have greater diagnostic value in children (tachypnoea, crepitations and a fall in blood oxygen saturation) or only occur in children (nasal flaring and grunting in children ≤12 months of age, inspiratory chest recession) (See Table 2). In developing countries, where access to radiological investigations may be limited, the absence of tachypnoea can help to rule the diagnosis out.[12] Overall, however, these studies indicate that clinical detection is as difficult in children as it is in adults.

Table 2: Range of positive and negative likelihood ratios reported for symptoms and signs of pneumonia in children

Symptom or Sign	LR+ (range)	LR- (range)
History		
Fever history [13]	1.2	0.4
Age >12 months [14]	1.5	0.6
Vital signs		

Elevated respiratory rates [15],[16],[14]	1.5-2.1	0.3 –0.7
Decreased breath sounds [13]	1.2 ns	0.8 ns
Nasal flaring [16-18]	1.2 – 3.7	0.8
Nasal flaring in ≤ 12 months of age [15]	5.4	0.7
Tachypnea [18], [19]	2.0 - 3.2	0.3
Grunting [18], [13]	3.2 – 16.2 ns	0.9 – 1.0 ns
Oxygen saturation ≤96% [14]	2.8	0.5
Respiratory distress (nasal flaring, grunting, retractions, tachypnea, rales or decreased breath sounds) [18]	1.6	0.0
Chest signs		
Chest retraction at inspiration [15 16]	2.4-2.5	0.7 – 0.8
Crepitations [18]+, [16 17]	1.3 – 2.1	0.4 – 0.8
Crackles [13]	1.6	0.8
Retractions [13]	1.6 ns	1.0 ns

Ns: Not significant
Study 16 was conducted in a developing country; studies 13 and 14 were conducted in emergency departments; and studies 18 and 19 had significant methodological limitations, such as only a proportion of children receiving the reference test.

Laboratory investigations

- The common investigations used in the diagnosis of pneumonia (erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP) and white cell count (WCC) are diagnostically unreliable on their own.[11,20] However, they have been shown in logistic regression models to add to the information from the clinical history and examination. The range of likelihood ratios is, however, too wide to give a summary figure.[20]
- Microbiological testing to identify the responsible organism needs to be considered in patients with pre-existing lung conditions and those at risk of tuberculosis. However, the high false negative rates (related to technical difficulties in growing the infective organism) render it hopelessly inaccurate.

When should a chest X-ray (CXR) be ordered?

Clinical guidelines are remarkably inconsistent in the recommendations that they make regarding when to order a CXR in patients with a suspicion of pneumonia.[21]
The decision to order a CXR depends on the probability of pneumonia following a clinical assessment. The discussion above has shown that the probability of pneumonia in a patient in whom the clinical picture is positive is no more than 13%.
Therefore, if a doctor orders a CXR for every patient suspected of pneumonia, only one of every eight CXRs will show evidence of pneumonia. If doctors only order CXRs in patients who have changes in their vital signs, this reduces the number of CXR requests by 40%, but also misses 38% of patients subsequently shown to have pneumonia.[5]

Does the diagnosis of community-acquired pneumonia matter?

Several studies have also suggested that not all cases of pneumonia in ambulatory patients (even with microbiological evidence of susceptible bacterial infection) require

antibiotics.[2,5,22] Those in whom the diagnosis is important are those with a poor prognosis, that is those with:[1]

- Co-morbid illness, especially neurological disease;
- Tachypnoea ($\geq$28 breaths/min);
- Hypothermia ($\leq 37^0$C);
- Hypotension ($\leq$ 100 mm Hg systolic);
- Certain abnormal laboratory tests: raised serum creatinine, leucopenia, extreme leucocytosis, hypoxaemia ($PaO_2 \leq$50 mm Hg);
- A chest X-ray (once it is taken) showing infiltration of more than 1 lobe.

Example

The GP is called one evening to visit a 64 year old man who has mild Parkinson's disease. Over the previous 2 days he has developed a fever and is coughing up yellow phlegm. Examination confirms the fever. His pulse is 110, his respirations 25/minute and the blood pressure 110/70. In addition the GP finds some coarse crackles at both bases which do not clear with coughing.

She judges that he is unwell enough to have a mild to moderate pneumonia but her examination has not really altered the probability much either way. The crackles could be due to atelectasis rather than pneumonia. He is not well enough to go for a chest X-ray and she guesses that he'll either be better or worse before the results of any blood tests are available. She treats him empirically with an antibiotic.

When she revisits next day he is clearly less well, although the only new findings are that his blood pressure has fallen to 90/60 and his respiratory rate has risen to 28/minute. She decides he is now sufficiently ill for her to say that he has pneumonia, despite the paucity of specific signs.

She requests admission on the basis of 3 poor prognostic features: Parkinson's disease, tachypnoea and hypotension.

How can we differentiate asthma from acute bronchitis?

Summary

If the possibility of asthma is raised in a patient with an acute lower respiratory infection, perform spirometry, including a trial of a bronchodilator.

This dilemma commonly arises in two situations: when a patient with a respiratory infection develops wheeze; and when an apparent acute respiratory infection fails to settle in the expected time.

- Acute bronchitis is an ambiguous clinical label. Many GPs, and indeed clinical trials, define acute bronchitis as '*acute cough with purulent or productive sputum*', even though the most accepted diagnostic system defines it as '*acute cough with scattered or generalised abnormal chest signs*'.[23]
- The diagnosis of asthma depends on symptoms of cough and/or wheeze, supported by abnormal spirometry and a response to a bronchodilator (see *Asthma* page 000).
- A cough associated with an undifferentiated acute respiratory tract infection is likely to last at least two weeks in more than half of patients, and three weeks in 35%.[24] However, other common causes of an acute cough lasting more than a week include

asthma, chronic sinusitis, and gastro-oesophageal reflux disease.[25] In one study, up to one third of adult patients with a cough lasting more than two weeks had asthma on objective testing.[26] The asthma may be transient or chronic, but is also predictive of further episodes following acute respiratory infections, and may be predictive of long-term respiratory problems.[27,28]

- A Cochrane review has demonstrated that overall there is no benefit from the use of bronchodilators in patients with acute bronchitis, but patients with evidence of airflow obstruction (wheezing, bronchial hyper-responsiveness or decreased FEV_1 values) do show an improvement in average symptom scores.[29]

In conclusion

* When there is wheezing or cough which continues following an acute respiratory infection, perform spirometry and a trial of a $beta_2$ agonist.

Can streptococcal sore throats be differentiated from non-streptococcal sore throats?

Summary

- No individual symptom or sign is able to rule in or rule out the diagnosis of streptococcal sore throat.
- Clinical prediction rules and rapid antigen detection increase the specificity of the diagnosis.
- The GP's intuitive tendency to treat the more severely ill patients with penicillin is borne out by most of the predictive features of the clinical prediction rules: exudates, glands, fever, considerable difficulty on swallowing. Features that predict streptococcal infection that are less obvious intuitively are the absence of cough, age <15 and a short history.

Why making the differentiation matters

There is evidence that treating streptococcal sore throat with antibiotics is beneficial, although any effect is quite small:

- A Cochrane review shows that antibiotics shorten the duration of symptoms by about 1 day in adults.[30]
- Children demonstrate a faster resolution of clinical signs and symptoms with immediate antibiotics.[31]
- Treatment reduces the risk of complications, such as rheumatic fever and quinsy, although the incidence of these complications is relatively rare in developed countries.[30]

One possible reason for the disappointingly modest response to antibiotics is that many cases of sore throat are caused by non-bacterial agents, especially viruses. Since most of the complications of sore throat (which cast more of a sinister shadow than the illness itself), are related to streptococcal infection, most diagnostic effort has been focussed on trying to differentiate streptococcal from non-streptococcal sore throat. This practice varies widely and is much more common in North America than Europe or Asia.

The initial probability of streptococcal sore throat

Group A beta-haemolytic Streptococcus (GABHS) is the most common causative organism for sore throat that can be isolated. It is found more commonly in children than among infants and adults. In studies of prevalence in office-based practice, the proportion of sore throats due to streptococcal infection in adults is 5–10% and in children 20-25%. The proportion is higher in indigenous populations, such as Australian Aborigines, and Native Americans, and is also higher in the autumn and winter months.[32] *Beta-haemolytic streptococci Groups C and G* also cause a similar clinical illness. A Norwegian study found *C* or *G* present in 9% of patients with a sore throat.[33]

Diagnostic accuracy of signs and symptoms for streptococcal sore throat

No sign or symptom is sufficiently accurate to rule in or rule out the diagnosis of streptococcal sore throat.[32] Clinical features that can help rule the diagnosis in are tonsillar exudates, pharyngeal exudates and exposure to another person with streptococcal throat in the previous two weeks (see Table 3). Clinical features that help to rule out the diagnosis are the absence of tender anterior cervical nodes, the absence of tonsillar enlargement, and the absence of exudate (see Table 4). The presence of a scarlatiniform rash or palatine petechiae is uncommon, but very specific for the diagnosis of streptococcal sore throat.

Table 3. Statistics for the most useful clinical features in making the diagnosis of streptococcal sore throat.[32]

Insert Table 3 here

PPV is the probability if the test is positive. 100% -NPV is the probability if the test is negative. Based on a pre-test probability of 10%.

Table 4. Statistics for the most useful clinical features in refuting the diagnosis of streptococcal sore throat.[32]

Insert Table 4 here

PPV is the probability if the test is positive. 100% -NPV is the probability if the test is negative. Based on a pre-test probability of 10%.

Combinations of clinical features

- A number of studies have attempted to determine if combinations of symptoms and signs can be used. One of the first was developed by Centor et al (1981) and has been validated in 4 populations against a reference standard of throat culture.[34] In the Centor rule, one point is assigned for each of the following:
  a) presence of tonsillar exudate;
  b) the presence of swollen tender anterior cervical nodes;
  c) the absence of cough; and
  d) history of fever.

- Another version of the score, by McIsaac[35] adds one point if the age of the patient is <15 years and deducts one point if the age is ≥ 45 years.
- In Lindbaek's Norwegian study 3 indicators were found which independently increased the probability of Group A streptococcal infection:[33]
    1. considerable pain on swallowing (OR 2.5; 95%CI 1.4 to 4.5),
    2. age 3 – 14 (OR 2.6; 95%CI 1.4 to 5.0) and
    3. a short history (symptoms for 3 days or less) (OR 2.0; 95%CI 1.1 to 3.5).

Scoring the clinical prediction rules

- Based on a pre-test probability of 10%, a Centor score of 1 reduces the probability of *Streptococcus* being cultured from the sore throat to 3% (LR 0.3), while a score of 4 raises the probability to only 40% (LR 6.3). If the pre-test probability is higher, whether because of a higher rate in the community or because that individual has been exposed to a known case, the post-test probabilities will be correspondingly higher.
- Based on the same pre-test probability of 10%, a McIsaac score of 1 reduces the probability of *Streptococcus* being cultured from the sore throat to 5% (LR 0.5), while a score of 4 or 5 raises the probability to only 35% (LR 4.9).[35]

The throat swab

Two further difficulties are that:

a) the finding of a positive throat swab for *Streptococcus* does not prove that the *Streptococcus* is the cause of the sore throat. The specificity of the throat swab is at most 80%. Two to five per cent of adults are carriers of GABHS.[36,37] A further 7% carry haemolytic streptococci Groups B, C or G.[36] In patients under 15 years of age, 11% are GABHS carriers.[36] A positive swab is therefore not proof of infection.
b) a negative throat swab does not rule out streptococococcal infection. In Lindbaek's Norwegian study a first swab missed 13% of positive cultures that were detected on a repeat swab.[33] Even if it is assumed that no further positives remained undetected that gives a sensitivity of 87%.

The rapid antigen test

The newer techniques have operating characteritics that rival those of the throat swab: sensitivity 97%, specificity 95%.[33 38] However, in order to be cost effective they are usually limited to those with higher probabilities following the application of a clinical prediction rule. Populations where the risks of complications are greatest (indigenous populations, third world countries) are those that are least likely to be able to afford them.[39]

Example

A boy of 18 presents with a sore throat 2 days before an important examination. His GP doesn't use any of the clinical prediction rules formally, partly because she can't remember how to score them and partly because she is sceptical about their apparent accuracy. She has, however, a shrewd idea of which symptoms and signs predict streptococcal infection and which do not.

She notes that his youth is in favour of streptococcal infection, although not as much as if he were under 15. Everything else, however, is against it: there are no exudates, no fever, no recent known exposure to streptococcal infection, no tender glands, no tonsillar

swelling. He even has a cough and runny nose and a relatively long course: the symptoms have been developing over 5 days.
The GP does not have access to a rapid antigen test. She reckons that the probability of streptococcal infection is in the region of 1% and that if she took a throat swab and it was positive it would probably be a false positive. She tells her patient that his chance of responding to penicillin is less than his chance of being brought out in a rash by it. He agrees to continue to suck (sugar-free) lozenges.

How can we diagnose acute otitis media (AOM)?

Summary
- The presence, or absence, of earache helps to rule in, or rule out, the diagnosis, but is less helpful in younger children.
- A red, cloudy, bulging or immobile eardrum helps to confirm the diagnosis.
- Crying is not the *cause* of a red eardrum.[40]

Definition and causative organisms
AOM is the presence of a middle ear effusion in conjunction with the rapid onset of one or more signs or symptoms of inflammation of the middle ear.[41]
The most common bacterial pathogens are *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*,[42] but childhood vaccination against pneumococcal disease and Haemophilus influenzae b may have changed the frequency of causative pathogens in recent years.[43] Infection with these organisms is not specific for the ear, and will frequently cause overlapping or sequential infection with other areas of the respiratory tract.

Why does diagnosis matter?
- Overall, trials of antibiotics to treat AOM suggest only a modest benefit, with the number of patients who have pain at 2 to 7 days being reduced from 22% to 16%.[44] The possible benefits of antibiotics are also offset by an almost equivalent risk of side effects, such as nausea, vomiting and diarrhoea. In some parts of the world (especially Scandinavia and the Netherlands) antibiotics are rarely used for acute otitis media. In others (especially the USA) it is still the norm.
- In some groups of patients the benefit of antibiotics is more marked: e.g. children under two years of age, children with high fever, those who are vomiting or who have bilateral disease.[45-47]
- Accurate diagnosis of an ill child helps to reduce parental concern.
- Diagnosis allows the primary care team to check that the transient deafness associated with AOM does settle. If it does not, the child's language acquisition or education may suffer unless one of a variety of compensations are set in place (such as ensuring talking is louder, hearing aids provided temporarily, or even referral for grommet tympanotomy).

The initial probability of AOM

By the age of two years, over 90% of children have had at least one episode of AOM and more than half have had two or more episodes. In a survey of children presenting to ambulatory care offices in the US, AOM was present in about 20% of children 0-5 years of age, 10% of children 6-10 years of age and 5% of children 11-15 years of age.[48]

The diagnostic accuracy of the history and examination for AOM

Although the gold standard for the diagnosis of AOM is based on findings from tympanocentesis, most studies of diagnostic accuracy have compared the clinical features of AOM against findings on pneumatic otoscopy.[49] Almost all of these studies have been conducted in paediatric or otolaryngology settings, and therefore they may be less accurate in primary care settings where the incidence is lower. It is well recognised that misdiagnosis of AOM is common in the community.[50]

See Table 5 for the contribution made by symptoms and signs to the diagnosis of AOM.

Table 5: Diagnostic accuracy of the history and examination for AOM (the most useful features are in bold)

Symptoms	**LR+ (range)**	**LR- (range)**
Ear pain [51-53]	**3.0 – 7.3**	**0.4 – 0.6**
Fever [51-53]	0.8 – 2.6	0.3 – 1.4
Signs		
Cloudy [54]	**6.7**	**0.4**
Distinctly red [54]	**3.0**	**0.8**
Bulging [54]	**13.7**	**0.6**
Retracted [54]	1.6	0.9
Impaired mobility [54]	**3.4**	**0.1**

These LRs for signs differ from those calculated in a recent systematic review in which rather different results from a paediatrician and an ENT surgeon were combined.[55] We have used the figures for the paediatrician as being nearer to those likely in general practice.

Comments

- Earache is one of the most helpful clinical features in diagnosing AOM, but is unlikely to be identified in young children, and is therefore less helpful and less accurate in younger children.
- Symptoms and signs that do not help to diagnose AOM are vomiting, cough and rhinitis.

Example

A child age 3 is brought by her mother because she has been febrile and has cried all the previous night. She is rubbing both ears and her mother is convinced that this is an ear infection.

Examination reveals two normal drums and a slightly runny nose.

The GP reckons that, with an initial probability of 20%, the normal drums reduce this to <2%. His experience tells him that rubbing the ears is not specific for ear infection and he has never found any research evidence to alter that view.
He explains to the mother that this is likely to be an upper respiratory viral infection and that paracetamol is the best treatment.

Can avian influenza be differentiated from human forms?

Summary

- Avian 'flu cannot be reliably distinguished clinically from other forms of influenza.
- Suspect it in a patient who has close contact with birds, especially ill birds, who presents with fever, especially if there are respiratory or gastrointestinal symptoms.

Avian influenza A (H5N1) virus is a highly pathogenic virus that spreads quickly through bird flocks with a mortality rate approaching 100%. Cases in humans have been reported since 1997, with an upsurge of human cases reported by the WHO since January 2004. Currently the spread of H5N1 virus from person to person has been limited (if at all) and all cases have involved close contact with an infected bird, mostly in previously healthy children and young adults. In recent outbreaks among humans in Asia and Europe, the mortality rate amongst patients hospitalised with the disease has been >50%[56] and the majority of patients have developed severe bilateral pneumonia requiring ventilatory support. However, it is possible that the cases described so far are only the most severely ill; those with more trivial infections are less likely to have been examined by health authorities.

From the current limited series of hospital cases, there were no clinical features that distinguished avian 'flu from other severe cases of influenza. Among 12 patients with influenza A H5N1 virus infection identified by virus isolation, the common presenting complaint for all patients was fever. Eight had symptoms or signs of upper respiratory tract infections and five had clinical and radiological evidence of pneumonia at presentation.[57] In addition to respiratory symptoms, a large proportion of patients also reported gastrointestinal symptoms such as diarrhoea, vomiting and abdominal pain, which are common in children with human influenza, but not in adults. In some cases, diarrhoea and fever were the dominant symptoms. Unlike human infections with H7 or H9 viruses, conjunctivitis was not prominent in H5N1 infected patients.

The diagnosis is confirmed by PCR detection of viral nucleic acids in respiratory specimens.

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