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Infectious mononucleosis

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Infectious mononucleosis is commonly seen in both the community and the hospital setting. Patients usually present with a sore throat and often presume that an antibiotic is required. It is therefore important to dispel the many myths relating to the condition with appropriate patient education. Knowledge of the clinical course of the disease, as well as potential complications, is paramount. In an information age, difficult questions may arise for a general practitioner, emergency doctor, or trainee in ear, nose, and throat medicine. The aim of this review is to assist those who encounter infectious mononucleosis in the adolescent and adult population.

What is infectious mononucleosis and what causes it?

It would be most accurate to consider infectious mononucleosis as a non-genetic syndrome, defined by the classic triad of fever, pharyngitis, and cervical lymphadenopathy, where lymphocytosis is also present. For many doctors the terms Epstein-Barr virus and infectious mononucleosis are synonymous. Epstein-Barr virus causes approximately 90% of the cases of infectious mononucleosis, with the remainder due largely to cytomegalovirus, human herpesvirus 6, toxoplasmosis, HIV, and adenovirus.^{1 w4} The World Health Organization's ICD-10 (international classification of diseases, 10th revision) has four subheadings for infectious mononucleosis (or B27 in the manual.^{w5}) To confuse things further the multiple synonyms for infectious mononucleosis (glandular fever, monocytic angina, Pfeiffer's disease, Filatov's disease, Drusenfeiber, and even the kissing disease) are still included in ICD-9, which will be in use in the United States until 1 October 2015.^{w6}

The Epstein-Barr virus is a ubiquitous herpesvirus, with more than 90% of the world's population infected by adulthood.^{w7} The virus is one of our most effective parasites^{w8} and remains as a lifelong, latent infection, by integrating itself into the life cycle of healthy B lymphocytes.^{2 w9} There is persistent low grade replication and the virus is shed intermittently into pharyngeal secretions, particularly saliva, through which it is transmitted.^{w10 w11}

SOURCES AND SELECTION CRITERIA

We performed an electronic search through Medline, Scopus, Google Scholar, the Cochrane Database of Systematic Reviews, and the Cochrane central register of controlled trials using the search terms "infectious mononucleosis", "glandular fever", "Epstein-Barr virus", "corticosteroids", and "aciclovir". The search was limited to articles in English. We excluded studies carried out primarily on children. Priority was given to data from meta-analyses, reviews, and randomised controlled trials. Research on infectious mononucleosis was also given priority over articles exclusively relating to Epstein-Barr virus. We also examined guidelines produced by the US Center for Disease Control and Prevention and the UK National Institute for Health and Care Excellence, as well as clinical trials registries of the United States, United Kingdom, and European Union.^{w1-w3}

These low titres of infectious virus account for the low to moderate contagiousness of the disease and the apparent requirement of intimate contact for disease transmission.^{w12} During an active infection the viral load may be increased, and therefore some precautions about contact should be mentioned (cough etiquette, hand hygiene, kissing, sharing food or utensils); however, as most of the population is positive for Epstein-Barr virus, special precautions against transmission are not necessary in most cases.^{w13} Childhood infection, which is usually subclinical, is associated with poor hygiene and over-crowding. In lower socioeconomic groups most of the population will have acquired immunity by adolescence.³ After an incubation period of four to seven weeks,^{w14} Epstein-Barr virus infection of adolescents or adults results in infectious mononucleosis in up to 70% of cases.⁴ Most symptoms tend to resolve in two to four weeks, although approximately 20% of patients continue to mention a sore throat at one month.^{w15} Reactivation of Epstein-Barr virus may occur in immunocompromised patients^{w17} and, rarely, in immunocompetent patients, which may lead to Epstein-Barr virus associated

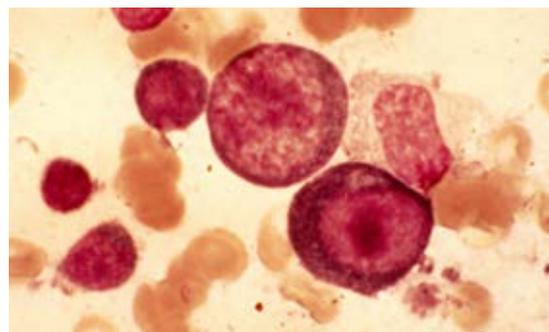
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- ▶ Sudden cardiac death in athletes (*BMJ* 2015;350:h1218)
- ▶ Temporomandibular disorders (*BMJ* 2015;350:h1154)

THE BOTTOM LINE

- Infectious mononucleosis is a clinical diagnosis, caused by Epstein-Barr virus in 90% of cases, although in some patients (pregnancy, high risk HIV population) further investigations are warranted
- Treatment should be supportive, with steroids given only in cases of airway compromise
- Treatment with antiviral agents has yet to be shown to be of benefit
- Patients wanting to return to contact sports before one month should undergo abdominal ultrasonography to rule out splenomegaly
- Splenic rupture should be considered with any abdominal pain in infectious mononucleosis



Infectious mononucleosis characterised by enlarged atypical lymphocytes

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Diagnostic tests for infectious mononucleosis			
Tests	Sensitivity (%)	Specificity (%)	Comment
Infectious mononucleosis			
Full blood count:			
L/WCC > 50% + 10% atypical lymphocytes ^{w75}	61	95	An increase in lymphocyte count tends to lead to a greater specificity but poorer sensitivity ⁸
L/WCC > 35%	84	72	
Monospot	71-98	91-99	Results vary between different available commercial kits ^{w76}
Antibody to VCA or EBNA	97	94	May have replaced monospot as standard investigation in some countries
Bacterial tonsillitis			
Antistreptolysin O titre			Peak value 3-6 weeks after infection, and thus not of value in acute setting
Throat swab	78	99	Delay of 2-3 days for result ^{w77}
Rapid streptococcal ^{w78} antigen test	84	94	Increased cost
L/WCC=lymphocyte to white cell count ratio; VCA=antiviral capsid antigen; EBNA=Epstein-Barr virus nuclear antigen.			

lymphoproliferative conditions. These conditions are a heterogeneous group of diseases that often need to be treated with chemotherapy.^{w18} Diagnoses depend on the specific disease but are often associated with an increased viral load.^{w19} Chronic active Epstein-Barr virus infection is a rare condition that is typified by severe, chronic, or recurrent infectious mononucleosis-like symptoms after a well documented primary infection with Epstein-Barr virus in a previously healthy person.⁵ Chronic active Epstein-Barr virus infection is occasionally associated with the development of lymphoma.^{w20}

How is it diagnosed?

Infectious mononucleosis may account for as little as 1% of patients who present with a sore throat to their doctor.^{w21} Non-specific prodromal symptoms of fever, chills, and malaise may be seen in infectious mononucleosis. These symptoms may also be present in cases of viral pharyngitis, commonly caused by rhinovirus, adenovirus, and coronavirus. Whereas these viruses generally give rise to symptoms of a common cold,^{w21} clinically infectious mononucleosis should be suspected in anyone who presents with fever, pharyngitis, and cervical lymphadenopathy (the classic triad).^{w22} Lymphadenopathy may be prominent in both the anterior and the posterior triangles of the neck, which distinguishes infectious mononucleosis from bacterial tonsillitis (where the lymphadenopathy is usually limited to the upper anterior cervical chain). These signs were found in 98% of patients with a diagnosis of infectious mononucleosis.⁶ Other common physical signs include palatal petechiae (25-50%), splenomegaly (8%),^{w15} hepatomegaly (7%), and jaundice (6-8%),^{w23} with a transitory derangement of liver function tests (in particular increased aspartate aminotransferase and alanine aminotransferase levels, returning to normal after 20 days) seen in 80-90% of patients.⁷ Anecdotally, a “whitewash” exudate on the tonsils may also help to distinguish infectious mononucleosis from the more speckled exudate of bacterial tonsillitis and the erythema of a viral pharyngitis that is void of exudate. In the primary care setting a clinical diagnosis alone may be sufficient to allow adequate management of a patient. However, should a definitive diagnosis be sought, the Hoagland criteria state that in patients presenting with clinically suspected infec-

tious mononucleosis and at least a 50% lymphocytosis (10% atypical), the diagnosis should be confirmed by the heterophile antibody (monospot) test.⁶ Using a lower rate of lymphocytosis^{w24 w25} has been shown to give a greater rate of false negative results (table).^{8 w26 w27} The heterophile test may also be falsely negative in up to 25% of adults in the first week of symptoms.^{1 6} It is not always necessary definitively to diagnose a cause for infectious mononucleosis, but specific antibody tests are available. Patients are considered to have a primary Epstein-Barr virus infection if they are positive for antiviral capsid antigen IgM but do not have antibodies to Epstein-Barr virus nuclear antigen, which would suggest past infection. Levels of antiviral capsid antigen IgG will also increase in the acute phase and persist for the rest of the patient’s life, whereas the antiviral capsid antigen IgM will disappear after 4-6 weeks. The presence of antiviral capsid antigen IgG and Epstein-Barr virus nuclear antigen suggest past infection.⁹ A recent review found that real time polymerase chain reaction and measurement of Epstein-Barr virus viral load provide useful tools for the early diagnosis of infectious mononucleosis in cases with inconclusive serological results.¹⁰ In a small number of cases, where the patient is either pregnant or in a high risk group for HIV infection (injecting drug user or men who have sex with men), further testing for cytomegalovirus, HIV, and other possible causes for infectious mononucleosis should be undertaken.^{w28 w29} Figure 1 presents an algorithm for diagnosing infectious mononucleosis.^{w30}

How is it treated?

Infectious mononucleosis is a viral illness in most cases, and as such it can be treated with rest, hydration, analgesia, and antipyretics. Inadvertent treatment with ampicillin results in a fine macular rash in 90% of patients.^{w8} This should be distinguished from an urticarial rash seen in an allergic reaction. Studies have shown that symptoms experienced by patients are more severe for infectious mononucleosis than for bacterial tonsillitis.^{w16} Antiviral treatment with aciclovir has been shown significantly to decrease the rate of oropharyngeal Epstein-Barr virus shedding.^{w31} Some early trials found a significant positive overall effect in cases of infectious mononucleosis treated with aciclovir^{w32} and that it was useful in severe cases, with airway compromise. However, a meta-analysis of five studies found no evidence to support its use in the acute setting: an improvement in oropharyngeal symptoms was observed in 25 out of 59 (42.4%) patients treated with aciclovir and in 18 out of 57 (31.6%) control patients (odd ratio 1.6, 95% confidence interval 0.7 to 3.6; P=0.23).¹¹ Other antiviral treatments such as valaciclovir and ganciclovir^{w33} have shown some promise in the treatment of severe infectious mononucleosis and its complications and immunocompromised people. Two trials are in progress,^{w2} but at present the routine use of both drugs is not advocated.^{w34} Anaerobic antibacterial agents such as metronidazole have been suggested to hasten recovery in infectious mononucleosis by suppression of the oral anaerobic flora that contribute to the inflammatory process.^{w35} This finding was borne out in some clinical studies,^{w36-w41} with a recent randomised controlled trial showing the beneficial effects of metronidazole in severe infectious mononucleosis by shortening

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The incidence of splenic rupture is less than 1%

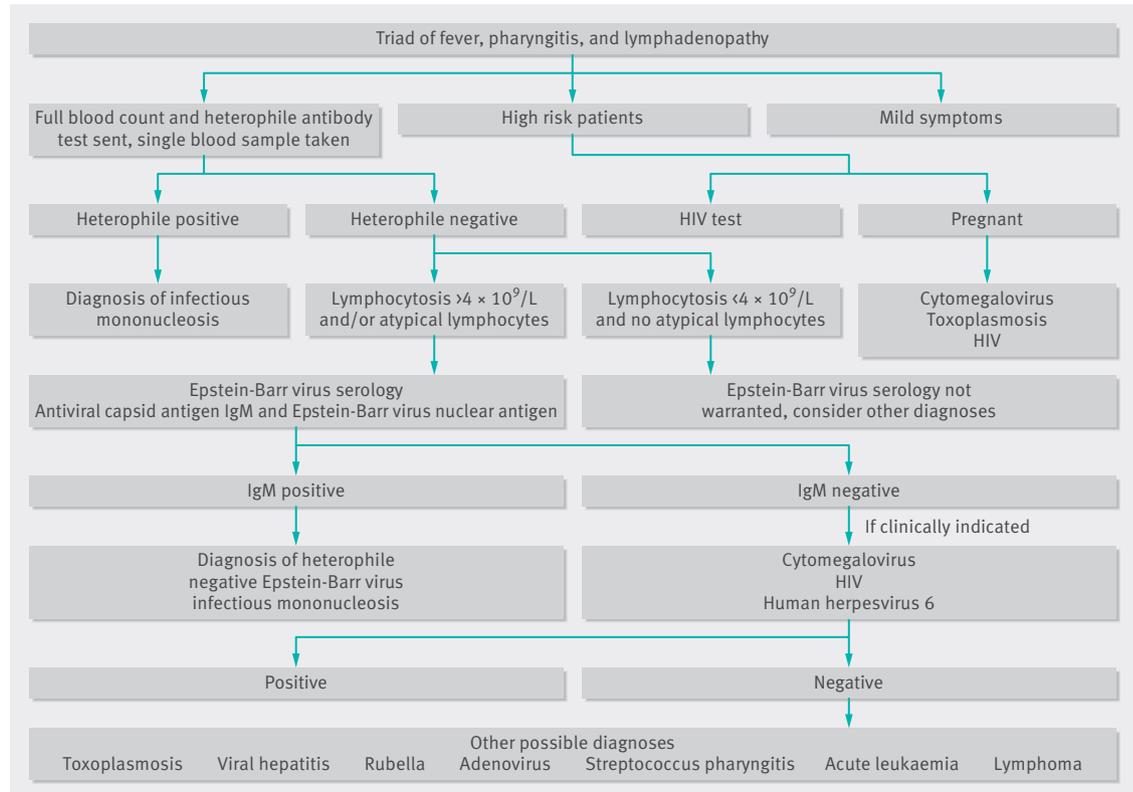


Fig 1 | Algorithm for diagnosing infectious mononucleosis

hospital stays.¹² Larger trials may be required before the use of metronidazole is routinely recommended.

Are steroids of use in the treatment of infectious mononucleosis?

Several early reports supported the use of corticosteroids in the treatment of infectious mononucleosis.^{w42} Further trials showed these effects to be short lived, with no significant difference between the control and intervention arm.^{w43} A Cochrane review was therefore undertaken, which concluded that there was insufficient evidence and the trials were too few, heterogeneous, and of poor quality to recommend steroid treatment for symptom control in glandular fever.¹³ Another more recent Cochrane review concluded that corticosteroids increased the likelihood of both resolution and improvement of pain in participants with sore throat¹⁴; however, this review excluded publications on patients with a diagnosis of infectious mononucleosis. Steroid treatment should be considered in cases of airway emergency, in an attempt to temporise or preclude the need for intubation or tracheotomy.^{w44} Despite these guidelines, the use of corticosteroids remains widespread on a day to day basis.^{w45} Several reports have mentioned the adverse effects of corticosteroid use in infectious mononucleosis, including cases of peritonsillar cellulitis, acute onset diabetes mellitus, and neurological sequelae.^{w46}

Does infectious mononucleosis lead to chronic fatigue syndrome?

Chronic fatigue syndrome is defined as severe fatigue and disabling musculoskeletal and cognitive symptoms without another explanation that lasts for at least six months and

results in severe impairment in daily functioning.^{w47} There has been much debate about the cause of this disorder. Some authors suggest that it is precipitated by an acute infection, such as infectious mononucleosis, as many patients relate the onset of their illness to an initial infection from which they never recovered.^{w48} Prospective studies have reported an incidence of chronic fatigue syndrome of 7.3-12% in adults six months after infectious mononucleosis.^{w49 w50} However, the relation between chronic fatigue syndrome and infectious mononucleosis is still questionable. A study of over 1300 patients diagnosed as having infectious mononucleosis by serology, found that although 10% of patients reported fatigue none fulfilled the criteria for chronic fatigue syndrome.¹⁵ The cause of chronic fatigue syndrome is likely to be multifactorial.

When is it safe to return to sports?

Splenomegaly, evident on ultrasonography if not on palpation, occurs in almost all cases of infectious mononucleosis, and the risk of splenic rupture has been well established.^{w54} A considerable number of 15-21 year olds will have infectious mononucleosis every year,^{w16} and many of this population will be involved in contact sports.^{w55} Strenuous or contact sports (for example, football, gymnastics, rugby, hockey, lacrosse, wrestling, diving, and basketball) or activities associated with increased intra-abdominal pressure, such as weightlifting, may put athletes at most risk.^{w56} Although recommendations of when to return to sport range from three,^{w57} four,^{w58} eight, and even up to 24 weeks,^{w59} no clinical guidelines are specific to infectious mononucleosis. The incidence of splenic rupture is less than 1%^{w15} and most

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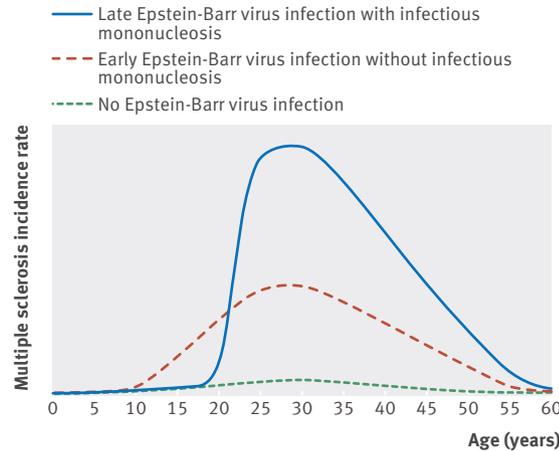


Fig 2 | Incidence of multiple sclerosis by Epstein-Barr virus infection. Adapted from Thacker et al 2006¹⁹

occur in the initial three weeks of infectious mononucleosis, although cases have been described much later.^{w60} Cases of spontaneous splenic rupture have also been described in the literature and doctors should have a high index of suspicion when abdominal pain is reported in the setting of infectious mononucleosis.^{w61} A recent study involved weekly ultrasound examinations until resolution of splenomegaly (fig 1). A mean increase in splenic length of 33.6% was observed, with a peak in enlargement on average 12.3 days from the onset of clinical symptoms. Most cases of splenomegaly had resolved by 4-6 weeks and there was a predictable rate of splenic regression of approximately 1% each day after reaching peak enlargement.¹⁷ Similar results were reported in another paper, with spleens normalising at one month in 84% of participants.^{w62} One study recommended that athletes wanting to return to contact sport at 3-4 weeks should have an ultrasound examination to ensure that the spleen had returned to normal size.^{w62} A systematic review published in 2014 advocated individualised recommendations for athletes,¹⁸ and future work in this area may concentrate on splenic volume to allow a more accurate assessment of splenomegaly and risk.

Is multiple sclerosis caused by infectious mononucleosis?

There is evidence that a history of infectious mononucleosis significantly increases the risk of multiple sclerosis¹⁹ and that this association is far stronger than with other common childhood infections or afflictions.^{w63} A meta-analysis concluded that the risk of multiple sclerosis seems to be greatest in those who were infected with Epstein-Barr virus at a later age (incidence begins to increase in adolescence, peaks around age 25 to 30 years, and declines to nearly zero by age 60), with moderate risk for those infected with Epstein-Barr virus in early childhood, and close to zero risk in those not infected (fig 2).¹⁹ A more recent meta-analysis showed that Epstein-Barr virus is present in 100% of cases of multiple sclerosis and therefore it has been suggested that the virus is not only a risk factor but also a prerequisite of multiple sclerosis.^{w64} Whether the association between multiple sclerosis and Epstein-Barr virus demonstrates a causal relation is, however, strongly debated.^{w64}

Although controversial, if proponents of the infectious mononucleosis-multiple sclerosis theory are correct, a

vaccine against Epstein-Barr virus in theory could eradicate multiple sclerosis. In the only phase II trial of an Epstein-Barr virus vaccine in humans, rates of infectious mononucleosis were reduced in adults who were seronegative for Epstein-Barr virus, but the vaccine did not affect the rate of Epstein-Barr virus infection.^{w65} The development of a vaccine is challenging for several reasons, not least the long period between primary infection with Epstein-Barr virus and the development of many Epstein-Barr virus related tumours or multiple sclerosis.²⁰ To add further to the controversy it has been suggested that in lieu of a vaccine, a smaller, but still substantial, number of cases of multiple sclerosis could be prevented by exposing children to Epstein-Barr virus infection before adolescence.¹⁹

Is there an increased risk of lymphoma or other cancers after infectious mononucleosis?

The association of Epstein-Barr virus with malignancies such as Burkitt’s lymphoma^{w66} in children and nasopharyngeal carcinoma^{w67} is well established. This review, however, focuses on patients presenting with infectious mononucleosis and it can be difficult to differentiate studies on Epstein-Barr virus and infectious mononucleosis about the risk of future malignancies. Two large Scandinavian cohort studies found a 2.55 to 2.83 times increased risk of Hodgkin’s lymphoma in patients with a diagnosis of infectious mononucleosis by heterophile antibody tests.^{21 w68} The results were similar in a recent British record linkage paper, which found a 3.44 risk ratio of Hodgkin’s lymphoma in the infectious mononucleosis cohort.²² A review on Epstein-Barr virus related malignancies from 2014 commented that Hodgkin’s lymphoma is the only Epstein-Barr virus related malignancy, other than nasopharyngeal carcinoma, for which there is a body of evidence accumulated over time that establishes a strong association.^{w69} For other malignancies, a large prospective study found no clear association between a history of clinical infectious mononucleosis and risk of invasive breast cancer,^{w70} and one of the cohort studies found that lung cancer was significantly less likely in the cohort with infectious mononucleosis.^{w71}

Can infectious mononucleosis cause any complications?

Infectious mononucleosis in most cases resolves over a period of weeks, but may occasionally be exacerbated by a wide variety of complications. A list of complications can be found at www.cdc.gov/epstein-barr/hcp.html. Neurological disorders may occur in 1-5% of patients.^{w72} These include encephalitis, meningoencephalitis, seizures, optic neuritis, sudden sensorineural hearing loss, idiopathic facial palsy, and Guillain-Barré syndrome among others.^{w73} Haematological complications are more common, in particular haemolytic anaemia (3%) and thrombocytopenia (25-50%),^{w72} but also, rarely, aplastic anaemia, pancytopenia, and agranulocytosis. Other rare acute complications include myocarditis, pericarditis,^{w74} pancreatitis, interstitial pneumonia, rhabdomyolysis, and psychological complications (“Alice in Wonderland” syndrome). The strength of association of infectious mononucleosis with many of these complications is based on scattered case reports, and the evidence of causation in many instances is unconvincing.^{w72}