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REVIEW ARTICLE

Infectious Mononucleosis: An Updated Review

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Abstract: ***Background*:** Infectious mononucleosis is common among adolescents and young adults. Although the majority of cases resolve spontaneously, life-threatening manifestations, and complications have been recognised.

***Objective*:** The purpose of this article is to familiarize clinicians with the clinical manifestations, evaluation, diagnosis, and management of infectious mononucleosis.

***Methods*:** A search was conducted in October 2022 in PubMed Clinical Queries using the key terms "infectious mononucleosis" OR "Epstein-Barr virus" OR "EBV". The search strategy included all clinical trials, observational studies, and reviews published within the past 10 years. Only papers published in the English literature were included in this review. The information retrieved from the aforementioned search was used in the compilation of the present article.

***Results*:** Infectious mononucleosis, caused by Epstein-Barr virus, most commonly affects adolescents and adults aged 15 to 24 years. Epstein-Barr virus is transmitted primarily in saliva. Infectious mononucleosis is characterized by a triad of fever, tonsillar pharyngitis, and lymphadenopathy. Fatigue may be profound but tends to resolve within three months. Periorbital and/or palpebral edema, typically bilateral, occurs in one-third of patients. Splenomegaly and hepatomegaly occur in approximately 50% and 10% of cases, respectively. A skin rash, which is usually widely scattered, erythematous, and maculopapular, occurs in approximately 10 to 45% of cases. Peripheral blood leukocytosis is observed in most patients; lymphocytes make up at least 50% of the white blood cell differential count. Atypical lymphocytes constitute more than 10% of the total lymphocyte count. The classic test for infectious mononucleosis is the demonstration of heterophile antibodies. The monospot test is the most widely used method to detect the serum heterophile antibodies of infectious mononucleosis. When confirmation of the diagnosis of infectious mononucleosis is required in patients with mononucleosis-like illness and a negative mono-spot test, serologic testing for antibodies to viral capsid antigens is recommended. Infectious mononucleosis is a risk factor for chronic fatigue syndrome. Spontaneous splenic rupture occurs in 0.1 to 0.5% of patients with infectious mononucleosis and is potentially life-threatening. Treatment is mainly supportive. Reduction of activity and bed rest as tolerated are recommended. Patients should be advised to avoid contact sports or strenuous exercise for 8 weeks or while splenomegaly is still present. Most patients have an uneventful recovery.

***Conclusion*:** Infectious mononucleosis is generally a benign and self-limited disease. Prompt diagnosis is essential to avoid unnecessary investigations and treatments and to minimize complications. Splenic rupture is the most feared complication. As avoiding exposure to EBV is almost impossible, the most effective way to prevent EBV infection and infectious mononucleosis is the development of an effective, safe, and affordable EBV vaccine that can confer life-long immunity.

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1. INTRODUCTION

Infectious mononucleosis is characterized by a triad of fever, tonsillar pharyngitis, and lymphadenopathy, where lymphocytosis and atypical lymphocytes are typically present [1-3]. The condition was first described in 1887 by Nil Filatov, a Russian physician, as "idiopathic adenitis" [4]. The clinical triad of fever, pharyngitis, and lymphadenopathy was described in 1889 by Emil Pfeiffer, a German physician, as "Drüsenfieber" or "glandular fever" [5]. The term "infectious mononucleosis" was coined in 1920 by Sprunt and Evans to describe a group of college students with a febrile pharyngeal illness and laboratory findings of absolute lymphocytosis and atypical mononuclear cells in the blood [6]. The characteristic atypical lymphocytes, also known as Downey cells, were described by Downey and McKinlay in 1923 [7]. The Epstein-Barr virus (EBV) was identified in 1964 by Anthony Epstein and Yvonne Barr using electron microscopy in cultured lymphoma blast cells from tissue samples of patients with Burkitt lymphoma [8]. The association between infectious mononucleosis and EBV was pointed out by Henle *et al.* in 1968 [9]. Prompt and accurate diagnosis of infectious mononucleosis is essential to guide appropriate laboratory tests and treatments while at the same time avoiding the need for unnecessary expensive exploratory tests and inappropriate use of antibiotics. An updated review of the topic is therefore in order and is the purpose of the present article.

A search was conducted in October 2022 in PubMed Clinical Queries using the key terms "infectious mononucleosis" OR "Epstein-Barr virus" OR "EBV". The search strategy included all clinical trials (including open trials, non-randomized controlled trials, and randomized controlled trials), observational studies, and reviews (including narrative reviews and meta-analyses) published within the past 10 years. Only papers published in the English literature were included in this review. The information retrieved from the above search was used in the compilation of the present article.

2. EPIDEMIOLOGY

Infectious mononucleosis most commonly affects adolescents and young adults with a peak at 15 to 24 years of age [10-14]. The disease is not considered highly contagious [13, 15]. The overall incidence is approximately 12 per 1000 university students per year whereas the incidence is less than 1 case per 1000 persons per year in individuals younger than 10 years of age [16, 17]. The sex incidence is approximately equal [18, 19]. EBV infection is seen more commonly in individuals belonging to lower socioeconomic groups in developing countries where crowding and intrafamilial spread are common. Most primary EBV infections are subclinical and not apparent in young children. Therefore, less than 10% of these children develop clinical infections after exposure to EBV [10, 20]. On the other hand, primary EBV infection in adolescents and young adults results in infectious mononucleosis in approximately 75% of cases [21, 22]. Since most primary infections occur in older individuals in developed countries, symptomatic infectious mononucleosis is seen more commonly in this older age group [23]. Worldwide, approximately 90% of adults have serological evidence of previous clinical/subclinical EBV infection by 30 years of age [21]. As such, primary disease is uncommon in individuals over 30 years of age. Infectious mononucleosis is approximately 30 times more common in White Americans than in Black Americans [10]. Presumably, this is due to earlier exposures to EBV in Black Americans, resulting in subclinical manifestations in young children [13, 14, 18]. By the same token, infectious mononucleosis is uncommon in middle age and elderly individuals because of previous exposure to EBV [13, 14]. Infectious mononucleosis occurs worldwide with no yearly cycle or consistent seasonal peak [19].

There is a genetic predisposition to infectious mononucleosis [24]. Hwang *et al*. compared concordance for infectious mononucleosis in monozygotic and dizygotic twin pairs from the population-based California Twin Program [25]. The California Twin Program is a population-based registry of twins born in California between 1908 and 1982. Of the 6,926 twin pairs recruited into the study, one member of 611 and both members of 58 twin pairs reported a history of infectious mononucleosis. Pairwise concordance in monozygotic and dizygotic twin pairs was 12.1% (standard error = 1.9%) and 6.1% (standard error = 1.2%), respectively. The relative risk (hazard ratio) of developing infectious mononucleosis in monozygotic compared to dizygotic unaffected co-twins was 1.9 (95% confidence interval: 1.1 to 3.4; $p = 0.03$), over the follow-up period. The results are compatible with a heritable contribution to the risk of infectious mononucleosis [25]. Rostgaard and coworkers used data from the Danish Civil Registration System and the Danish National Hospital Discharge Register to study rate ratios of infectious mononucleosis in a cohort of 2,823,583 Danish children born between 1971 and 2011 [26]. A total of 16,870 cases of infectious mononucleosis were observed during 40.4 million person-years of follow-up from 1977 to 2011. The rate ratios and the associated 95% confidence intervals were 9.3 (3 to 29) in same-sex twins, 3 (2.6 to 3.5) in siblings, 1.9 (1.6 to 2.2) in parents, 1.4 (1.3 to 1.6) in second-degree relatives, and 1 (0.9 to 1.2) in third-degree relatives of patients with infectious mononucleosis. There was no overlap in the 95% confidence intervals for those 4 classes of relationships, thereby strengthening the conclusion that the degree of relatedness increased the likelihood of contracting infectious mononucleosis [26].

A preliminary study showed that low uric acid levels increase the risk of infectious mononucleosis, and this effect is more pronounced in females [27]. Another preliminary study showed that patients with infectious mononucleosis had significantly lower serum vitamin D levels at the time of infection than in the control group [28]. Future well-designed, large-scale, randomized, double-blind studies may provide us with more information in these areas.

3. ETIOLOGY

Most primates are infected with EBV. Only humans are infected with human EBV. EBV, also known as human herpesvirus 4 (HHV4), is the primary cause of infectious mono-

nucleosis and is the first human tumor virus discovered [29, 30]. EBV is a human lymphotropic virus, which belongs to the gamma herpesvirus subfamily within the *Lymphocryptovirus* genus and Herpesviridae family [30-32]. The virus is composed of an enveloped, hexagonal nucleocapsid that surrounds the double-stranded viral DNA genome [30]. The viral genome encodes more than 80 proteins and 46 functional small untranslated RNAs and is 150 to 200 nm in diameter and approximately 170 kilobase pairs in length [29-35].

4. PATHOPHYSIOLOGY

Humans are the only known reservoir of EBV [30, 32]. Infectious mononucleosis is typically transmitted person-to-person *via* exposure to saliva which contains EBV. The usual route of spread is by oral contact such as through deep kissing (a major route of transmission; hence its colloquial appellation, "the kissing disease"), or food sharing [21, 36]. In this regard, children can acquire the infection after eating food that has been chewed by an EBV-infected individual [37]. The shedding of EBV in saliva persists for approximately 6 months after illness onset [10, 13]. Less commonly, the virus is transmitted by sexual contact, blood transfusion, hematopoietic cell transplant, solid organ transplant, or sharing utensils [37-42].

EBV infects and replicates primarily in oropharyngeal B-lymphocytes (CD21) in lymphoid tissue (Waldeyer ring) and, to a lesser extent, in the epithelial cells of the oropharynx and salivary glands [43, 44]. Glycoproteins in the viral envelope play an important role in allowing the virus to attach and enter the host B-lymphocytes and epithelial cells [36]. Infection of B-lymphocytes stimulates their replication and their antigen-independent differentiation into memory B-lymphocytes [22, 45]. Circulating B-lymphocytes spread the infection throughout the entire reticular endothelial system resulting in a lymphoproliferative response and enlargement of lymphoid tissue in the lymph nodes, liver, and spleen [12, 43]. Infection of B-lymphocytes mounts a humoral and cellular response in an attempt to control the proliferation of infected B-lymphocytes [16]. A higher concentration of EBV increases the number of infected B-lymphocytes which induces the production of antibodies directed against viral and unrelated antigens found on horse and sheep erythrocytes [10].

The disease course is associated with atypical lymphocytes in peripheral blood and internal lymphoid organs. The atypical lymphocytes seen in infectious mononucleosis are T-lymphocytes of the CD8+ subset, with a smaller contribution from CD4+ cells [46]. The relative, as well as absolute, increase in CD8+ lymphocytes result in a transient reversal of the normal 2:1 CD4+/CD8+ (helper/suppressor) T-lymphocyte ratio [47]. The cytotoxic T-lymphocytes release a multitude of cytokines that cause the classical manifestations of infectious mononucleosis [18].

The usual outcome of B-lymphocytes infected with EBV is persistent latent infection. *In vitro*, during latency, the infected lymphocytes and epithelial cells establish infected cell lines that perpetuate the infection [12]. Intermittent excretion of the virus in salvia accounts for viral spread and persistence in the population [48].

5. CLINICAL MANIFESTATIONS

The incubation period from the time of viral exposure to the development of infectious mononucleosis is approximately 4 to 8 weeks [21, 37]. In children, the incubation period may be shorter. Prodromal symptoms, which may last for 1 to 2 weeks, include malaise, anorexia, headache, low-grade fever, chills, myalgia, and arthralgia [12].

The classic symptoms of infectious mononucleosis are sore throat, fever, swollen and tender cervical lymph nodes, and fatigue [49-51]. The patient's temperature is typically low-grade but may reach 38.9ºC to 40ºC [52]. The acute symptomatic phase usually lasts for 2 to 4 weeks [49, 52]. Fatigue may be profound but tends to resolve within three months [12, 49]. In the selected individuals, fatigue can last a lot longer. In a study of 57 consecutive patients with infectious mononucleosis attending Edinburgh University, female students were significantly more likely to report fatigue at 6 months after diagnosis than male students (34% *versus* 5%; $p = 0.012$) [53]. Anorexia, decreased appetite, sweating, headache, and body aches are frequent symptoms [10, 37, 44]. Other symptoms such as nausea, vomiting, abdominal pain, nasal stuffiness, rhinorrhea, cough, and photophobia are less common [10, 21, 37].

On examination, the pharynx is usually diffusely inflamed. There is often marked tonsillar enlargement with thick tonsillar exudates (Fig. **1**) [12, 51]. The tonsillar exudate may appear white, yellow, or gray. Palatal petechiae with streaky hemorrhages and uvular edema may be present [37, 44]. Periorbital and/or palpebral edema, typically bilateral, occurs in one-third of patients with infectious mononucleosis (Hoagland sign) early in the course of the disease and disappears in a few days [54-60]. The Hoagland sign, when present, is useful to distinguish infectious mononucleosis from streptococcal pharyngitis and other viral causes of pharyngitis [53, 54, 56].

Fig. (1). Tonsillar enlargement with exudates in a 15-year-old girl with infectious mononucleosis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Lymphadenopathy occurs most commonly in the posterior cervical lymph nodes (Fig. **2**) followed by posterior auric-

ular lymph nodes, and anterior cervical lymph nodes, and is typically symmetrical [13, 14, 51, 61]. At times, lymphadenopathy may become generalized which, when present, helps to distinguish infectious mononucleosis from other causes of pharyngitis [3, 61]. Lymphadenopathy tends to peak in the first week of the disease and then subsides over the next two to three weeks. Splenomegaly (typically 3 to 4 times the normal size) and hepatomegaly occur in approximately 50% and 10% of the cases, respectively [13, 14, 62, 63]. Tenderness in the left upper abdominal quadrant may be present in patients with splenomegaly. The splenomegaly tends to recede by the third week of the illness [10]. Jaundice is present in less than 10% of young adults with infectious mononucleosis [18].

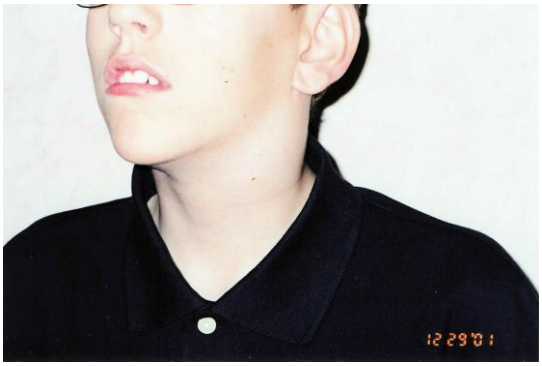

Fig. (2). Posterior cervical lymphadenopathy in a 17-year-old male with infectious mononucleosis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

A skin rash is seen in approximately 10 to 45% of all cases of infectious mononucleosis [18]. The rash is usually transient, widely scattered, erythematous, and maculopapular or morbilliform (Figs. **3** and **4**) [64, 65]. Sites of predilections include the trunk and arms [12]. Typically, the rash appears during the first few days of illness and lasts 1 to 6 days [12]. The rash is nonpruritic [12]. Between 80 and 90% of patients who are treated with ampicillin or amoxicillin experience a generalized, pruritic maculopapular, urticarial, or petechial rash [66, 67]. Other authors found an incidence rate between 15 and 33% [68-70]. In one study, the overall incidence of rash in patients with infectious mononucleosis was 30% (72/238), with 33% (57/173) of patients having received antibiotics and 23% (15/65) without receiving antibiotics [69]. Typically, the rash develops 2 to 10 days after exposure to the antibiotic [46, 71]. Other antibiotics that have been implicated in inducing a skin rash in the setting of infectious mononucleosis include methicillin [72], levofloxacin [73], cefprozil [74], cephalexin [75], erythromycin [76], azithromycin [77, 78], telithromycin [79], and piperacillin/tazobactam [80]. The mechanism responsible for the antibiotic-induced skin rash in the setting of infectious mononucleosis is not well understood. Some authors speculated that EBV suppresses interleukin-10 activity which results in an increase of type 1 helper T-lymphocytes, which may contribute to the development of delayed hypersensitivity reactions [70]. Occasionally, a petechial or urticarial rash may be seen but erythema nodosum is rare [10].

Fig. (3). Erythematous, maculopapular eruption on the chest, abdomen and upper extremities. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fig. (4). Erythematous, maculopapular eruption on the back. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The severity and duration of symptoms can vary greatly, ranging from weeks to months [81]. Patients with high viral loads at presentation have significantly higher illness severity scores associated with fatigue [12]. Generally, patients aged over 30 years at the onset of illness, recent use of nonsteroidal anti-inflammatory drugs (NSAIDS), and more importantly, patients with immunodeficiencies experience a more severe form of the disease and have a longer duration of the illness [82].

Several clinical variants exist. Some patients with infectious mononucleosis may present with fever and cervical lymphadenopathy without tonsillar pharyngitis or marked cervical lymphadenopathy out of proportion to the pharyngeal symptoms, the so-called “glandular form” of infectious mononucleosis [42, 44]. Other patients present with fever and fatigue with mild or absent pharyngitis and lymphadenopathy [44]. Lingual tonsillitis is an uncommon, often unrecognized manifestation of infectious mononucleosis [83]. Older adults often do not present with the classical symptoms of infectious mononucleosis [84, 85]. Rather, they often present with fever (95%), lymphadenopathy (47%), pharyngitis (43%), hepatomegaly (42%), splenomegaly (33%), hepatic dysfunction (27%) or a skin rash (12%) [84].

6. DIAGNOSIS

The diagnosis should be suspected in an adolescent or young adult with fever, sore throat, malaise, fatigue, and an erythematous morbilliform rash, especially when tonsillar enlargement with thick tonsillar exudates, palatine petechiae, periorbital/palpebral edema, posterior cervical lymphadenopathy, and splenomegaly are present [55, 86]. The likelihood of infectious mononucleosis is reduced with the absence of lymphadenopathy [12, 86]. The presence of lymphocytosis and increased atypical lymphocytes increases the likelihood of infectious mononucleosis [12]. Atypical lymphocytes more than 10% of the total lymphocyte count have a sensitivity of 75% and a specificity of 92% for infectious mononucleosis [18]. A lymphocyte count < 4 x 10^9/L, on the other hand, has a negative predictive value for infectious mononucleosis [19]. If infectious mononucleosis is suspected, a monospot test is the best initial diagnostic test because the test is relatively inexpensive, fast, and easy to perform [19]. If the patient does not have classic infectious mononucleosis syndrome yet the monospot test is positive, measurement of viral capsid antigen (VCA)-IgM, VCA-IgG, and IgG antibody to Epstein-Barr nuclear antigen (EBNA) and, if necessary, detection of EBV DNA with polymerase chain reaction (PCR) should be considered to clarify the diagnosis [10, 16].

6.1. Differential Diagnosis

The clinical features of mononucleosis-like syndrome mimic those of infectious mononucleosis. Mononucleosis-like syndrome is caused most often by cytomegalovirus infection [87-93]. Less commonly, the syndrome can be caused by human immunodeficiency virus (HIV), human herpesvirus-6, -7, and -8, influenza virus, adenovirus type 12, rubella virus, hepatitis B virus, *Borrelia burgdorferi*, *Borrelia mayonii*, *Arcanbacterium haemolyticum*, and *Toxoplasma gondii* [13, 90, 94-97]. Medications such as antimicrobials (*e.g*., isoniazid, minocycline) and anticonvulsants (*e.g*., carbamazepine, phenytoin) may also cause a mononucleosis-like syndrome [98-100].

Other differential diagnoses include streptococcal pharyngitis (fever, sore throat, beefy red pharynx, erythematous and enlarged tonsils with or without exudates, enlarged tender anterior cervical lymph nodes, strawberry tongue, scarlatiniform rash, palatal petechiae), viral pharyngitis (fever, sore throat, rhinorrhea, non-productive cough, concurrent conjunctivitis), drug eruption (history of medication use, rapid evolution of pruritic morbilliform or maculopapular exanthem, usually subsides within 14 days after the offending medication has been discontinued, absent systemic symptoms), rubella (low-grade fever, erythematous maculopapular rash spreading cephalocaudally from the face downwards, retroauricular/ posterior cervical/ suboccipital lymphadenopathy, with or without arthralgia/arthritis), measles (high fever, erythematous maculopapular rash spreading cephalocaudally from the face downwards, at least one of the three "C"s: coryza, cough, or conjunctivitis), Lyme disease (skin rash often with central clearing at the site of tick bite, fatigue, anorexia, headache, neck stiffness, myalgias, arthralgias, regional lymphadenopathy, fever), scrub typhus (fever, eschar at the site of the infecting chigger bite, nonpruritic, macular or maculopapular rash, intense generalized headache, diffuse myalgias, nausea, vomiting, diarrhea, cough, lymphadenopathy, relative bradycardia), Gianotti-Crosti syndrome (abrupt onset of a papular or papulovesicular eruption with a symmetrical and acral distribution, malaise, low-grade fever, lymphadenopathy), hemophagocytic lymphohistiocytosis (fever, splenomegaly, hemophagocytosis in spleen, bone marrow and/or lymph nodes, cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia), and Kikuchi-Fujimoto disease (fever, night sweats, headache, sore throat, fatigue, nausea, vomiting, weight loss, arthralgia, unilateral tender posterior cervical lymphadenopathy, splenomegaly, hepatomegaly) [101-113].

7. LABORATORY STUDIES

Patients suspected to have infectious mononucleosis should have a complete blood cell count with differential count and a peripheral smear performed. Peripheral blood leukocytosis (10 to 20 x 10^9/L) is observed in most patients with infectious mononucleosis; lymphocytes make up at least 50% of the white blood cell differential count [12]. Atypical lymphocytes (also called Downey cells) are mature T-lymphocytes that have been antigenically activated; they constitute greater than 10% of the total lymphocytes in individuals with infectious mononucleosis [114]. These atypical lymphocytes vary in size but tend to be larger overall and to have vacuolated basophilic cytoplasm; eccentrically placed, indented, or folded nuclei; and an increase cytoplasmic/nuclear ratio [12]. The majority of these lymphocytes are CD8+ cytotoxic T-cells [10, 21]. An absolute increase in atypical lymphocytes during the second week of the illness is characteristic of infectious mononucleosis [48].

An erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) should be considered. The ESR and CRP are elevated in most patients with infectious mononucleosis but are usually not elevated in patients with group A streptococcal pharyngitis [104]. These tests, however, do not differentiate infectious mononucleosis from other causes of mononucleosis-like syndrome.

The classic test for infectious mononucleosis is the demonstration of heterophile antibodies which peak 2 to 6 weeks after infection with EBV and usually disappear over 6 months [48]. The heterophile antibodies of infectious mononucleosis are IgM antibodies that can agglutinate sheep and horse erythrocytes but not guinea pig kidney cells [115]. This adsorption property distinguishes this response from the heterophile response found in patients with serum sickness and rheumatic diseases and some normal persons [12]. In the classic Paul-Bunnell test, sheep erythrocytes are used as the substrate and agglutinate in the presence of heterophilic antibodies. The monospot test, a latex agglutination test using horse erythrocytes as the primary substrate, is the most widely used method to detect the serum heterophile antibodies of infectious mononucleosis [116]. The test is fast (results are

obtainable within 10 minutes), inexpensive, and approximately 90% specific and 70 to 90% sensitive [48, 116]. In a recent study of 199 athletes (86 men, 113 women; age: 18 to 23 years) who had symptoms of infectious mononucleosis and had both monospot tests and EBV antibody titers performed at the same time, the authors found that the monospot test had a sensitivity of 80% and a specificity of 90.6% [117]. One of the disadvantages of heterophile tests is that they may be negative in the very early stage of the disease as heterophil antibodies peak between 2 and 6 weeks of disease [116]. The false negative rate is as high as 25% in the first week, 5 to 10% in the second week, and 5% in the third week of the illness [10]. Another disadvantage is that the heterophile tests are unreliable in children younger than 4 years because of the high incidence of false-negative results [22]. Approximately 40% of children younger than 4 years of age do not develop heterophile antibodies following a primary EBV infection [37]. Generally, patients with a mononucleosis-like syndrome not caused by EBV do not have serum heterophile antibodies. However, false-positive results have been reported in patients with HIV infection, Lyme disease, rheumatoid arthritis, systemic lupus erythematosus, cytomegalovirus infection, rubella, viral hepatitis, dengue, babesiosis, leukemia, lymphoma, and pancreatic cancer [118-122].

Tests for antibodies to VCA are more sensitive and specific than the heterophile test but rapid results are usually not obtainable [18, 37]. When confirmation of the diagnosis of infectious mononucleosis is required in patients with mononucleosis-like illness but with a negative monospot test, serologic testing for antibodies to viral capsid antigens (VCA-IgM, VCA-IgG) is recommended [16]. The negative likelihood ratio for the heterophile test is 0.14 to 0.18 [18]. On the other hand, the negative likelihood ratio for detecting VCA is 0.03 [18]. The VCA-IgM antibody signals a recent infection and wanes approximately 3 months later [10]. On the other hand, VCA-IgG antibody persists past the stage of acute infection and signals the development of immunity [16]. Typically, IgG antibody to EBNA is not detectable until 6 to 12 weeks after the onset of symptoms and tends to persist for life [10]. As such, the presence of IgG EBNA during an acute illness rules out primary EBV infection [21]. The presence of elevated IgG EBNA titers has the same significance as elevated VCA-IgG titers and can be used to distinguish between acute and previous EBV infections [91]. PCR to detect EBV DNA can be a useful diagnostic tool when the monospot test and IgG EBNA are negative and the VCA-IgM is positive, especially in patients younger than 4 years of age or immunocompromised patients with atypical clinical features of infectious mononucleosis [48, 123].

Liver function tests may be considered as impaired liver function is common in patients with infectious mononucleosis [124]. Mild to moderate elevations of liver enzymes such as alanine transaminase (ALT) and aspartate aminotransferase (AST) occur in 80 to 90% and bilirubin in 5% of patients with infectious mononucleosis, respectively [124, 125]. The serum alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) levels, however, are not usually elevated in patients with infectious mononucleosis [124, 125]. Recent studies have shown that routine assessment of liver function is not required in immunocompetent adults with infectious mononucleosis with subclinical derangement of liver function [126, 127].

8. COMPLICATIONS

In infectious mononucleosis, the spleen is usually increased 3 to 4 times its normal size [128]. Moderate splenomegaly occurs in approximately 20% of patients with infectious mononucleosis [12]. Splenomegaly, evident on palpation and ultrasonography, occurs in approximately 50% and 100%, respectively, of all cases of infectious mononucleosis at some stage of the disease [12, 44]. The splenomegaly is usually asymptomatic [2, 12]. Splenic rupture occurs in 0.1 to 0.5% of patients with infectious mononucleosis and is potentially life-threatening [129-138]. The condition is spontaneous in more than 50% of cases, with no history of specific trauma [44]. Splenic rupture typically occurs in males under 30 years of age, 2 to 21 days after the onset of the disease [139-144]. Spontaneous rupture of the spleen after the fourth week of the illness is rare [145, 146]. Splenic infarction is a rare complication of infectious mononucleosis [147-156]. The condition occurs mostly in adolescents and young adults, especially in those with underlying diseases such as spherocytosis and sickle cell traits [148, 157]. The diagnosis should be considered in patients with infectious mononucleosis who have concurrent left upper quadrant abdominal pain [148, 152, 156].

Fatigue is the most common lingering symptom which may be severe and persistent [44]. Infectious mononucleosis is a risk factor for chronic fatigue syndrome [158, 159]. Chronic fatigue syndrome typically presents with persistent fatigue (at least one year), musculoskeletal symptoms, and cognitive impairment, resulting in severe impairment of daily functioning [158]. The reported incidence of chronic fatigue syndrome following infectious mononucleosis ranges from 9 to 12% [158, 160]. Predisposing factors include female sex and premorbid disorders [33, 161].

Children and adolescents with infectious mononucleosis are at increased risk for multiple sclerosis, independent of shared familial factors [162-174]. A 2006 meta-analysis of 14 studies (11 case-control studies, 3 cohort studies) concluded that the relative risk of multiple sclerosis after infectious mononucleosis was 2.3 (95% confidence interval: 1.7 to 3; $p < 10$ [-8]) [173]. In a recent cohort study of 32,116 outpatients (16,058 patients with infectious mononucleosis matched to a cohort of 16,058 patients without infectious mononucleosis based on age and sex) in Germany with a 10-year follow-up period, the incidence of multiple sclerosis was 22.6 cases and 11.9 cases per 100,000 person-years among patients with and without infectious mononucleosis, respectively [167]. In regression analysis, infectious mononucleosis was significantly associated with the incidence of multiple sclerosis (hazard ratio: 1.86; 95% confidence interval: 1.09 to 3.16). Subgroup analysis showed that the strongest association was in the age group between 14 and 20 years

(hazard ratio: 3.52; 95% confidence interval: 1.00 to 12.37). The association was stronger in males compared to females.

Infectious mononucleosis is a risk factor for depression [175]. In a prospective cohort study of 1,440,590 singletons born in Denmark by Danish-born parents with 21,830,542 person-years follow-up, infectious mononucleosis was associated with an increased risk for subsequent depression (hazard ratio: 1.40; 95% confidence interval: 1.26 to 1.56) [175].

Other complications are rare and are based mainly on isolated case reports. These complications include upper airway obstruction due to massive lymphoid hyperplasia and mucosal edema of the soft palate and tonsils [176-181], idiopathic hypersomnia [182, 183], peritonsillar/intratonsillar abscess [184-187], tonsillar hemorrhage [188, 189], ageusia [190], anosmia [190], sinusitis [191, 192]; necrotising fasciitis [193], secondary bacteremia [194], obstructive sleep apnea [176, 180, 181], aplastic anemia [12], autoimmune hemolytic anemia [195-197], thrombocytopenia [198-202], agranulocytosis [203, 204], pancytopenia [91], disseminated intravascular coagulopathy [44], hemophagocytic lymphohistiocytosis or hemophagocytic syndrome [205-211], hypoalbuminemia, hypogammaglobulinemia, anhidrosis [212], dry eye syndrome [213], conjunctival edema [213], conjunctivitis [213], dacryoadenitis [213], oculoglandular syndrome [213], episcleritis [213], keratitis [214], iritis [213], uveitis [215], retinitis [213], retinal necrosis [216], papilledema [213l], ophthalmoplegia [213], optic neuritis [213], polyglandular syndrome [12], thyroiditis [217], type 1 diabetes mellitus [218], cranial nerve palsy (*e.g.*, facial nerve palsy, abducens nerve palsy, oculomotor nerve palsy) [219-223], peripheral neuritis [44], aseptic meningitis [10], meningoencephalitis [224], encephalitis [225-227], acute disseminated encephalomyelitis (ADEM) [228], cerebellitis [229], myalgic encephalomyelitis/chronic fatigue syndrome [230-232], Lemierre syndrome [233, 234], cerebral infarction [235], transverse myelitis [19], Guillain-Barré syndrome [221, 236], peripheral neuritis [10], "Alice-in-Wonderland" syndrome (distortion of sizes, shapes, and spatial relations of objects) [181], psychosis [13], myositis [10], dermatomyositis [218], rhabdomyolysis [81], arthritis [12], systemic lupus erythematosus [237-239], rheumatoid arthritis [237], subcutaneous nodules [240], Sjögren syndrome [237], Reye syndrome, pneumonia [10], pleural effusion [241], pulmonary nodules [195, 242], acalculous cholecystitis [243-250], cholestasis [251-255], hepatic dysfunction [124], hepatitis [256-261], hepatic failure [262, 263], pancreatitis [264, 265], hypertriglyceridemia [266], ascites [267], enteropathy [268], inflammatory bowel disease [218], acute appendicitis [269], visceral serositis [270], mesenteric adenitis [10], acute glomerulonephritis [271], acute interstitial nephritis [272, 273], tubulointerstitial nephritis [274], acute renal failure [272, 273], hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura [273, 275], nephrotic syndrome [274], genital ulceration [276, 277], epididymitis [278], orchitis [48], mediastinitis [279-281], arrhythmias [282], postural tachycardia syndrome [283], myocarditis [282], pericardial effusion [282], pericarditis [282], and chronic multiorgan dysfunction [37, 226]. Children with X-linked lymphoproliferative syndrome are at risk for fatal infectious mononucleosis. EBV has been shown to have a remarkably strong association with malignancies such as Burkitt lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, post-transplant lymphoproliferative disorder, gastric carcinoma, leiomyosarcoma, and nasopharyngeal carcinoma in certain patients, such as those who are immunocompromised [284-287]. In one study, *GATA2* deficiency was associated with severe infectious mononucleosis and EBV hydroa vacciniforme-like lymphoma [288]. Surprisingly, a recent study showed that females diagnosed with infectious mononucleosis had a lower risk of developing invasive breast cancer [289].

The economic burden associated with infectious mononucleosis can be substantial. In one study of 1,596 patients (946 females, 650 males; average age 32 years) with infectious mononucleosis, approximately 62% of all patients were on sick leave for an average of 20 days around the time of diagnosis [290]. Approximately 1% of patients were still on sick leave after 6 months of the diagnosis.

9. MANAGEMENT

As infectious mononucleosis usually resolves without intervention, treatment is mainly supportive. Acetaminophen or NSAIDs may be considered for the treatment of fever and sore throat [20]. These medications, however, are not effective in shortening the duration of the disease [20]. Aspirin should be avoided in children because its use is associated with risks of Reye syndrome and bleeding diathesis [18]. The provision of adequate fluid and nutrition is essential. In patients with infectious mononucleosis who have coexisting bacterial infection which requires antibiotic treatment, clindamycin and clarithromycin may be suitable alternatives, due to the eruption that occurs with concomitant aminopenicillin use [291].

Reduction of activity and bed rest as tolerated are recommended [12]. Patients should be advised to avoid contact sports, heavy lifting, and strenuous exercise for 4 to 8 weeks or while splenomegaly is still present to reduce the risk of splenic rupture [44, 128, 138]. In patients with chronic fatigue syndrome attributable to infectious mononucleosis, vigorous physical activity during the acute stage of the illness when the virus is active may worsen the fatigue and prolong its course [292]. A preliminary study on 24 patients with infectious mononucleosis showed that Robuvit® (Horphag Research Ltd.), a natural extract from French oak wood, was effective, safe, and well-tolerated for the treatment of infectious mononucleosis-related fatigue [293]. Well-designed, large-scale, randomized, double-blind, and placebo-controlled studies are necessary to evaluate the efficacy of this agent.

A Cochrane systematic review of seven trials (n = 362) on the use of corticosteroids for symptom control in infectious mononucleosis concluded that there was insufficient evidence (trials were too few, heterogeneous, and of poor quality) to recommend the routine use of corticosteroids in the management of infectious mononucleosis [40]. The use of corticosteroids may be considered in those with impend-

ing or established airway obstruction [14, 294]. Some authors also consider the use of corticosteroids in those with life-threatening conditions such as severe thrombocytopenic purpura, hemolytic anemia, aplastic anemia, massive splenomegaly, myocarditis, and hepatic failure [44, 48, 295]. The recommended dose of oral prednisone is 1 mg/kg per day (maximum 60 mg/day) for 5 to 7 days [48]. The risks and benefits of using corticosteroids should be taken into consideration. Indiscriminate use of corticosteroids may lead to serious adverse events such as bacterial superinfection and immunosuppression.

Antiviral agents (acyclovir, ganciclovir, valacyclovir, valganciclovir) have been used for the treatment of infectious mononucleosis [296-301] but have not been shown to be effective in the majority of cases [298, 299]. Inhibition of virus replication does not affect the proliferation of latently infected cells. For this, T-cell immunity is required. A 2017 Cochrane systematic review of seven randomized controlled trials (n = 333) comparing antivirals *versus* placebo or no treatment in infectious mononucleosis found that the effectiveness of antiviral agents (acyclovir, ganciclovir, valacyclovir, valganciclovir) in infectious mononucleosis is uncertain [298]. As such, antiviral agents are not recommended for the routine treatment of infectious mononucleosis [103]. The use of antiviral agents may be considered in patients with severe complications such as encephalitis or in immunocompromised patients [12]. In a recent study, 128 children sick enough to be admitted to the Hangzhou Children's Hospital with infectious mononucleosis were randomized to receive an intravenous infusion of ganciclovir (n = 64) or acyclovir (n = 64) for a total of 7 days [302]. A comparison of clinical efficacy between the two groups showed that the total effective rate was higher in the ganciclovir group than that in the acyclovir group (92.19% *versus* 73.44%; $p < 0.05$). The time to the disappearance of the symptoms and signs (such as fever, angina, adenopathy, splenomegaly, and hepatomegaly) in the ganciclovir group was lower than in the acyclovir group ($p < 0.05$). The EBV-DNA negative conversion rate was higher in the ganciclovir group than that in the acyclovir group (81.25% *versus* 60.93%; $p < 0.05$). The incidence of side effects during treatment was lower in the ganciclovir group than that in the acyclovir group ($p < 0.05$). Side effects of ganciclovir and acyclovir include, among others, thrombocytopenia, hepatotoxicity, nephrotoxicity, and gastrointestinal dysfunction [302]. Therefore, antiviral agents have to be used with caution and only when necessary. Also, well-controlled randomized clinical trials are needed to determine the true efficacy of antiviral agents for the treatment of hospitalized patients with infectious mononucleosis.

10. PREVENTION

Patients with infectious mononucleosis should avoid kissing others. The sharing of food and drink as well as personal items such as eating utensils, drinking glasses, and toothbrushes should be discouraged. Frequent handwashing is advisable to reduce transmission of EBV to other individuals [37, 44].

As avoiding exposure to EBV is almost impossible, the most effective way to prevent EBV infection and infectious mononucleosis is the development of an effective, safe, and affordable EBV vaccine that can confer life-long immunity. In recent years, there has been a decrease in the prevalence of EVB antibodies among adolescents and young adults in many parts of the world [303-306]. It is conceivable that the number of adolescents and young adults who are most susceptible to infectious mononucleosis will increase; hence the importance to develop effective prophylactic EBV vaccines and treatment strategies [304]. In addition, effective prophylactic EBV vaccines have the potential for the prevention of complications such as EBV-related malignancies and multiple sclerosis [307].

Obstacles to EBV vaccine development include undefined correlates of immune protection, lack of appropriate animal models other than subhuman primates to test vaccine efficacy, lack of knowledge regarding the ideal EBV antigens for vaccination, lack of knowledge regarding the ideal vaccine delivery platform, limited data on adjuvant selection and immune responses, difficulty to find sponsorship from the industry, and proprietary issues [308-312]. Up until now, there has been no licensed commercially available vaccine for the prevention of EBV infection despite decades of effort [34]. Several prophylactic EBV vaccines are currently under development and promising signs of progress have been made [307, 311, 313-315]. Many of these vaccines contain two or more EBV glycoproteins (gp) such as gp350/220, gp42, gB, and gH, gL which are essential for the entry of the virus and its subsequent fusion with B-lymphocytes [307, 311]. Emerging evidence suggests vaccines containing these gp on the capsid of the virus can elicit neutralizing antibodies that would inhibit EBV infection of host B-lymphocytes and epithelial cells [310, 316]. It has been shown that immunization with the combination of EBV gp markedly increased the EBV-neutralizing antibodies compared to immunization with individual gp [29, 317]. Although some of the vaccines are moderately immunogenic, they do not provide immunity that is completely effective at preventing EBV infection [37, 309, 315, 318]. The addition of appropriate immune-stimulating adjuvants may improve the efficacy of EBV vaccines [317]. More research needs to be done in this area.

In 2022, Moderna initiated a clinical trial of an mRNA vaccine containing EBV gp350, gp42, gB, and gH/gL in 18- to 30-year-old adults [319]. The estimated completion date is June 2023. In the same year, the National Institute of Allergy and Infectious Diseases conducted a clinical trial of an adjuvanted gp350 ferritin nanoparticle vaccine in Matrix-MI in adults aged 18 to 29 years [320]. The estimated completion date is July 2025.

11. PROGNOSIS

In general, the prognosis is favorable [295]. Most patients with infectious mononucleosis have an uneventful recovery and develop durable immunity to the virus [13, 295]. The recurrence of the disease is very unusual [28, 321]. Gen-

erally, children recover more quickly than adults [12]. Severe complications are rare, and the overall mortality is low [38]. There is no evidence that infectious mononucleosis during pregnancy is teratogenic to the fetus [322].

CONCLUSION

Approximately 75% of adolescents and young adults with primary EBV infection develop infectious mononucleosis. Given the disease burden associated with infectious mononucleosis, the development of an effective, safe, and affordable EBV vaccine, especially for use in adolescents and young adults, has long been a priority for researchers in the field.

LIST OF ABBREVIATIONS

ALP	=	Alkaline Phosphatase
ALT	=	Alanine Transaminase
AST	=	Aspartate Aminotransferase
CRP	=	C-Reactive Protein
EBNA	=	Epstein-Barr Nuclear Antigen
EBV	=	Epstein-Barr Virus
ESR	=	Erythrocyte Sedimentation Rate
GGT	=	Gamma-glutamyl Transpeptidase
gp	=	Glycoproteins
HHV	=	Human Herpesvirus
HIV	=	Human Immunodeficiency Virus
NSAIDs	=	Nonsteroidal Anti-inflammatory Drugs
PCR	=	Polymerase Chain Reaction
VCA	=	Viral Capsid Antigen

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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