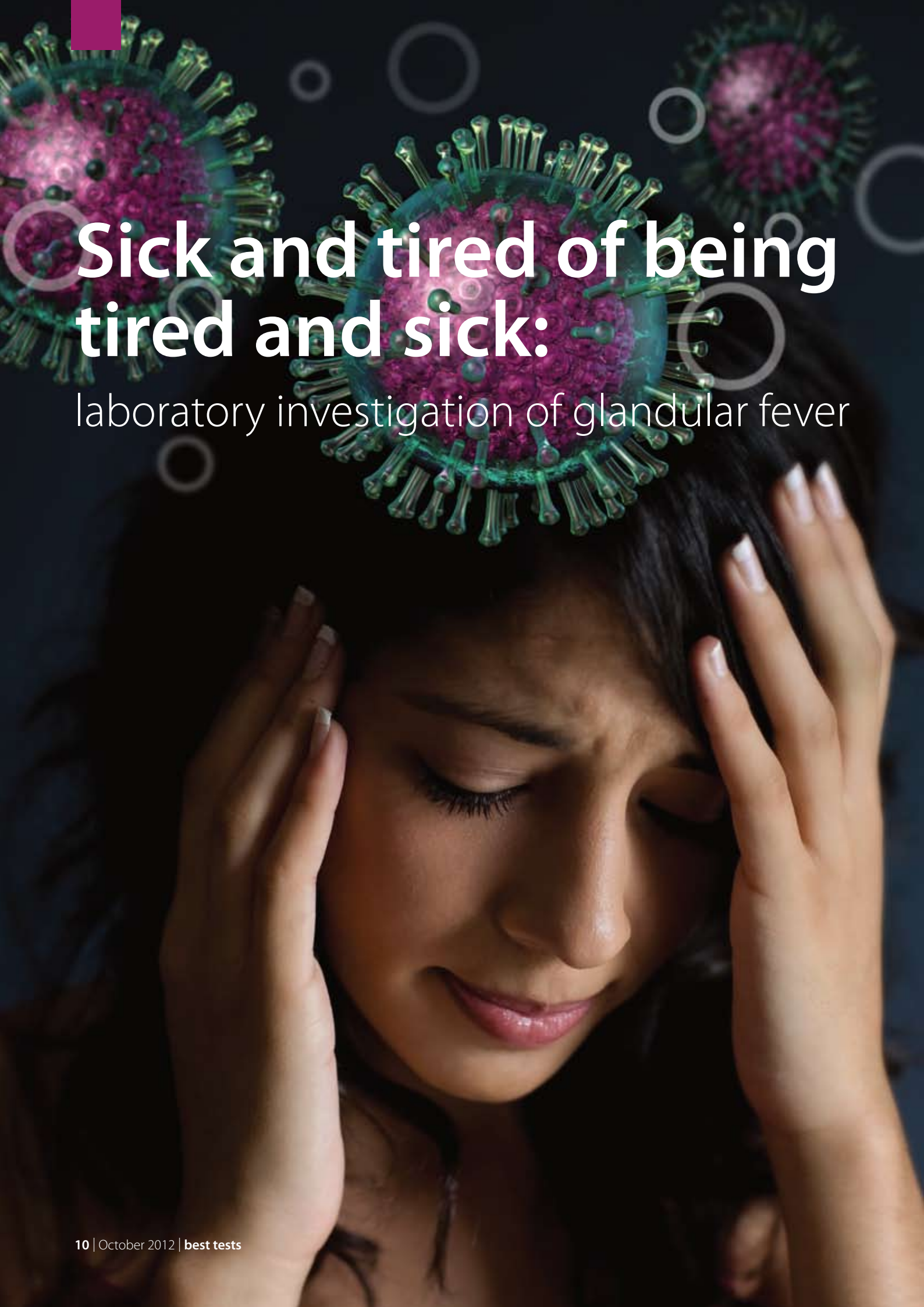
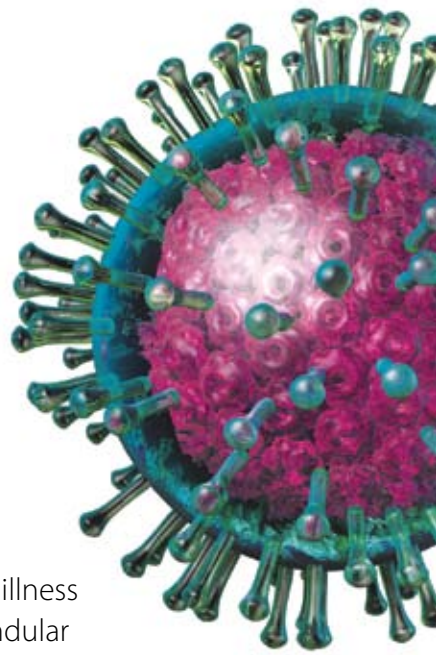
Sick and tired of being tired and sick:

laboratory investigation of glandular fever





Glandular fever (infectious mononucleosis) is a common, potentially debilitating illness that is most frequently seen in adolescents and young adults. A diagnosis of glandular fever can usually be made clinically, but laboratory testing is indicated if the clinical picture is unclear or where the risks of morbidity are high. The most appropriate testing regimen is dependent on age, history and symptoms.

The natural history of glandular fever

Infectious mononucleosis, commonly referred to as glandular fever, is a clinical syndrome comprising fever, pharyngitis and lymphadenopathy associated with atypical lymphocytosis. Acute Epstein-Barr virus (EBV) infection causes heterophile antibody positive infectious mononucleosis and accounts for approximately 90% of infectious mononucleosis cases.[1] Other important causes of infectious mononucleosis include cytomegalovirus, toxoplasmosis and acute HIV infection.

EBV is a member of the herpes virus family. As with other herpes viruses, EBV is a lifelong, predominantly latent and asymptomatic infection. EBV is spread primarily through saliva, which has led to glandular fever being called the "kissing disease", although droplet spread and the sharing of food and drink bottles contributes to transmission. There is no annual cycle of infection, and there is no difference in the incidence between males and females or between ethnicities.[1]

Epidemiological surveys indicate that more than 90% of adults worldwide are seropositive for EBV.[1] Approximately 50% of people contract the virus prior to age five years and have few, if any, symptoms.[1] Classic symptoms of glandular fever arise when acute EBV infection occurs in adolescents or young adults. The symptoms seen in older people may be less specific, although potentially more severe.[1]

Approximately 30 – 50% of adolescents or young adults exposed to EBV develop symptomatic glandular fever, following an incubation period of 30 – 50 days.[1] Symptoms persist for two to three months, although fatigue may be present for up to six months. An infected person sheds large numbers of viral particles for up to one year post-infection, after which time infectivity gradually declines.[1] Periodic viral shedding, and thus increased infectivity, occurs regularly throughout life, making attempts to limit the spread of glandular fever ineffective.

How to recognise glandular fever

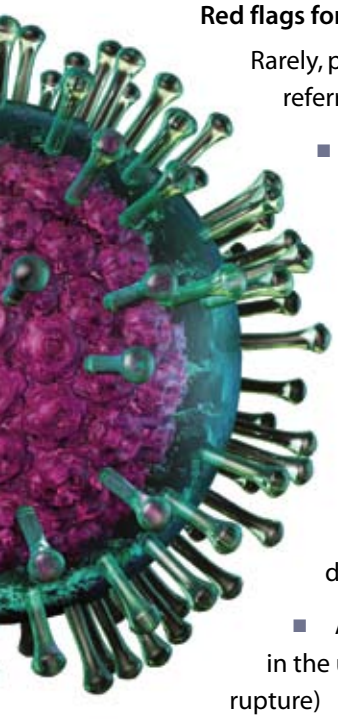
In many cases, glandular fever can be diagnosed clinically.[1] The classic symptoms are sore throat (usually with exudate), fever, enlarged cervical lymph nodes and fatigue. Headache, myalgia and chills are also common. Presentation many differ depending on the age of the patient. People aged 15 – 25 years are likely to have typical symptoms. Others have less specific symptoms; mild fever may be the only symptom in a child, and presentation of sore throat in a young child is unlikely to be glandular fever.[1] Older adults are more likely to present with abdominal discomfort and jaundice and have less obvious pharyngitis and lymphadenopathy.

On examination, signs of glandular fever include:[2]

- Lymphadenopathy – seen in almost all patients, posterior cervical lymphadenopathy is most common
- Pharyngitis – often with significant exudate and tonsil inflammation
- Fever
- Splenomegaly – detected in approximately half of patients on examination, but present in most
- Hepatomegaly –present in approximately 10 – 15% of patients, jaundice also may be present
- Palatal petechiae – also seen in streptococcal pharyngitis, but not viral pharyngitis
- Periorbital oedema
- Rash – present in less than 10% of patients, may be scarletiniform, morbilliform, urticarial or erythema multiforme-like

Recurrence of symptomatic glandular fever is unlikely

Recurrent glandular fever is unlikely.[3] Therefore, for most patients, a previous diagnosis of EBV infection will rule out glandular fever, but sometimes causes of infectious mononucleosis other than EBV should be considered. While the virus may reactivate periodically, reactivation is not associated with clinically significant symptoms except in people who are immunocompromised.[4]



Red flags for hospitalisation

Rarely, patients with glandular fever will require referral to hospital. Red flags include:

- Severe pharyngeal pain
- Excessive pharyngeal inflammation causing airway obstruction
- Insufficient fluid intake (signs of moderate to severe dehydration)
- Quinsy – inflammation of the tonsils to the extent that swallowing is not possible (can be seen on examination or if the patient is dribbling)
- Acute abdominal pain, particularly in the upper left quadrant (possible splenic rupture)

Other causes of sore throat should be considered

In some cases, glandular fever is clinically indistinguishable from other causes of sore throat. Streptococcal and viral pharyngitis should always be considered.

Viral pharyngitis is the most likely alternative diagnosis to glandular fever. The most frequent causes are adenovirus and influenza. Patients are likely to present with less severe lymphadenopathy and pharyngitis compared to those with glandular fever. Pharyngeal exudate is also likely to be less prominent. If the patient has palatal petechiae viral pharyngitis is unlikely: the patient has either glandular fever or streptococcal pharyngitis.

Streptococcal pharyngitis is more likely to be the cause of a sore throat in a younger child than glandular fever. Conversely, significant streptococcal pharyngitis rarely occurs in people aged over 15 years.[5] Streptococcal pharyngitis should be suspected in people from areas of New Zealand where there is an increased risk of rheumatic fever, and especially in those of Māori or Pacific ethnicity. It is reasonable to perform a throat swab when streptococcal pharyngitis is suspected, or consider empiric antibiotic treatment, particularly in high-risk areas.

Differentiating clinically between streptococcal pharyngitis and glandular fever is difficult. People with streptococcal infections have a reduced likelihood of hepatosplenomegaly and have less prominent fatigue compared to those with glandular fever. Lymphadenopathy in streptococcal pharyngitis is usually anterior cervical and submandibular, compared to posterior cervical for glandular fever.[2]

For further information see: "Rheumatic fever in Māori: what can we do better", BPJ 37 (Aug, 2011).

Testing for glandular fever

Laboratory investigation of glandular fever may not be necessary where the patient's clinical features suggest a diagnosis. Testing is recommended, however, wherever the clinical picture is unclear or an incorrect diagnosis has the potential to cause significant morbidity. Women who are pregnant and people who are immunocompromised should always have laboratory investigations requested, as the consequences of a missed diagnosis of acute HIV, toxoplasmosis or cytomegalovirus infection are more

Other causes of infectious mononucleosis

Acute EBV infection accounts for approximately 90% of infectious mononucleosis. Other causes should be considered when a patient, with suspected glandular fever, has an atypical presentation or risk factors for other causes are present. History, clinical presentation and, when indicated, testing may be required to help differentiate between the causes of infectious mononucleosis.

Diagnosis	Distinguishing features
Cytomegalovirus	Pharyngitis, fever, malaise, splenomegaly and lymphadenopathy. May be asymptomatic.
Acute HIV infection	Symptoms may be less specific and also include mucocutaneous ulceration, rash, headache or diarrhoea. If risk factors are present, HIV should be considered and laboratory testing arranged.
Viral hepatitis	Fever, abdominal pain, jaundice and malaise. Hepatomegaly is common. Pharyngitis, lymphadenopathy and splenomegaly are less likely.
Toxoplasmosis	Fever, lymphadenopathy and rash, but rarely pharyngitis. Transmission is usually via cat faeces or undercooked meat.
Human herpes virus-6	More common in young children (roseola, sixth disease). Fever of three to five days, widespread rash of macules and papules.

significant and may result in adverse foetal outcomes and increased morbidity and mortality.

When testing is indicated, the recommended tests are a full blood count (FBC) and a heterophile antibody test, followed by serology if the diagnosis remains unclear. Viral culture is not performed for diagnosis. (See Page 15 for specific recommendations for testing in children, older adults, women who are pregnant and people who are immunocompromised).

Start with a full blood count and a heterophile antibody test

A full blood count, when combined with findings from a clinical examination, can be highly suggestive of glandular fever.

The white blood cell count in a person with glandular fever averages between 12 – 18 x 10^9/L, with more than 50% being mononuclear lymphocytes.[1, 6] Atypical lymphocytes appear in the first week of symptomatic illness, increase to more than 20% of the total white blood cell count in the second week, and then decline over several weeks. A blood film with at least 10% atypical lymphocytes in a symptomatic person has a sensitivity of 75% and a specificity of 92% for the diagnosis of infectious mononucleosis, although not necessarily EBV infection.[1, 7] The differential diagnosis of atypical lymphocytosis includes acute viral infections, toxoplasmosis and drug hypersensitivity reactions.

Glandular fever is unlikely in a patient with a normal or reduced total white blood cells and lymphocytes, but patients who are tested within one week of symptom onset are less likely to have increased atypical lymphocytosis.

Heterophile antibody tests are used to confirm that glandular fever is due to acute EBV infection and to therefore rule out other causes of raised atypical lymphocyte counts.

Heterophile antibodies are a group of immunoglobulin M (IgM) antibodies induced by acute EBV infection that react to red blood cell antigens from other species. Heterophile

antibodies are present at clinically significant levels by the time of symptom onset and peak between two and five weeks later. Identifiable levels of heterophile antibodies may persist in a person with glandular fever for up to one year.

The presence of heterophile antibodies in a symptomatic adolescent or young adult has a sensitivity of approximately 90%, and specificity of almost 100% for glandular fever.[3] However, false-negatives occur in 25% of people early in the course of their illness (e.g. in the first week).[1] False-positives rates of 2 – 3% may be seen in patients with HIV infection, rubella, systemic lupus erythematosus and leukaemia, and older people or women who are pregnant.

Heterophile tests may be listed on laboratory request forms as Monospot, heterophile antibodies, infectious mononucleosis screen or Paul-Bunnell.

Throat swabs for pharyngitis should be taken where there is doubt about the differentiation of glandular fever from streptococcal pharyngitis. Practitioners should take into account the incidence of rheumatic fever in their area, and the likelihood of adverse sequelae of a missed diagnosis of streptococcal pharyngitis. The New Zealand sore throat guidelines state that the threshold for throat swab should be lower in a symptomatic patient with two or more of the follow features:[5]

- Māori or Pacific ethnicity
- Age 3 – 45 years (with the highest pre-test probability of a positive result in the age 3 – 14 year group)
- Living in lower socioeconomic areas of the North Island
- Past history of rheumatic fever

However, a positive result for streptococcus on a throat swab does not indicate whether there is an active infection or asymptomatic carriage, in which case glandular fever is still possible. Approximately 30% of people with primary glandular fever will have a non-symptomatic streptococcus carriage.[1]

Liver function tests are not routinely recommended as a diagnostic test for glandular fever. Tests are abnormal in more than 80% of people with glandular fever, but acute liver failure associated with EBV is very rare.[8] In addition, abnormalities in liver tests can be expected in all forms of infectious mononucleosis and in many other illnesses.

Liver tests should be considered for patients presenting with jaundice or significant hepatomegaly.[2] If measured, aspartate transaminase (AST) and alanine transaminase (ALT) levels more than ten times the upper limit of normal indicate that glandular fever is unlikely, and acute viral hepatitis should be considered.[7] Normal liver tests do not exclude glandular fever.

Where the diagnosis remains unclear, serology is recommended

If an initial FBC and heterophile tests fail to indicate glandular fever, specific EBV serology may be requested. Alternatively, FBC and heterophile tests may be repeated after seven days, followed by EBV serology if results are inconclusive.[9]

EBV serology tests provide a stage-specific diagnosis. The majority of the population is seropositive, so identifying a primary infection is important. The tests measure the activity of three kinds of antibody: viral capsid antigen (VCA) IgM and VCA IgG antibodies and anti-EB nuclear antigen (EBNA) antibodies.

VCA IgM antibodies are usually present at clinical levels from the outset of symptoms of glandular fever, and persist for two to four months before declining (Figure 1).[3] VCA IgG antibodies appear later than VCA IgM antibodies but persist for a much greater time, often for life.[3] EBNA antibodies appear six to twelve weeks after the onset of symptoms and also persist for life.[3]

The absence of EBNA antibodies indicates that the person has not had a previous glandular fever infection. VCA IgM and VCA IgG antibodies can then indicate if there is a current infection. An avidity test on the VCA IgG antibodies gives an indication of the time since infection – low avidity indicates recent infection and high avidity more than six to eight weeks since the acute infection.

The presence of EBNA antibodies indicates previous EBV infection. In a non-immunocompromised person this excludes acute EBV infection as an explanation for the current symptoms. In this case the initial diagnosis should be reconsidered, and other potential causes of infectious mononucleosis investigated.

Testing in older adults, children and people who are immunocompromised or pregnant

Specific EBV serology and FBC are recommended as the first-line tests for women who are pregnant, people who are immunocompromised, children and older people. Heterophile antibody tests are not necessary (and are also not used in children).

People who are immunocompromised and women who are pregnant should have specific EBV serology tests. It is necessary to confidently exclude other forms of infectious mononucleosis, as they are associated with adverse foetal outcomes.[1] Given the risks associated with primary cytomegalovirus and toxoplasmosis during pregnancy and the risk of mother-to-child transmission of HIV, definitive testing for other causes of infectious mononucleosis (i.e. tests for cytomegalovirus, toxoplasmosis and HIV) is also indicated in pregnant women presenting with infectious mononucleosis.[1]

Children and older adults require serology testing because heterophile antibody tests are less accurate outside of the age 12 – 25 year group. Heterophile antibody tests are likely to be falsely-negative in 50 – 75% of children, and older adults may remain reactive from a past infection or be falsely positive.[1]

The treatment of glandular fever

The management of glandular fever includes supportive treatment, identifying patients at immediate risk of complications, and education on the illness and expected symptom duration.

Women who are pregnant are not at an increased risk from glandular fever, but severe glandular fever during pregnancy may be associated with lower birth weight and pre-term delivery.[10]

Management at home

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) can be used to manage pain and fever. Consider prescribing liquid forms of these medicines to patients who are having difficulty swallowing. Corticosteroid and

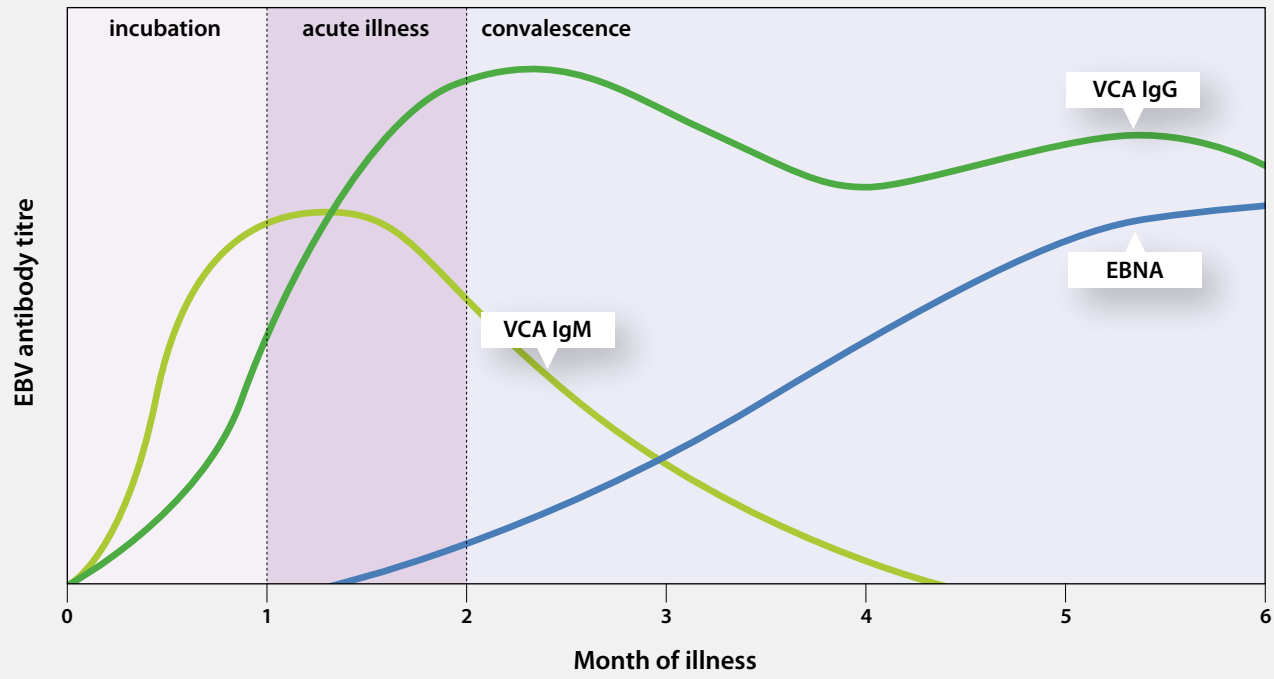


Figure 1: The antibody profile of EBV serology testing

antiviral treatment for EBV is not recommended due to a lack of evidence of clinical efficacy.[1] There is also no conclusive evidence for the effectiveness of alternative treatments such as vitamin C or B.

Adequate fluid and nutritional intake should be encouraged as anorexia and difficulty eating is present in many people with glandular fever. Alcohol consumption should be restricted.

Patients should be counselled on the likely time scale of the illness. Most symptoms will resolve within one month, but fatigue may be present for two to three months. Adequate sleep and rest is important for recovery, but complete bed rest should be discouraged. A recommendation for restriction from work or school may be considered for patients who are very unwell.

Measures or advice to limit the spread of infection are unlikely to be effective. Advice not to kiss or share food or drink bottles and to practice hand hygiene while symptomatic is sensible, but most people with glandular fever will remain contagious for at least one year following the onset of symptoms and will then become periodically re-infective throughout their lives. Usually, most people are seropositive for EBV and re-exposure does not carry a risk of symptom recurrence.

Amoxicillin may cause significant adverse effects

Amoxicillin should not be used in people with glandular fever, even where concurrent bacterial infection is suspected. Approximately 80 – 90% of people with acute EBV infection treated with amoxicillin (or ampicillin – not available in New Zealand) develop a red, diffuse maculopapular rash, similar to the morbiliform rash seen in measles infection.[2]

There is no specific guidance on how long amoxicillin should be avoided for, but most reactions occur during the acute illness phase. Patients with glandular fever treated with amoxicillin, who develop a rash, should not be recorded as having a beta-lactam allergy as this can adversely affect future antibiotic choices.

N.B. If a streptococcal infection cannot be ruled out, and empiric antibiotic treatment is indicated, penicillin V or erythromycin should be used.

Complications associated with glandular fever

The majority of people with glandular fever will have few, if any, long-term complications other than fatigue. However, glandular fever can be associated with a number of acute complications, including haematological and neurological complications, hepatitis, splenic rupture and upper airway obstruction.

Haematological complications will be present in approximately 25% – 50% of people with glandular fever, but are mild enough that they are unlikely to be apparent.[1] The most common haematological complications include haemolytic anaemia, thrombocytopenia, aplastic anaemia, purpura and haemolytic-uraemic syndrome. Neurological complications are rare, occurring in 1 – 5% of people, and urgent referral to hospital is required.[1] Neurological symptoms associated with glandular fever include facial-nerve palsy, meningocephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, cerebellitis, and optic neuritis.

Glandular fever is associated with a risk of splenic rupture

Splenic rupture is an extremely rare, but life-threatening complication of glandular fever. Patients should be advised to avoid strenuous activity and contact sport for at least three weeks after symptom onset.[1] Rupture of the spleen has been reported to occur in approximately 0.1 – 0.5% of people with glandular fever, and is not necessarily associated with trauma.[11] Risk peaks in the second to third week of the illness, but may persist for two months. Ultrasound to detect splenomegaly or the extent to which it is present, is not recommended as there is no direct relationship between the size of the spleen and the likelihood of rupture.[2]

Any patient that presents with acute abdominal pain, particularly in the upper left quadrant, within one to two months of a diagnosis of glandular fever should be referred to hospital.

Follow-up is usually not required

Most people with glandular fever make a full recovery. Fatigue sufficient to cause functional impairment will generally resolve within two to three months. Patients that display debilitating fatigue beyond this time should be assessed for other conditions such as depression, an

endocrine disorder or chronic fatigue. N.B. There is only limited evidence of a causal link between glandular fever and chronic fatigue syndrome.[12]

For further information about fatigue, see: "The laboratory investigation of tiredness", bpac[nz] (Feb, 2006).

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Best Tests
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