INFECTIOUS MONONUCLEOSIS

CHI Formulary Development Project

مجلس الضمان الصحي
Council of Health Insurance

January 2024

Table of Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

CHI	Council of Health Insurance
CMV	Cytomegalovirus
CNS	Central Nervous System
EBV	Epstein-Barr virus
ECCO	European Crohn's and Colitis Organization
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABHS	Group A β-hemolytic streptococcal
IBD	Inflammatory bowel disease
IDF	Insurance Drug Formulary
IM	Infectious Mononucleosis
MS	Multiple Sclerosis
NSAID	Non-Steroidal Anti-Inflammatory Drug
PTLD	Post-Transplant Lymphoproliferation/Lymphoma
SFDA	Saudi Food and Drug Authority
VCA	Viral Capsid Antigen

Executive Summary

The term "infectious mononucleosis" (IM) was coined in the 1920s to describe a group of students who shared similar throat symptoms and exhibited specific blood abnormalities. Only later did the identification of the Epstein-Barr virus (EBV) as the causative agent occur, confirmed through a positive heterophile test in a healthcare worker with known exposure. The primary cause of mononucleosis is EBV, a type of herpesvirus primarily transmitted through contact with saliva. Although the duration of oral shedding is not precisely defined, substantial shedding can persist for about six months after the onset of the illness. While transmission is generally person-to-person, mononucleosis is not highly contagious. Around 10% of EBV negative mononucleosis are caused by other viruses including cytomegalovirus (CMV), adenovirus, hepatitis A and B, human herpesvirus type 6 and 7, human immunodeficiency virus (HIV), toxoplasma, and rubella.

Following exposure, EBV infects the salivary gland and oropharynx epithelial cells, subsequently entering the bloodstream through lymphocytes in the tonsils. Lymphoid hyperplasia often results in generalized lymphadenopathy, tonsillitis, and hepatosplenomegaly. Infection of B-lymphocytes triggers the production of immunoglobulins, including heterophile antibodies. The virus replicates in the oropharynx with a preference for B-cells, spreading through the lymphatic system. The body's immune response generates antibodies, typically heterophile antibodies in over 90% of cases. EBV establishes a lifelong infection with periodic reactivation, posing a slight risk of EBV-induced malignancies in individuals with compromised immune systems.[1]

Classic symptoms of mononucleosis include fever, sore throat, fatigue, and tender lymph nodes, with an incubation period averaging 3-6 weeks. The classical triad comprises fever, pharyngitis, and lymphadenopathy, accompanied by headaches, malaise, and reduced oral intake.

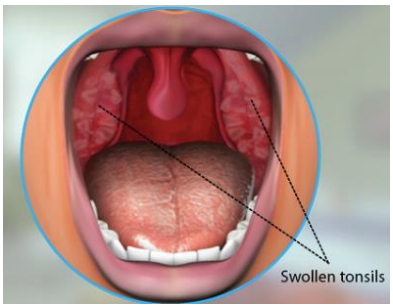

Figure 1. *Swollen tonsils in infectious mononucleosis (IM) caused by Epstein-Barr virus (EBV)*

Persistent fatigue may affect some individuals for months. Lymphadenopathy is more prevalent in the posterior cervical region, and pharyngitis often features tonsillar exudates. Splenomegaly is a key finding in up to half of patients, particularly those at risk of injury, such as active sports participants. Skin examination may reveal a nonspecific rash in some cases. Furthermore, EBV infection has been linked to nine types of cancer, including Hodgkin lymphoma, non-Hodgkin lymphoma, and nasopharyngeal carcinoma, and some autoimmune diseases.[2]

Antibodies to EBV are present in all populations globally, with approximately 90 to 95% of adults eventually becoming EBV-seropositive. In resource-limited countries, nearly 100% of individuals acquire EBV seropositivity by age four, while in lower socioeconomic groups in the United States, seroprevalence ranges from 25 to 50%. Childhood acquisition of EBV is often subclinical, with less than 10% of children exhibiting clinical infection despite high exposure rates. Symptomatic infection becomes more prevalent in adolescence and adulthood, traditionally peaking in the 15- to 24-year age range.

Mononucleosis is rare in adults, constituting about 2% of all adult pharyngeal diseases. This lower susceptibility in adults is attributed to prior exposure during childhood. The incidence of clinical infection is about 30 times higher in White Americans than in Black Americans, possibly reflecting earlier EBV exposure among the latter and a higher occurrence of asymptomatic infection in young children. Additionally, IM occurs more frequently in same-sex twins and first-degree siblings compared to second- and third-degree relatives, suggesting a genetic influence on disease development.[3,4]

In a retrospective study aiming to assess the epidemiological, clinical, and laboratory characteristics of primary EBV infection in children in western Saudi Arabia, 42 patients were identified with positive EBV viral capsid antigen (VCA) IgM. The majority (71%) exhibited typical features of IM, while 29% presented with non-typical symptoms. IM was more prevalent in early childhood (46.7%), whereas non-typical presentations were more common in infants below 1 year (50%). Adolescents showed lower incidence rates (6.7% and 16.7%, respectively). The time to diagnose EBV in the non-typical presentation group was longer than in the IM group. These findings suggest that primary EBV infection in healthy Saudi children is more frequent in younger age groups, with IM syndrome prevailing in early childhood, non-typical presentations in infants, and a lower incidence among adolescents (section 1.1.1).[5]

Primary EBV infections rarely require more than supportive therapy, which is typically employed in the treatment of mononucleosis. Antipyretic and anti-inflammatory medications are utilized to address symptoms such as fever, sore throat, and overall fatigue. It is important to promote hydration, rest, and proper nutrition. The routine use of corticosteroids is generally discouraged due to concerns

about immunosuppression. However, in cases involving airway obstruction, corticosteroids, along with potential consultation with an otolaryngologist, are recommended, along with appropriate airway management. In the quest to address IM, antiviral agents, notably acyclovir and its prodrug valacyclovir, have been examined. Despite the logical rationale behind acyclovir's mechanism of action, initial trials revealed no significant impact on the clinical course of IM, despite a temporary cessation of virus shedding during treatment. If antibiotics are mistakenly administered in mononucleosis patients, a generalized maculopapular rash may develop, commonly associated with amoxicillin but also possible with other antibiotics. Athletes are advised to refrain from sports during the initial phase of the illness (approximately three weeks) due to the observed splenic enlargement in around 50% of mononucleosis patients, posing a risk of splenic rupture. Most individuals who develop mononucleosis have an excellent outcome. The disorder is self-limited, and recovery is common in 2-4 weeks. The rare patient may develop a splenic rupture but even these cases are now managed conservatively if the patient remains hemodynamically stable.[6]

This report compiles all clinical and economic evidence related to IM according to the relevant sources. The ultimate objective of issuing IM guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to IM patients in Saudi Arabia. The focus of the review was on case series, meta-analysis and systematic reviews discussing IM. EBV infects approximately 90% of adults worldwide and is the primary cause of IM. Therefore, the focus of the report will be on treating IM caused by EBV.

Several classes and drugs can be used for the management of IM and are summarized in the table below.

Table 1. SFDA-Registered Drugs for the Treatment of IM

Drug	Indication	Dose	Level of evidence and HTA recommendation
Nonopoid Analgesics and Antipyretics			
Acetaminophen	*Supportive Therapy:* Symptomatic treatment of fever, throat discomfort and malaise	1g every 6hours	NICE: Positive Recommendation
Ibuprofen	*Supportive Therapy:* Symptomatic treatment of	200 to 400 mg every 4 to 6 hours as needed or 600 to	NICE: Positive Recommendation

	fever, throat discomfort and malaise	800 mg every 6 to 8 hours as needed	
Antivirals			
Acyclovir	Managing IM by inhibiting Viral DNA polymerase and preventing further replication of the virus.	800 mg 5 times daily	N/A
Valacyclovir	Managing IM by inhibiting Viral DNA polymerase and preventing further replication of the virus.	1g every 8 to 12 hours	N/A
Corticosteroids			
Prednisolone	Management of patients with specific EBV-associated complications (including airways obstruction) in combination with acyclovir	40 to 60 mg once daily	N/A
Prednisone	Management of patients with specific EBV-associated complications (including airways obstruction) in combination with acyclovir	40 to 60 mg once daily	N/A

Table 2. Non-SFDA-Registered Drugs for the Management of IM

Corticosteroids		
Drug	**Indication**	**Dose**
Dexamethasone *(Single oral dose)*	Treatment of children facing impending airway closure	0.25 mg/kg every six hours

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Recommendations

1.1.1 Primary Epstein–Barr Virus Infection in Healthy Children in Saudi Arabia: A Single Hospital-Based Study (*J Trop Pediatr*., 2021)

A retrospective analysis of electronic data was conducted on children admitted to Al-Jedaani Hospital and tested for EBV-VCA IgM between January 1, 2018, and December 31, 2019. The study aims to evaluate the epidemiological, clinical, and laboratory characteristics of primary EBV infection in children in western Saudi Arabia.

While EBV primarily infects individuals in late adolescence, its incidence in early childhood is rare. The infection typically presents as IM with symptoms such as fever, fatigue, lymphadenopathy, and exudative pharyngitis. However, younger patients may exhibit few or atypical symptoms, posing diagnostic challenges.

Among the 42 patients with positive EBV-VCA IgM, 71% presented with IM, while 29% had non-typical presentations. IM was more common in early childhood (46.7%), whereas non-typical presentations were prevalent in infants (50%). Adolescents were less affected in both groups (6.7% and 16.7%, respectively).

The efficacy of antiviral agents such as acyclovir and valacyclovir in treating acute IM remains uncertain. A prior meta-analysis indicated that treatment with high doses of acyclovir, with or without corticosteroids, can reduce viral replication and oropharyngeal shedding during the administration period(need the ref). However, it does not appear to lessen the severity or duration of symptoms or influence the ultimate outcome. In the standard protocol followed at Al-Jedaani Hospital, acyclovir therapy was administered to all patients, leading to the successful alleviation of symptoms within a median period of 2 days.

It's important to note that this study has limitations as it is retrospective and includes patients requiring hospital admission, potentially indicating a bias towards more severe cases of EBV. Additionally, the use of acyclovir therapy was not randomized. Despite these limitations, all patients experienced a positive outcome.[5]

1.2 North American Guidelines

1.2.1 American Academy of Family Physicians (AAFP) Epstein-Barr Virus Infectious Mononucleosis (2004)

In individuals aged 10 to 30 years experiencing symptoms such as sore throat, significant fatigue, palatal petechiae, and various types of adenopathy (posterior cervical, auricular, or inguinal), suspicion of IM is warranted. Currently, no evidence-based or consensus guidelines exist to direct the evaluation of patients with suspected IM. Therefore, recommendations, synthesized from the available evidence by the American Academy of Family Physicians, have been published.[7]

Diagnosis of IM

In a cohort of 500 patients with confirmed IM, nearly 98% exhibited classic symptoms, including sore throat, lymph node enlargement, fever, and tonsillar enlargement. This presentation is particularly common in adolescents, with older adults showing variations such as a lower likelihood of sore throat and adenopathy but a higher incidence of hepatomegaly and jaundice.

Hoagland's widely recognized criteria for IM diagnosis involve the presence of at least 50% lymphocytes and a minimum of 10% atypical lymphocytes, coupled with fever, pharyngitis, and adenopathy. Confirmation requires a positive serologic test. Although specific, these criteria lack sensitivity, making them more suitable for research purposes. Approximately half of patients with suggestive symptoms and a positive heterophile antibody test may not meet all of Hoagland's criteria.

Patients with streptococcal pharyngitis may present with similar symptoms like sore throat, fatigue, and adenopathy. Acute CMV infection and toxoplasmosis share characteristics with IM, including splenomegaly, hepatomegaly, lymphocytosis, atypical lymphocytosis, and possible false-positive heterophile antibody test results. Distinguishing between IM caused by EBV and similar syndromes from toxoplasmosis or CMV may not always be feasible or practical, as the management remains consistent.

IM is characterized by absolute and relative lymphocytosis, along with an increased proportion of atypical lymphocytes. Diagnostic criteria for the syndrome vary based on cutoff points, with higher cutoffs offering greater specificity but lower sensitivity. The Paul-Bunnell test, an initial serologic IM test, detected heterophile antibodies through red blood cell agglutination. Subsequent refinements, including guinea pig kidney serum absorption, improved specificity. Modern versions in latex agglutination or solid-phase immunoassay forms maintain specificity but are relatively insensitive, especially in the early weeks of illness. More sensitive tests detecting VCA-IgG and VCA-IgM outperform heterophile antibody tests in ruling out

EBV-induced IM (negative likelihood ratio, 0.03 versus 0.14-0.18). Elevated hepatic transaminase levels, occurring in about half of patients, and the presence of antibodies to Epstein-Barr nuclear antigen (EBNA) help distinguish between acute and previous infections, with positive EBNA indicating a prior infection.

Treatment of IM

The primary approach to treating IM involves comprehensive **supportive care**, encompassing adequate **hydration**, nonsteroidal anti-inflammatory drugs (**NSAIDs**), or **acetaminophen** for managing fever and myalgias, and **throat relief measures** such as lozenges, sprays, or gargling with a 2 percent lidocaine solution to alleviate pharyngeal discomfort. An earlier quasi-experimental study suggested that enforced bed rest could slow recovery, but in the absence of evidence supporting such a practice in various conditions, it is advisable for patients to gauge their return to regular activities based on their energy levels. Despite a meta-analysis of five randomized controlled trials showing reduced oropharyngeal shedding with acyclovir use, this treatment did not consistently offer significant clinical benefits and is not recommended. Similarly, ranitidine showed no significant benefits in IM. While corticosteroids have been proposed for treatment, earlier studies indicating potential benefits had methodologic limitations. A recent well-designed study found no advantage in combining acyclovir with prednisolone. Clinical experience and case reports support the use of corticosteroids in patients with significant pharyngeal edema causing or threatening respiratory compromise. In a small, double- blind, randomized trial of 40 children with suspected IM (33 of whom had confirmed IM), those who were given oral dexamethasone (0.3 mg per kg) had less pain at 12 hours but not at 24, 48, and 72 hours.

Prevention of complications and recurrence

In a 1975 report involving 500 consecutive IM patients, 30% exhibited group A β-hemolytic streptococcal (GABHS) pharyngitis, while 0.2% experienced rare complications such as splenic rupture, peritonsillar abscess, and rheumatic fever each. Additional studies reported GABHS pharyngitis rates of 3 to 4%, suggesting variability in incidence, potentially influenced by seasonal factors. Conducting a rapid strep test in IM patients is advisable, and antibiotics should be administered only if the test yields a positive result.

Splenomegaly is a common feature in IM, even in patients without palpable spleens as detected by ultrasound. Athletes are advised to abstain from contact sports for at least three to four weeks due to the estimated 0.1 percent risk of splenic rupture. Ultrasound imaging at three weeks can assist in making informed decisions about returning to athletic activities.

Long-term outcomes reveal that 9 to 22 percent of patients report persistent fatigue or hypersomnia six months post-infection. A six-month study observed a gradual resolution of symptoms, with fatigue requiring about two months for stabilization. The relationship between EBV infection and chronic fatigue syndrome remains uncertain, emphasizing that positive IgG tests for EBV do not imply causation.

Complications of EBV infection extend beyond typical IM symptoms. These include acute interstitial nephritis, hemolytic anemia, myocarditis, cardiac conduction abnormalities, neurologic abnormalities, encephalitis, meningitis, thrombocytopenia, and upper airway obstruction. This underscores the need for comprehensive medical management and monitoring, especially in severe or atypical cases. Patients experiencing any of these complications should seek prompt medical attention for proper diagnosis and intervention.

The main recommendations issued by the AAFP are summarized in table 3.

Table 3. AAFP Key Clinical Recommendations

Recommendation	Label
Fatigue, myalgias, and need for sleep may persist for several months after the acute infection has resolved.	B
Infectious mononucleosis should be suspected in patients 10 to 30 years of age who present with sore throat and significant fatigue, palatal petechiae, posterior cervical or auricular adenopathy, marked axillary adenopathy, or inguinal adenopathy.	B
Corticosteroids, acyclovir (Zovirax), and antihistamines are not recommended for routine treatment of infectious mononucleosis.	B
Atypical lymphocytosis of at least 20 percent or atypical lymphocytosis of at least 10 percent and lymphocytosis of at least 50 percent may signal infectious mononucleosis.	C
Corticosteroids may be helpful in patients with respiratory compromise or severe pharyngeal edema.	C
Patients with infectious mononucleosis should not participate in contact or collision sports for at least four weeks after the onset of symptoms and until they are asymptomatic.	C

1.3 Case Series, Meta-Analyses and Systematic Reviews

1.3.1 Treatment Options for Epstein-Barr Virus-Related Disorders of the Central Nervous System (*Infect Drug Resist*., 2023)

This review delineates the clinical manifestations of EBV-related central nervous system (CNS) disorders, situates them within the context of known EBV biology, and emphasizes existing treatment options along with prospective therapeutic approaches.[8]

While IM typically resolves on its own, the exploration of therapeutic and preventive interventions is justified due to both immediate and delayed complications. Post-IM, persistent fatigue afflicts 9–22% of patients after six months, and the risk of CNS disorders following IM ranges from 1–18%. Furthermore, beyond the 2- to 3-fold elevated risk of multiple sclerosis (MS), there is an increased susceptibility to other autoimmune disorders. Additionally, IM has an association with EBV-positive Hodgkin lymphoma.

In attempts to address IM, antiviral agents, primarily acyclovir and its prodrug valacyclovir, have been tested. Acyclovir, an acyclic guanosine derivative, necessitates viral kinase for phosphorylation, which is crucial for its activation. This results in its accumulation primarily within infected cells undergoing lytic productive infection. Acyclovir competes with the activated nucleotide deoxy-guanosine-triphosphate for the viral DNA polymerase, expressed solely during the lytic cycle, leading to chain termination after incorporation into the viral DNA. Despite the logical basis, initial trials of acyclovir in IM demonstrated no impact on the clinical course, even though virus shedding temporarily ceased during treatment.

Authors speculated whether the extended incubation time of IM (approximately four weeks) or the low concentrations of acyclovir in the oropharynx were potential obstacles. The lack of efficacy indicates that during clinically overt disease, latently infected B lymphocytes drive an overreactive immune response, while there is minimal impact on the lytic virus cycle associated with earlier stages of the primary infection. Corticosteroids were also found to be ineffective.

A Cochrane review of seven randomized controlled studies on acyclovir and its derivatives confirmed a reduction in viral shedding during treatment, though this effect was not sustained post-treatment. The treatment group exhibited a mean reduction in physician-assessed time to clinical recovery by five days and a mean reduction in the duration of lymphadenopathy by nine days. However, due to wide confidence intervals, the therapeutic efficacy of these antiviral agents in IM was deemed inconclusive. Intravenous acyclovir, commonly used for herpes encephalitis, has not been studied in the context of IM. Ganciclovir, an acyclic guanosine analog

effective in CMV infections, also failed to demonstrate therapeutic effects in a Chinese multicenter study on hospitalized pediatric patients with IM.

Vaccination against EBV is still in the early stages, despite over 25 years of trials. Due to the lifelong infection and mutual immunogenetic linkage between the virus and the host, the use of live attenuated EBV in vaccination is clearly contraindicated. To achieve prophylaxis against EBV-associated disorders, there is a rationale for vaccinating infants to induce neutralizing antibodies before maternal antibodies diminish. However, it remains uncertain if persistent immunity can be attained, and repeat boosters may be necessary to prevent later lytic infections.

An alternative approach is to generate neutralizing anti-EBV immunity in seronegative teenagers without triggering IM. The theoretical objection arises from the higher risk of MS associated with the EBV seropositive state. However, epidemiological studies indicate that IM itself is linked to an increased risk of MS, and the teenage population will mostly be seropositive two or three decades later. The rationale encompasses the prevention of IM, immediate complications, lymphomas, and other EBV-related malignant disorders. An additional benefit could be the potential prevention of MS (and other autoimmune disorders), establishing EBV as a prerequisite for MS.

Experimental trials with vaccines based on EBV-like viruses in primates demonstrated the expansion of EBV-specific T cell lines against new EBV epitopes. The first clinical trial of an EBV vaccine in 1995 utilized gp340 (gp350) expressed in vaccinia virus, aiming to produce neutralizing antibodies against gp350, a key component for the virus's attachment and entry into host cells. Subsequent studies combining lytic proteins were more effective than those based on gp350 alone.

Human Phase 1 and 2 studies since 2002, performed in children and adolescents, have shown promising effects. Vaccination with recombinant gp350 induced seroconversion in a significant percentage of participants, preventing IM with a mean efficacy rate of 78%. A tetramer of gp350 and an mRNA vaccine based on late lytic EBV glycoproteins are being explored, with ongoing clinical trials to assess their effectiveness in preventing IM.

While most vaccine trials focus on latent-phase proteins such as EBNA and LMP, there is a lack of trials targeting the induction of a T cell response against lytic glycoproteins. Notably, no IM vaccine is currently in clinical use.

1.3.2 Second European Evidence-Based Consensus on the Prevention, Diagnosis and Management of Opportunistic Infections in Inflammatory Bowel Disease (*J Crohns Colitis*., 2014)

Over the past decade, the treatment paradigm for inflammatory bowel disease (IBD) has undergone a significant transformation with the widespread adoption of immunomodulators. However, the heightened use of immunomodulation, including considerations related to the EBV, raises concerns regarding the potential for opportunistic infections in IBD patients. Recognizing the complexities associated with these infections, the European Crohn's and Colitis Organization (ECCO) undertook a comprehensive update on opportunistic infections in IBD, encompassing six major topics, with one specifically focusing on EBV. The resulting guidance provides insights into the prevention, detection, and management of opportunistic infections across all age groups with IBD.[9]

Impact of immunomodulator therapy on the natural history of the disease

In individuals with intact immune systems EBV-infected B-cells circulate with minimal expression of latency genes, evading destruction by EBV-specific cytotoxic T-lymphocytes. However, when T-cell immunosurveillance is compromised, such as in post-transplant situations, heightened expression of EBV latent genes leads to the proliferation of infected B-cells, increasing the risk of post-transplant lymphoproliferation/lymphoma (PTLD). Primary EBV infection within the first-year post-transplant significantly elevates the risk of PTLD. Pre-transplant EBV IgG testing identifies susceptible individuals, and post-transplant EBV DNA surveillance allows for early detection of primary infection, enabling prompt reduction of immunosuppression. Recent data suggests a small but increased risk of lymphoma, especially among IBD patients on thiopurines. In a cohort of nearly 20,000 patients, current thiopurine therapy showed a hazard ratio of 5.28 for the development of lymphoproliferative disorders.

Preventive measures

There is currently no available vaccine for EBV. While prophylaxis with acyclovir has been shown to reduce the risk of lymphoma in renal transplant recipients, the low risk of lymphoma in IBD does not warrant this approach. It is advisable to consider EBV IgG screening before initiating immunomodulator therapy. For EBV seronegative patients, the clinician may opt for anti-TNF monotherapy over thiopurines, based on individual clinical discretion.

Diagnostic approach and screening of the underlying infection

The Paul–Bunnell and monospot tests are not ideal for diagnosing primary EBV infection. Diagnosis relies on detecting IgM and IgG against the EBV viral capsid antigen with negative EBNA1 IgG, which typically appears later. Post-transplant EBV viral load monitoring is highly sensitive in high-risk HSCT and seronegative solid organ transplant recipients, but specificity is limited. In IBD, sequential EBV viral load measurements after immunomodulator introduction show minimal increases without associated EBV-related disease. Biopsy diagnosis by a specialist hematopathologist is essential to distinguish IM from lymphoproliferative disease, non-Hodgkin's lymphoma, and Hodgkin's disease, including EBER in situ hybridization for EBV detection. Immunohistochemistry for EBV is not a substitute, as viral proteins like LMP-1 may not be expressed.

Treatment of the underlying infection

Acyclovir therapy does not improve the course of IM in healthy individuals. Steroid therapy may be considered for airway obstruction. However, antiviral agents have no established role in treating established PTLD, reflecting the limited role of productive viral infection.

1.3.3 College of Family Physician of Canada Review on the Use of Corticosteroids for Infectious Mononucleosis (2023)

More than 90% of the global population has been infected with the EBV, the primary cause of IM. Common IM symptoms include fatigue, fever, pharyngitis, and cervical or generalized lymphadenopathy. However, these symptoms are often underreported in young children. IM transmission occurs through various means, including saliva (earning it the colloquial name "kissing disease"), blood, semen, blood transfusions, and organ transplantation.[10]

Diagnosis:

Diagnosis primarily relies on symptoms reported during an initial visit to a primary care provider, physical examination, and, in some cases, Forssman antibody testing.

Treatment:

Once a clinical or laboratory diagnosis has been established, the treatment of IM involves measures such as rest, promoting hydration, and addressing symptoms like fever and pharyngitis. Pharmacological options encompass nonsteroidal anti-inflammatory drugs, acetaminophen, and throat lozenges or sprays containing anesthetics. Antiviral medications, including acyclovir and valacyclovir, have demonstrated minimal to no alleviation of symptoms. Combinations of prednisone and acyclovir have similarly shown varying or limited overall effectiveness.

Corticosteroids exert anti-inflammatory properties by interacting with inflammatory genes. Specifically, upon binding with receptors, responsive elements modify the expression of inflammatory genes, influencing cytokines, chemokines, adhesion molecules, and inflammatory enzymes. These agents are recommended for patients with severe complications of IM, such as airway obstruction, autoimmune hemolytic anemia, and thrombocytopenia. However, their use for symptom relief is not considered standard and has demonstrated varying degrees of efficacy.

A Cochrane review, analyzing 7 randomized controlled trials involving 362 participants aged 14 to 30 with IM, found that corticosteroid treatment showed some effectiveness in alleviating pharyngitis pain in two trials. In one study, a starting dose of 10 mg of prednisolone or cortisone (tapered over 8 days) was associated with reduced pain at 12 hours but not at 36 hours. Another trial found that children aged 8 to 18 receiving oral dexamethasone shortly after diagnosis reported relief of pain at 12 hours compared to those who received a placebo but not at 24 hours.

Combining corticosteroids with antiviral drugs, such as oral acyclovir and prednisolone, showed a reduction in pharyngitis pain from days 2 to 4 but not at 14 days in a study of 94 patients. Another trial comparing prednisone and acetylsalicylic acid on fever in 38 university students found a noticeable reduction in fever with a 12-day corticosteroid course but not with a 6-day course.

However, in four of the seven studies analyzed, no significant differences in symptom outcomes, including fever, pharyngitis, fatigue, or anorexia, were reported with corticosteroid use. Bolden's study on the effects of 6- and 12-day courses of oral prednisone found no difference in psychiatric scores and a reduction in fever only with the 12-day course. Other studies evaluating different corticosteroid regimens also found no significant differences in various symptoms, indicating mixed results in the efficacy of corticosteroids for symptom relief in IM.

Section 2.0 Drug Therapy

2.1 Nonopioid Analgesics

2.1.1 Acetaminophen

Information on Acetaminophen is detailed in the table below.[11]

Table 4. Acetaminophen Drug Information

SCIENTIFIC NAME ACETAMINOPHEN	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	B27
Drug Class	OTHER ANALGESICS AND ANTIPYRETICS
Drug Sub-class	ANILIDES
ATC Code	N02BE01
Pharmacological Class (ASHP)	Nonopioid analgesics
DRUG INFORMATION	
Dosage Form	Tablets (for adults) Syrup (for pediatrics)
Route of Administration	Oral administration
Dose (Adult) [DDD]	1g every 6hours
Maximum Daily Dose Adults	4g
Dose (pediatrics)	10 to 15 mg/kg/dose every 4 to 6 hours
Maximum Daily Dose Pediatrics	75mg/kg
Adjustment	Use with caution in patients with hepatic diseases. Limited, low-dose therapy is usually well-tolerated.
Prescribing edits	**N/A**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A

G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Acute hepatotoxicity may result from intentional or unintentional overdose in adult and pediatric patients.
Drug Interactions	**Category X:** • Metyrapone
Special Population	N/A
Pregnancy	Acetaminophen crosses the placenta. The use of acetaminophen in recommended doses during pregnancy has not been associated with an increased risk of miscarriage or still birth; however, an increase in fetal death or spontaneous abortion may be seen following maternal overdose if treatment is delayed.
Lactation	Acetaminophen is present in breast milk. Nonopioid analgesics are preferred for lactating patients who require pain control.
Contraindications	N/A
Monitoring Requirements	Serum acetaminophen levels.
Precautions	In patients with G6PD deficiency or hepatic impairment. When used for self-medication, patients should be aware if symptoms get worse or new symptoms appear.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Acetaminophen.**

Table 5. Acetaminophen HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Acetaminophen	NICE[12]	**January 2018** Consider using paracetamol for the management of pain or fever, and if preferred and appropriate, ibuprofen. Additionally, it is recommended to counsel individuals on maintaining adequate fluid intake. Explain to adults that they may choose to use medicated lozenges with local anesthetics, NSAIDs, or antiseptics to alleviate symptoms, although their efficacy in reducing pain may be limited.
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Acetaminophen

Acetaminophen, also known as Paracetamol, is a widely used analgesic and antipyretic medication. Its mechanism of action involves inhibition of the enzyme cyclooxygenase, primarily in the central nervous system, which results in reduced synthesis of prostaglandins. In the context of IM, acetaminophen is often employed to manage pain and fever, providing symptomatic relief for individuals with this condition. The usual dose depends on factors such as age and weight, with careful consideration given to avoid exceeding recommended limits to prevent potential liver toxicity. For adults, the recommended dose is 1g every 6 hours, with a maximum daily dose of 4g. In pediatrics, the dosage is 10 to 15 mg/kg/dose, administered every 4 to 6 hours, with a maximum daily dose of 75mg/kg/day. Common side effects are generally mild but may include nausea and allergic reactions. Importantly, paracetamol is generally considered safe for use in pregnant and breastfeeding women when used at recommended doses. Its use

during pregnancy is often preferred over other pain medications. The use of Acetaminophen is supported by NICE.

2.1.2 Ibuprofen

Information on Ibuprofen is detailed in the table below.[13]

Table 6. Ibuprofen Drug Information

SCIENTIFIC NAME IBUPROFEN	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	B27
Drug Class	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
Drug Sub-class	PROPIONIC ACID DERIVATIVES
ATC Code	M01AE01
Pharmacological Class (ASHP)	Non opioid analgesics, Nonsteroidal anti-inflammatory drugs.
DRUG INFORMATION	
Dosage Form	Tablets (for adults) Oral suspensions (for pediatrics)
Route of Administration	Oral administration
Dose (Adult) [DDD]	200 to 400 mg every 4 to 6 hours as needed or 600 to 800 mg every 6 to 8 hours as needed.
Maximum Daily Dose Adults	3.2g
Dose (pediatrics)	4 to 10 mg/kg/dose (maximum dose: 600 mg/dose) every 6 to 8 hours.
Maximum Daily Dose Pediatrics	40mg/kg
Adjustment	If CrCl ≤ 30 mL/minute, avoid use due to increased risk of acute kidney injury.
Prescribing edits	**AGE**

AGE (Age Edit):	Ibuprofen is not recommended for children weighing less than 7 kg or 6 months.
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	• Cardiovascular effects: acute myocardial infraction, cerebrovascular accident, and hypertension. • Gastrointestinal effects: gastrointestinal ulcer and inflammation • Hematological effects: prolonged bleeding time. • Hepatic effects: transaminase elevation. • Kidney effects: Hemodynamically mediated acute kidney injury, interstitial nephritis (with or without nephrotic syndrome), and renal papillary necrosis.
Drug Interactions	**Category X:** • Abrocitinib • Acemetacin • Ketorolac • Aminolevulinic Acid • Macimorelin • Mifamurtide
Special Population	N/A
Pregnancy	The use of nonsteroidal anti-inflammatory drugs close to conception may be associated with an increased risk of miscarriage due to

	cyclooxygenase-2 inhibition interfering with implantation. Treatment in pregnant women should be individualized.
Lactation	Ibuprofen is present in breast milk. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother
Contraindications	Hypersensitivity to ibuprofen (anaphylactic reactions, serious skin reactions) or any component of the formulation, history of asthma, urticaria, or allergic-type reaction to aspirin.
Monitoring Requirements	Monitor response (pain, range of motion, grip strength, mobility, ADL function), inflammation; observe for weight gain, edema; monitor renal function
Precautions	May cause CNS effects (dizziness, drowsiness), hyperkalemia, ophthalmic events (blurred vision). May increase the risk of aseptic meningitis and bronchospasm in sensitive patients.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IM patients by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.
The recommendations below are for ibuprofen.

Table 7. Ibuprofen HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Ibuprofen	NICE[12]	**January 2018** Consider using paracetamol for the management of pain or fever, and if preferred and appropriate, ibuprofen. Additionally, it is recommended to counsel individuals on maintaining adequate fluid intake. Explain to adults that they may choose to use medicated lozenges with local anesthetics, NSAIDs, or antiseptics to alleviate symptoms, although their efficacy in reducing pain may be limited.
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Ibuprofen

Ibuprofen, a nonsteroidal anti-inflammatory drug, exerts its analgesic, anti-inflammatory effects by inhibiting the enzyme cyclooxygenase, which plays a role in the synthesis of prostaglandins. In the management of IM, ibuprofen is used for the treatment of fever, throat discomfort, and malaise. The usual dose varies based on factors such as age, weight, and the severity of symptoms. However, caution is advised due to the potential risk of gastrointestinal irritation and increased bleeding tendencies. For adults, the recommended dose is 200 to 400 mg every 4 to 6 hours as needed, or 600 to 800 mg every 6 to 8 hours as needed, with a maximum daily dose of 3.2g. In pediatrics, the dosage is 4 to 10 mg/kg/dose, with a maximum single dose of 600 mg, administered every 6 to 8 hours, and a maximum daily dose of 40mg/kg/day. Common side effects include gastrointestinal discomfort, and in rare cases, more serious complications like ulcers or bleeding may occur. Ibuprofen is generally not recommended during the third trimester of pregnancy, and caution is advised during breastfeeding, with consultation with healthcare professionals recommended for personalized guidance. The use of ibuprofen is supported by NICE.

2.1.3 Aspirin, Loxoprofen and Naproxen

Ibuprofen is not the only SFDA-registered NSAID for the management of IM. Naproxen, aspirin, and loxoprofen are also prescribed, each with its own recommended dose, safety considerations (contraindications and warnings) and prescribing edits[14–16].

Table 8. SFDA-Registered NSAIDs for the Management of Mononucleosis

Drug	Dose	Indication	Safety issues	Prescribing Edits
Aspirin [17]	Oral: 325 mg to 1 g every 4 to 6 hours as needed. Maximum daily dose: 4 g.	Supportive therapy: symptomatic treatment of fever, throat discomfort and malaise.	• Risk of gastrointestinal ulcers and serious bleeding. Use with caution in patients with platelets and bleeding disorders. • Risk of serious cardiovascular thrombotic events.	**AGE**: aspirin is not used in pediatric less than 16 years old.
Loxoprofen[19]	60mg 3 times daily.			**AGE:** The safety of Loxoprofen in low birth weight infants, newborn infants, Infants and toddlers, Children and adolescents has not been established.
Naproxen[18]	250 to 500mg every 12h as needed. Maximum daily dose: 1.5g			**AGE**: aspirin is not used in pediatric less than 12 years old.

2.2 Antivirals

2.2.1 Acyclovir

Information on Acyclovir is detailed in the table below[20].

Table 9. Acyclovir Drug Information

SCIENTIFIC NAME ACYCLOVIR	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	B27
Drug Class	DIRECT ACTING ANTIVIRALS
Drug Sub-class	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS
ATC Code	J05AB01
Pharmacological Class (ASHP)	Antivirals
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	800mg 5 times daily
Maximum Daily Dose Adults*	4g daily
Dose (pediatrics)	10 to 20mg/kg/dose every 8h.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal impairment

CrCl[b]	Oral			IV	
	If the usual dose is 400 mg every 12 hours	If the usual dose is 200 mg 5 times daily	If the usual dose is 800 mg 5 times daily	If the usual dose is 5 mg/kg/dose every 8 hours	If the usual dose is 10 mg/kg/dose every 8 hours
>50 mL/minute/1.73 m^2	No dosage adjustment necessary.	No dosage adjustment necessary.	No dosage adjustment necessary.	No dosage adjustment necessary.	No dosage adjustment necessary.
25 to 50 mL/minute/1.73 m^2	No dosage adjustment necessary.	No dosage adjustment necessary.	No dosage adjustment necessary.	5 mg/kg/dose every 12 hours	10 mg/kg/dose every 12 hours
10 to <25 mL/minute/1.73 m^2	No dosage adjustment necessary or reduce to 200 mg every 12 hours[c]	No dosage adjustment necessary or reduce to 200 mg every 8 hours[c]	800 mg every 8 hours	5 mg/kg/dose every 24 hours	10 mg/kg/dose every 24 hours
<10 mL/minute/1.73 m^2 (not on dialysis)	200 mg every 12 hours	200 mg every 12 hours	200 mg every 12 hours or 400 mg every 12 hours (severe infections)[d]	2.5 mg/kg/dose every 24 hours	5 mg/kg/dose every 24 hours

Hemodialysis, intermittent (thrice weekly):

Oral:

If the usual recommended dose is 200 mg 5 times daily or 400 mg every 12 hours: Administer 200 mg every 12 hours. Administer after dialysis when given on a dialysis day or administer an additional dose after each dialysis.

If the usual recommended dose is 800 mg 5 times daily: Administer a loading dose of 400 mg, followed by a maintenance dose of 200 mg every 12 hours, plus an additional 400 mg dose after each dialysis session.

IV: 2.5 to 5 mg/kg/dose every 24 hours. Administer after dialysis when given on a dialysis day.

Peritoneal dialysis:

Oral:

If the usual recommended dose is 200 mg 5 times daily or 400 mg every 12 hours: Administer 200 mg every 12 hours.

If the usual recommended dose is 800 mg 5 times daily: Administer 600 to 800 mg every 24 hours.

IV: 2.5 to 5 mg/kg/dose every 24 hours, no supplemental dose needed.

Prescribing edits*	**ST**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A

PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	While acyclovir can suppress viral shedding in EBV patients, significant clinical benefits have not been consistently demonstrated; therefore, its use in this case is not recommended. Combinations of prednisone and acyclovir have similarly shown varying or limited overall effectiveness.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	• Acute kidney injury • Neurotoxicity • Thrombotic microangiopathy
Drug Interactions*	**Category X:** • Cladribine • Fezolinetant • Foscarnet • Netilmicin • Zoster vaccine • Varicella virus vaccine
Special Population	N/A
Pregnancy	Acyclovir crosses the placenta and based on extensive registry data, shows no increased risk of birth defects in pregnancies exposed during the first trimester. Despite a potential association with gastroschisis observed in one study, untreated cases also exhibited increased risk. Pregnancy-induced changes may alter acyclovir pharmacokinetics, requiring dose adjustments due to increased renal clearance. Acyclovir is recommended for treating genital herpes and varicella during pregnancy to reduce complications and transmission, but caution is advised, especially with

	intravenous use in the third trimester due to potential renal adverse effects.
Lactation	Acyclovir is present in breast milk. Although the manufacturer recommends that caution be exercised when administering acyclovir to patients who are breastfeeding, acyclovir is considered compatible with breastfeeding.
Contraindications	Hypersensitivity to acyclovir, valacyclovir, or any component of the formulation.
Monitoring Requirements	• Serum electrolytes • Hydration status • Serum creatinine • Symptoms of neurotoxicity
Precautions	Extravasation in IV administration.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for acyclovir in EBV. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Acyclovir

Acyclovir, after undergoing subsequent phosphorylation steps, ultimately inhibits the viral DNA polymerase and prevents further replication of the viral genome. While acyclovir is primarily indicated for herpes simplex and varicella-zoster infections, its use in EBV infections is limited due to a **lack of significant efficacy**. The usual prescribed dose is 800mg 5 times daily. In the context of pregnancy, acyclovir is generally considered safe when the benefits outweigh the risks. Limited data suggest low transfer to breast milk, making it compatible with breastfeeding. Common side effects include nausea and headache, with rare instances of reversible renal impairment, particularly with high doses or in patients with predisposing factors. Overall, careful consideration of individual circumstances and risks is essential when prescribing acyclovir to pregnant or breastfeeding women. There are no specific recommendations issued by the HTA bodies for acyclovir.

2.2.2 Valacyclovir

Information on Valacyclovir is detailed in the table below[21].

Table 10. Valacyclovir Drug Information

SCIENTIFIC NAME VALACYCLOVIR	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	B27
Drug Class	DIRECT ACTING ANTIVIRALS
Drug Sub-class	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS
ATC Code	J05AB11
Pharmacological Class (ASHP)	Antivirals
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	1g every 8 to 12h
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	20mg/kg/dose every 8h
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal impairment

CrCl	If usual recommended dose is 500 mg every 24 hours	If usual recommended dose is 1 g every 24 hours or 500 mg every 12 hours	If usual recommended dose is 1 g every 12 hours	If usual recommended dose is 1 g every 8 hours	If usual recommended dose is 2 g every 12 hours for 2 doses
≥50 mL/minute	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary
30 to <50 mL/minute	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary	1 g every 12 hours	1 g every 12 hours for 2 doses
10 to <30 mL/minute	500 mg every 48 hours	500 mg every 24 hours	1 g every 24 hours	1 g every 24 hours	500 mg every 12 hours for 2 doses
<10 mL/minute	500 mg every 48 hours	500 mg every 24 hours	500 mg every 24 hours	500 mg every 24 hours	500 mg as a single dose

Hemodialysis, intermittent (thrice weekly): 500mg every 24h
Peritoneal dialysis: 500mg every 24h

Prescribing edits*	**ST**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	While valacyclovir can suppress viral shedding in EBV patients, significant clinical benefits have not been consistently demonstrated; therefore, its use in this case is not recommended. Combinations of prednisone and valacyclovir have similarly shown varying or limited overall effectiveness.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	• Acute kidney injury • Neurotoxicity • Thrombotic microangiopathy
Drug Interactions*	**Category X:** • Cladribine • Fezolinetant • Foscarnet

	• Netilmicin • Zoster vaccine • Varicella virus vaccine
Special Population	N/A
Pregnancy	Valacyclovir and Acyclovir cross the placenta and based on extensive registry data, shows no increased risk of birth defects in pregnancies exposed during the first trimester. Despite a potential association with gastroschisis observed in one study, untreated cases also exhibited increased risk.
Lactation	Valacyclovir is rapidly metabolized to acyclovir. Following administration of valacyclovir, acyclovir is present in breast milk; unchanged valacyclovir has not been detected in breast milk. Acyclovir is present in breast milk. Although the manufacturer recommends that caution be exercised when administering acyclovir to patients who are breastfeeding, acyclovir is considered compatible with breastfeeding.
Contraindications	Hypersensitivity to acyclovir, valacyclovir, or any component of the formulation.
Monitoring Requirements	• Serum electrolytes • Hydration status • Serum creatinine • Symptoms of neurotoxicity
Precautions	Extravasation in IV administration.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for valacyclovir in EBV. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Valacyclovir

Valacyclovir is an antiviral medication that undergoes rapid conversion to acyclovir in the body. Acyclovir, a nucleoside analogue, selectively inhibits viral DNA synthesis by targeting the enzyme DNA polymerase. Valacyclovir's prodrug nature enhances its oral bioavailability, allowing for less frequent dosing compared to acyclovir. It is primarily utilized in the treatment of infections caused by herpes simplex virus and varicella-zoster virus, including genital herpes, shingles, and cold sores. Its use in EBV mononucleosis is limited due to the **lack of clinical efficacy**. The typical dose for herpes zoster is 1000 mg three times daily for 7 days. Common side effects include headache, nausea, and abdominal pain. While valacyclovir is generally considered safe during pregnancy, its use should be carefully evaluated based on the individual's medical condition and potential risks. Consultation with a healthcare professional is crucial for pregnant or breastfeeding women to determine the appropriate course of action and ensure the well-being of both mother and child. There are no specific recommendations issued by the HTA bodies for valacyclovir.

2.3 Corticosteroids

2.3.1 Prednisone, Prednisolone and Dexamethasone

Prednisone, prednisolone, and dexamethasone are corticosteroids used for the management of patients with specific EBV-associated complications, including airways obstruction. Each has its own recommended dose, safety considerations (contraindications and warnings), and prescribing edits[22,23].

Table 11. Corticosteroids for the Management of Mononucleosis

Drug	Dose	Indication	Safety issues	PE
Prednisone	PO: 40 to 60 mg once daily	Management of patients with specific EBV-associated complications (including	• Adrenal suppression (tertiary adrenal insufficiency). • CNS and psychiatric/behavioral effects.	QL: used for 5 to 14 days.
Prednisolone	PO: 40 to 60 mg once daily			QL: used for 5 to 14 days.

Dexamethasone	PO: 0.25 mg/kg every six hours	airways obstruction) in combination with acyclovir.	• Cushingoid features/Cushing syndrome. • GI effects. • Hyperglycemia. • Infection. • Neuromuscular and skeletal effects. • Ocular effects.	QL: Single oral dose.

- In a multicenter, placebo-controlled study involving 94 patients with acute IM, the combination of acyclovir and prednisolone was found to reduce the oropharyngeal shedding of the virus. However, this intervention did not influence the duration of symptoms or lead to an earlier return to school or work.
- A subsequent meta-analysis of seven studies found insufficient evidence to endorse the use of steroids for symptom relief. Moreover, two studies reported severe complications in patients assigned to the corticosteroid group compared to those receiving a placebo.
- Corticosteroids, along with urgent consultation with an otolaryngologist, are warranted for individuals experiencing imminent airway obstruction, as evidenced by clinical manifestations such as difficulty breathing or dyspnea in the recumbent position.
- Information on the optimal dosing and duration of corticosteroid therapy is limited. A case series detailed successful treatment of children facing impending airway closure with a single oral dose of dexamethasone (0.25 mg/kg every six hours), but the duration of treatment was not specified. Once clinical improvement is achieved, a gradual tapering of the corticosteroid dose over 7 to 14 days is advisable.
- Corticosteroid therapy may also be considered for individuals with severe, overwhelming, life-threatening infections (such as fulminant liver failure) or other complications like severe hemolytic or aplastic anemia. However, the data supporting the benefits of corticosteroids in these situations are less robust compared to the evidence for treating IM-related airway obstruction.
- Due to the potential for serious adverse reactions (growth suppression, interfere with endogenous corticosteroid production) in the breastfeeding infant, some manufacturers recommend discontinuing corticosteroids.

- In routine cases of IM, we do not recommend corticosteroid therapy, as the illness typically resolves on its own. There are theoretical concerns about immunosuppression, especially with a virus that has been causally linked to various malignancies. Nevertheless, corticosteroids may be considered in the management of patients with specific EBV-associated complications.

Section 3.0 Key Recommendations Synthesis

Infectious mononucleosis (IM), the main clinical manifestation of EBV infection, presents with initial symptoms such as malaise, headache, and low-grade fever. Subsequent signs include tonsillitis, pharyngitis, lymph node enlargement, and atypical lymphocytes in the blood. While most cases recover within one to two weeks, fatigue can persist. Severe symptoms like palatal petechiae may occur, and different presentations exist, including the glandular form with disproportionate lymph node enlargement and a systemic form with fever and fatigue. Splenomegaly is common, but jaundice and hepatomegaly are rare. Recovery is typically uneventful, and durable immunity develops. Diagnosing EBV infection can be challenging, requiring consideration of symptoms, medical history, and context, with repeat testing sometimes necessary. There's no vaccine for EBV, and prevention involves avoiding activities that may transmit the virus. Antiviral or immunomodulatory treatments' effectiveness for EBV remains unclear, and primary infections usually require supportive therapy.

Supportive care, including the use of acetaminophen or NSAIDs, is the mainstay of treatment for individuals with IM or other primary EBV manifestations. Adequate fluids, nutrition, and rest are recommended, with strenuous activity avoided for at least three weeks after the onset of IM.

The use of corticosteroids in EBV-induced IM has been debated. While studies have shown some improvement in symptoms with corticosteroids, they are not recommended for routine cases due to the self-limiting nature of IM and concerns about immunomodulation. However, oral prednisone, prednisolone or dexamethasone may be considered in cases of impending airway obstruction or severe complications like liver failure or aplastic anemia.

Acyclovir, an antiviral nucleoside analogue, has been studied for specific therapy in acute EBV infections. While it can suppress viral shedding, significant clinical benefits have not been consistently demonstrated.

Meta-analyses of trials, including intravenous therapy in severe cases, failed to show a clear advantage over a placebo. Notably, acyclovir's effectiveness is limited to inhibiting replicating EBV, making its utility questionable in diseases associated with latent infection. Some anecdotal evidence supports its use in EBV-induced

hemophagocytic lymphohistiocytosis, where replicating EBV has been demonstrated.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of IM.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

1. Mohseni M, Boniface MP, Graham C. Mononucleosis. *Prim Care Update Ob Gyns*. 2023;2(5):152-156. doi:10.1016/1068-607X(95)00034-5
2. Dunmire SK, Verghese PS, Balfour HH. Primary Epstein-Barr virus infection. *Journal of Clinical Virology*. 2018;102:84-92. doi:10.1016/J.JCV.2018.03.001
3. Gares V, Panico L, Castagne R, Delpierre C, Kelly-Irving M. The role of the early social environment on Epstein Barr virus infection: a prospective observational design using the Millennium Cohort Study. *Epidemiol Infect*. 2017;145(16):3405. doi:10.1017/S0950268817002515
4. Kuri A, Jacobs BM, Jacobs BM, et al. Epidemiology of Epstein-Barr virus infection and infectious mononucleosis in the United Kingdom. *BMC Public Health*. 2020;20(1). doi:10.1186/S12889-020-09049-X
5. Zaki A. Primary Epstein–Barr Virus Infection in Healthy Children in Saudi Arabia: A Single Hospital-Based Study. *J Trop Pediatr*. 2021;67(1). doi:10.1093/TROPEJ/FMAA121
6. Thompson SK, Doerr TD, Hengerer AS. Infectious mononucleosis and corticosteroids: management practices and outcomes. *Arch Otolaryngol Head Neck Surg*. 2005;131(10):900-904. doi:10.1001/ARCHOTOL.131.10.900
7. Epstein-Barr Virus Infectious Mononucleosis - American Family Physician. Published online 2004. Accessed December 14, 2023. www.aafp.org/afp.
8. Andersen O, Ernberg I, Hedström AK. Treatment Options for Epstein-Barr Virus-Related Disorders of the Central Nervous System. *Infect Drug Resist*. 2023;16:4599. doi:10.2147/IDR.S375624
9. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Published online 2013. doi:10.1016/j.crohns.2013.12.013
10. Gomes K, Goldman RD. FEBRUARY | FÉVRIER 2023 | Canadian Family Physician | Le Médecin de famille canadien 101 Child Health Update. 69. doi:10.46747/cfp.6902101
11. Acetaminophen (paracetamol): Drug information - UpToDate. Accessed December 16, 2023. https://ezproxy.usj.edu.lb:2071/contents/acetaminophen-paracetamol-drug-information?search=acetaminophen&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1

12. Sore throat (acute): antimicrobial prescribing NICE guideline. Published online 2018. Accessed December 16, 2023. www.nice.org.uk/guidance/ng84

13. Ibuprofen: Drug information - UpToDate. Accessed December 4, 2023. https://www.uptodate.com/contents/ibuprofen-drug-information?search=ibuprofen&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1

14. Acute pharyngitis in children and adolescents: Symptomatic treatment - UpToDate. Accessed December 23, 2023. https://www.uptodate.com/contents/acute-pharyngitis-in-children-and-adolescents-symptomatic-treatment?search=management%20of%20mononucleosis%20ibuprofen&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

15. Kazama IE, Miura CB, Nakajima Corresponding Author T, Kazama I. Nonsteroidal Anti-Inflammatory Drugs Quickly Resolve Symptoms Associated with EBV-Induced Infectious Mononucleosis in Patients with Atopic Predispositions. Published online 2016. doi:10.12659/AJCR.895399

16. Infectious Mononucleosis - Infections - MSD Manual Consumer Version. Accessed December 23, 2023. https://www.msdmanuals.com/home/infections/herpesvirus-infections/infectious-mononucleosis

17. Aspirin: Drug information - UpToDate. Accessed December 23, 2023. https://www.uptodate.com/contents/aspirin-drug-information?search=aspirin&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1

18. Naproxen: Drug information - UpToDate. Accessed December 23, 2023. https://www.uptodate.com/contents/naproxen-drug-information?search=naproxen&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F199859

19. Loxoprofen: International drug information (concise) - UpToDate. Accessed December 23, 2023. https://www.uptodate.com/contents/loxoprofen-international-drug-information-concise?search=loxoprofen&source=panel_search_result&selectedTitle=1~1&usage_type=panel&kp_tab=drug_international&display_rank=1

20. Acyclovir (systemic): Drug information - UpToDate. Accessed December 14, 2023. https://www.uptodate.com/contents/acyclovir-systemic-drug-information?search=aciclovir&source=panel_search_result&selectedTitle=1~142&usage_type=panel&showDrugLabel=true&display_rank=1

21. Valacyclovir: Drug information - UpToDate. Accessed December 14, 2023. https://www.uptodate.com/contents/valacyclovir-drug-information?sectionName=Kidney%20Impairment%20(Adult)&topicId=10034&search=valaciclovir&usage_type=panel&anchor=F50991799&source=panel_search_result&selectedTitle=1~110&showDrugLabel=true&kp_tab=drug_general&display_rank=1#F232784

22. Rezk E, Nofal YH, Hamzeh A, Aboujaib MF, Alkheder MA, Al Hammad MF. Steroids for symptom control in infectious mononucleosis. *Cochrane Database Syst Rev*. 2015;2015(11). doi:10.1002/14651858.CD004402.PUB3

23. Tynell E, Aurelius E, Brandell A, et al. Acyclovir and Prednisolone Treatment of Acute Infectious Mononucleosis: A Multicenter, Double-Blind, Placebo-Controlled Study. *J Infect Dis*. 1996;174(2):324-331. doi:10.1093/INFDIS/174.2.324

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
(((((((Mononucleosis, Infectious[MeSH Terms]) OR (Glandular Fever[Title/Abstract])) OR (Fever, Glandular[Title/Abstract])) OR (Burkitt Lymphoma Virus[Title/Abstract])) OR (Lymphoma Virus, Burkitt[Title/Abstract])) OR (E-B Viruses[Title/Abstract])) OR (Herpesvirus 4 (gamma), Human[Title/Abstract])) OR (Mononucleosis Viruses, Infectious[Title/Abstract])	In the last 5 years	("infectious mononucleosis"[MeSH Terms] OR "glandular fever"[Title/Abstract] OR "fever glandular"[Title/Abstract] OR (("Burkitt"[All Fields] OR "burkitt s"[All Fields] OR "burkitts"[All Fields]) AND "lymphoma virus"[Title/Abstract]) OR (("Lymphoma"[MeSH Terms] OR "Lymphoma"[All Fields] OR "lymphomas"[All Fields] OR "lymphoma s"[All Fields]) AND "virus burkitt"[Title/Abstract]) OR "e b viruses"[Title/Abstract] OR ((((("herpesviridae"[MeSH Terms] OR "herpesviridae"[All Fields] OR "herpesvirus"[All Fields]) AND "4"[All Fields]) AND ("gamma rays"[MeSH Terms] OR ("gamma"[All Fields] AND "rays"[All Fields]) OR "gamma rays"[All Fields] OR "gamma"[All Fields] OR "gamma s"[All Fields] OR "gammae"[All Fields] OR "gammas"[All Fields])) AND "Human"[Title/Abstract]) OR (("infectious mononucleosis"[MeSH Terms] OR ("Infectious"[All Fields] AND "mononucleosis"[All Fields]) OR "infectious mononucleosis"[All Fields] OR "mononucleosis"[All Fields]) AND "viruses infectious"[Title/Abstract])) AND (y_5[Filter])	361

Appendix C. Treatment Algorithm

Symptomatic treatment

- Acetaminophen or nonsteroidal antiinflammatory (ibuprofen) drugs are recommended for the treatment of fever, throat discomfort, and malaise.
- Adequate fluids and nutrition is also appropriate.
- Although getting adequate rest is prudent, bed rest is unnecessary.

Antiviral treatment

- Acyclovir or Valacyclovir are nucleoside analogues that inhibits permissive EBV infection through inhibition of EBV DNA polymerase.

Corticosteroids treatment

- Oral corticosteroids (dexamethasone and prednisolone), in combination with acyclovir, are warranted in individuals with impending airway obstruction.
- Corticosteroid therapy may also be considered in those with severe, overwhelming, life-threatening infection (eg, fulminant liver failure) or other complications such as severe hemolytic or aplastic anemia.