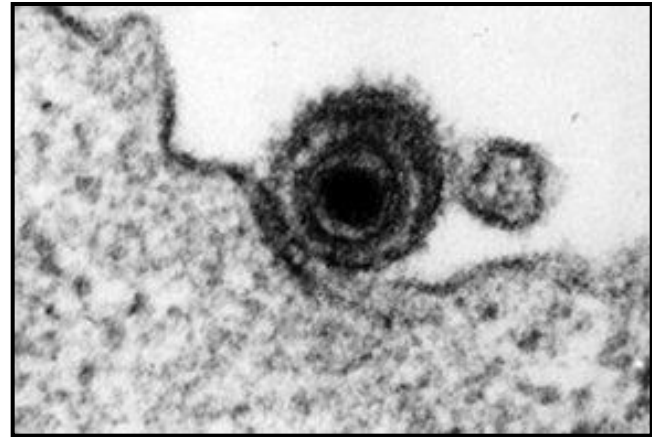


EBV Hepatitis



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Objectives

- EBV .. Introduction
- Immune response to EBV infection
- EBV hepatic manifestations
- How does EBV induce liver injury?
- Dx
- Therapy ?



EBV ...

- EBV , a member of the herpesvirus family (HHV-4)
- Is one of the most common viruses, infecting more than 90% of humans and persisting throughout life.
- Most EBV primary infections of infants and children are asymptomatic or have nonspecific symptoms
- Infections of adolescents and young adults frequently result in symptomatic infectious mononucleosis (IM) with an EBV-induced polyclonal B-cell proliferation.



EBV ...

- More than 50% of IM patients present with the triad of fever, generalized lymphadenopathy, and pharyngitis.
- Approximately 10% of symptomatic patients have splenomegaly, palatal petechiae, and hepatomegaly.
- Although a strong antibody response to EBV occurs, the infection is controlled by cytotoxic T-cell response.

- Cohen J.I. *N. Engl. J. Med.*,(343) ; 2000 : 481—492
Papatheodoridis G.V. et al. *J. Hepatol.* (23) ;1995: 348--350



EBV ...

- Less commonly, severe complications occur such as hemolytic anemia, myocarditis, hepatitis, splenic rupture, hemophagocytic syndrome, Guillain-Barré syndrome, meningitis and encephalitis; these can be fatal in rare cases.

(Cohen J.I., *N. Engl. J. Med.*, Volume: 343, Issue: 7 (2000), pp. 481—492)

- Most of the sever IM complications are associated with congenital or acquired immunodeficiency
- *The main cause of death in sever IM is fulminant hepatic failure (50% of the cases)*

(*Feranchak et al. Liver Transplantation and Surgery (4) 1998: 469-476*)



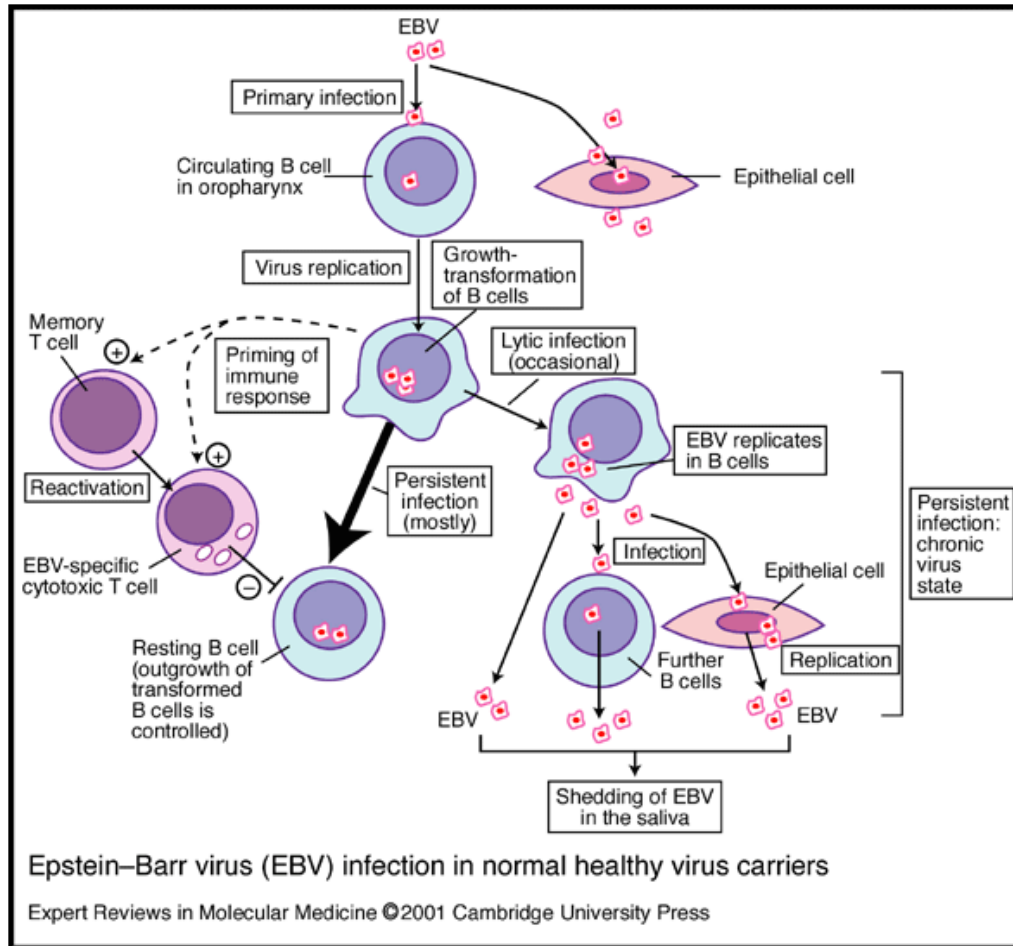
EBV complications

Table 3. Complications of primary EBV infection

Organ/system	Complication
Liver	Clinical jaundice (5%), abnormal liver function tests (80–90%), fulminant hepatitis (rare)
Respiratory	Respiratory tract obstruction, interstitial pneumonitis (rare)
Neurological*	Encephalitis, acute cerebellar syndrome, aseptic meningitis, Guillain-Barré syndrome, cranial nerve palsy especially VII, transverse myelitis, seizures, mononeuritis, optic neuritis, cerebral haemorrhage
Spleen	Splenic rupture 0.1–0.5% spontaneous or after mild trauma, usually males, splenic infarction
Haematological	Thrombocytopenia, haemolytic anaemia, neutropenia, haemorrhage secondary to mucosal ulceration
Secondary infection	Streptococcal sore throat, sepsis in association with neutropenia
Psychiatric	Depression, anxiety
Renal	Haematuria, interstitial nephritis, glomerulonephritis (rare)
Cardiac	Myocarditis, pericarditis, arrhythmia, electrocardiogram changes
Immunological	Depressed cell mediated immunity

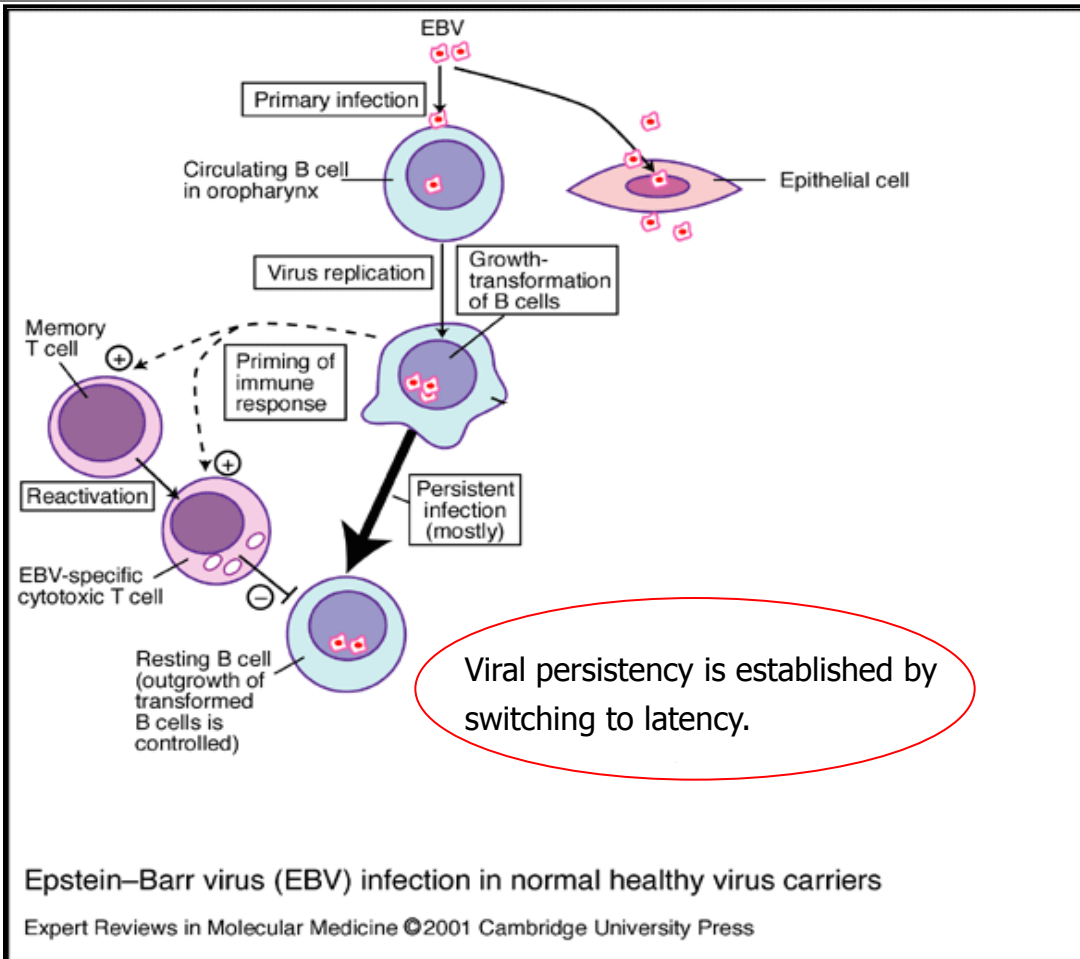
*Pharyngitis, lymphadenopathy may be absent

Immune response to EBV



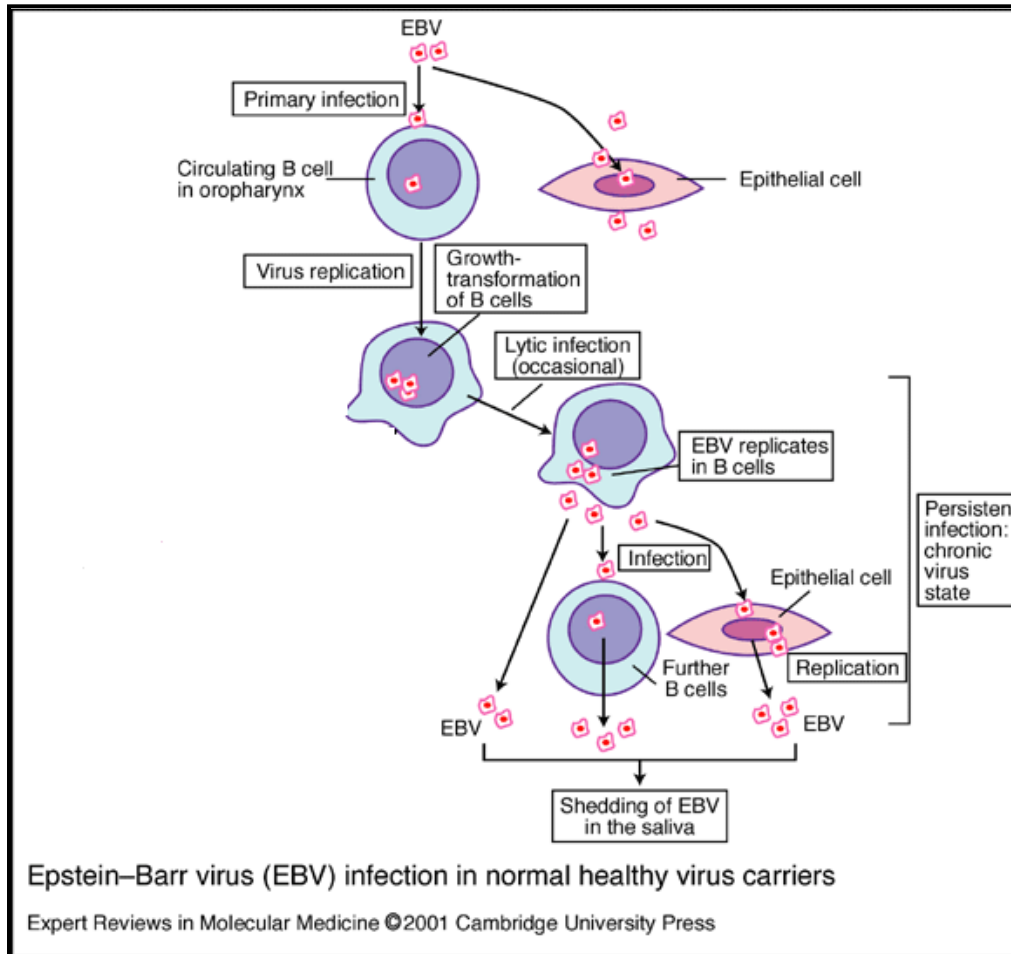
Immune response to EBV

a strong, T-cell adaptive immune response (NK & Cytotoxic T cells) is formed against EBV antigens to control EBV infected B cells proliferation in immunocompetent hosts.



Viral persistency is established by switching to latency.

Immune response to EBV





Immune response to EBV

- Transmitted through contact with saliva (the 'first kiss' disease), the EBV initially infects the epithelial cells of the oropharynx or directly infect resting B cells.
- During primary infection, EBV attachment and entry into oropharynx epithelial cells is believed to occur via cell-to-cell contact with the infecting saliva lymphocytes.
- EBV actively replicates in these cells, and newly secreted virions may either spread to other epithelial cells across lateral membranes or infect host B lymphocytes .
- Although EBV stimulates B cells to proliferate, a strong, T-cell adaptive immune response (NKC & Cytotoxic T cells) is formed against EBV antigens to control EBV infected B cells proliferation in immunocompetent hosts.



Immune response to EBV

- A lifelong equilibrium follows between viral expression and host defence mechanisms.
- When this balance is broken, like during immunosuppression, viral reactivation occurs, often accompanied by clinically significant entities, including the development of lymphomas and other tumours.

(Negro F. Journal of Hepatology (44)2006, 839-841)



EBV – Hepatic manifestations

- The most common is the transient, self-limited elevation of liver enzymes during IM (50- 80%).
- Hepatomegaly occurs in 10% of the patients
- Jaundice occurs in about 5–7% of cases (secondary to IHC or Hemolytic anemia).
- Chronic hepatitis tentatively linked to EBV has rarely been reported

- Shaukat A. et al. *Hepatol Res*, Volume: 33, (2005) : 24—26

- Kimura H et al. *Hum Pathol*, Volume: 32, (2001), pp. 757--762



EBV – Hepatic manifestations

- Severe hepatitis is infrequent at the time of primary EBV infection of immunocompetent individuals
- Sporadic cases of acute liver failure caused by primary EBV infection have been reported in the literature, with an overall mortality of 87%.
- Those cases seen primary in patients with congenital or acquired immunodeficiency.
- These include recipients of organ or bone marrow transplants, AIDS patients, SCID, X-linked lymphoproliferative disease , complement deficiency.

(Markin R.S., et al. *Gastroenterology*, Volume: 93, (1987): 1210—1217)



EBV – Hepatic manifestations

- Finally, despite its definite oncogenic potential, there is NO convincing evidence linking EBV and the development of liver carcinoma , with the exception of the lymphoepithelioma-like variant of both hepatocellular and cholangiocellular carcinoma.
(Herrmann K., Niedobitek G., *J Pathol*, Volume: 199, (2003), pp. 140--145)



Mechanism of hepatic injury

- *NO direct EBV cytopathic effect has been proven on hepatocytes so far.*
- EBV receptors (CD 21) have been found on B-lymphocytes in the liver but not on hepatocytes
- T-cells and NKC were found in liver parenchyma, (may be implicated in liver cell necrosis through inflammatory markers & cytokine release)



Mechanism of hepatic injury

- TNF alfa, IF gamma & Fas ligand produced by cytotoxic lymphocytes has been shown to induce liver injury
- Those inflammatory markers has been found to be in high levels in the plasma of those patients.



Mechanism of hepatic injury

- In addition, EBV infection of T lymphocytes has also been recently described.
- Kimura et al showed in a case report that there is an EBV infection of T lymphocytes in addition to B cells while the control patients of IM without severe hepatitis had infected B lymphocytes only.

(Kimura et al. Hum. Path. 2001; 23:257-62)

- ? Is T cell infection lead to subsequent uncontrolled clonal expansion that might be responsible for the severe spectrum of EBV hepatitis ?



Mechanism of hepatic injury

- *It appears that severe liver injury is primarily caused by the intense immune response to viral antigens expressed by infected hepatocytes*



Mechanism of hepatic injury

- Drug-induced cross hepatotoxicity is also possible resulting in hepatocyte necrosis.
- Many drugs cause a hepatotoxic reaction without a dose-related pattern including acetaminophen, aspirin and clarithromycin

Feranchak et al. Liver Transplantation and Surgery (4) 1998: 469-476



Histopathology

- Histology typically demonstrates mononuclear infiltrate within portal tracts and along sinusoids in a distinct single file pattern.
- Occasional plasma cells and neutrophil polymorphs may be present.
- Kupffer cells are prominent and occasional granulomatous foci may be present.
- Hepatocellular necrosis is uncommon but occurs in severe cases.
- T lymphocytes usually predominate in the biopsy of severe hepatitis.

Feranchack A et al. Liver Transplantation & Surgery(6);1998: 469-474

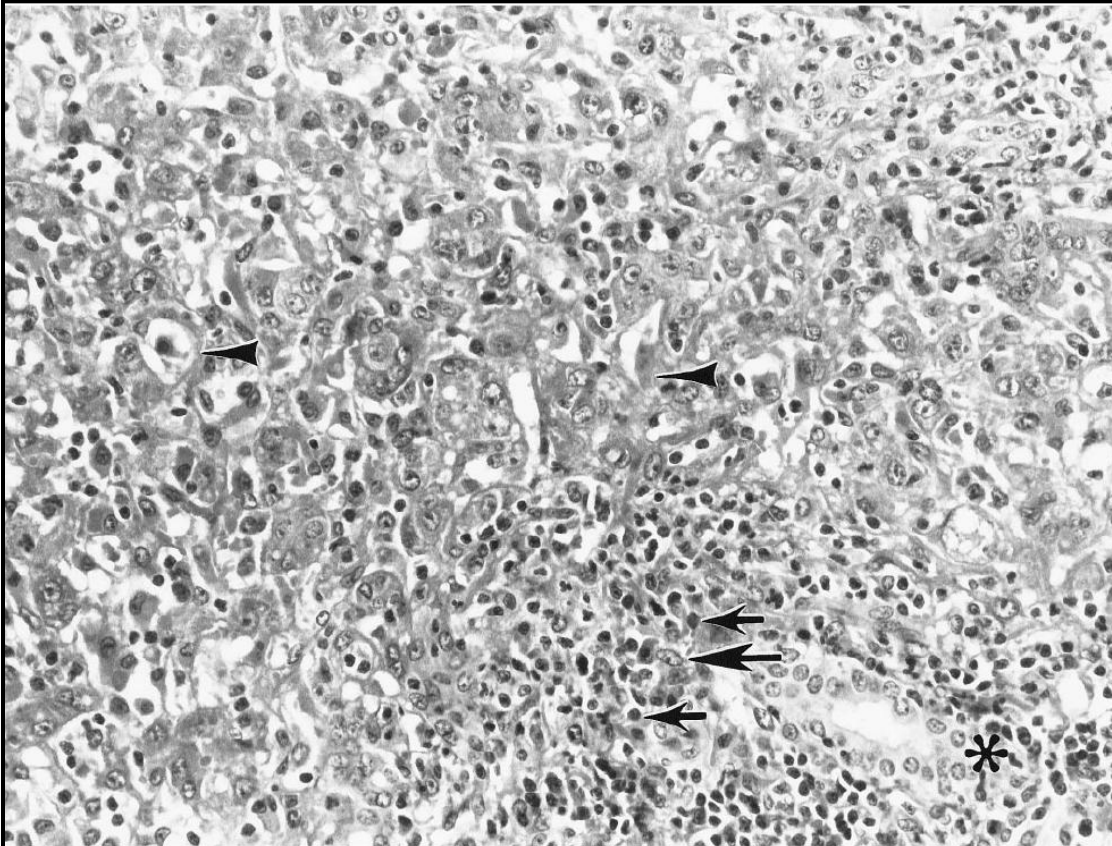
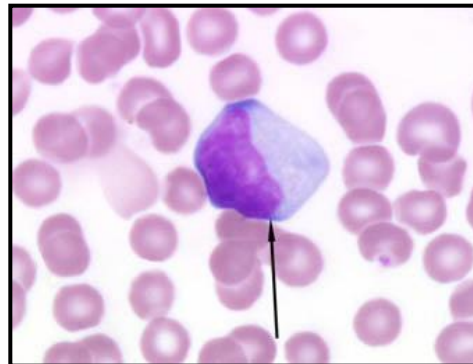
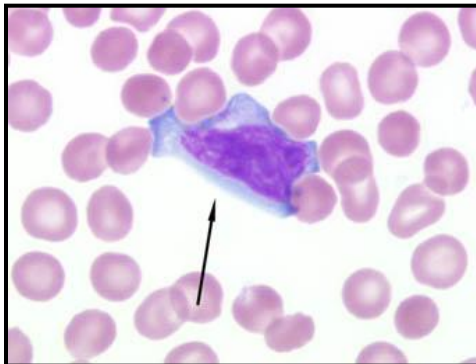


Figure 2. Histology of the liver explant showing marked panlobular hepatocyte necrosis and lymphocytic infiltrate that tends to concentrate in portal areas (*). Note lymphocytic infiltrate of bile duct basement membrane and intraepithelial lymphocytes (adjacent to asterisk). Within the portal inflammation, larger atypical B-lymphocytes (arrow) and small T-lymphocytes (small arrows) are seen. Note degenerating hepatocytes (open arrows). (Hematoxylin and eosin; original magnification $\times 200$).

Dx of EBV infection

- The vast majority of cases of IM can be identified clinically by the presence of pharyngitis, lymphadenopathy (usually on the neck), and fever
- CBC: elevated WBC, an increased total number of mononuclear/lymphocytes cells , greater than 10% atypical lymphocytes (seen more in the 2nd week of the infection)



Atypical lymphocyte is a T cell responding to the EBV-infected B cells



Dx of EBV infection: Monospot test:

- It detects primarily IgM heterophile antibodies.
- It typically observed during the first 2 wks of infection and gradually disappear over 6 months
- 85 % +ve in older children & adults
- False-negative tests occur in about 10-15% of patients and are most common in children younger than 4 years of age
- False-positive results may be found in a small number of patients and are usually attributed to and infection by Rubella, Hepatitis, Systemic lupus or erythematosus (SLE), leukemia



Dx of EBV infection:

- > 10 % of Atypical lymphocyte + positive monospot → diagnostic for acute infection



Dx of EBV infection: serology

- 4 serological parameters are essential for the detection of EBV-specific antibodies : VCA (IgG), VCA IgM, and EBNA IgG & Early Antigen (EA).
- VCA IgG: seen early in the infection course (may appear faster than IgM) & persist for life (not differentiate active infection from old one)
- VCA IgM: indicate active & recent infection (but transient)
- EA: indicate active & recent infection
- EBNA: appear after several wks-months of the infection & persist for life long (it's presence exclude active primary infection)



Dx of EBV infection: serology

	VCA IgG	VCA IgM	EA	EBNA
No previous infection	-	-	-	-
Acute/ Recent infection	+	+	+/-	-
Past infection (at least 2-4 months)	+	-	-	+

Red book – 27th edition; 2006



PCR

- Detection of DNA PCR in serum, plasma & tissues
- Useful in immunocompromised patients & complex clinical problems



Therapy of EBV infections

- Supportive therapy (self limiting disease)
- Treatment of EBV infections with acyclovir has been shown to reduce the oro-pharyngeal shedding of the virus, but the duration of the symptoms was not different from the group of patients treated with a placebo (The symptoms are primary due to immune response to the virus).

(Torre D; Tambini R. Scand J Infect Dis 1999;31(6):543-7.)



Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study

- In a multicenter, placebo-controlled study of 94 patients with acute uncomplicated IM, the combination of acyclovir and prednisolone reduced oropharyngeal shedding of the virus but did not affect the duration of symptoms or lead to an earlier return to school or work

[Tynell E et al. J Infect Dis 1996 Aug;174(2):324-31.]



Therapy in fulminant EBV hepatitis

- Therapeutic issues in fulminant EBV hepatitis are scarce.
- Acyclovir has not been shown to be efficacious for treatment of severe EBV hepatitis.

(Kimura et al. Hum. Path. 2001; 23:257-62)



Ganciclovir and the treatment of Epstein-Barr virus hepatitis

(Adams LA, et al. Journal of Gastroenterology and Hepatology 21(2006) 1758–1760)

- Adams LA, et al. report treating 2 adult immuno-competent patients with EBV hepatitis & normal coagulation profile using Ganciclovir
- Ganciclovir was started in both cases as an IV (5 mg/kg BID then switched to oral for 10 days course)
- They report significant rapid improvement in LFT using Ganciclovir

(Adams et al. Journal of Gastroenterology and Hepatology 21(2006) 1758–1760)

Ganciclovir and the treatment of Epstein-Barr virus hepatitis

(Journal of Gastroenterology and Hepatology 21(2006) 1758–1760)

LA Adams *et al.*

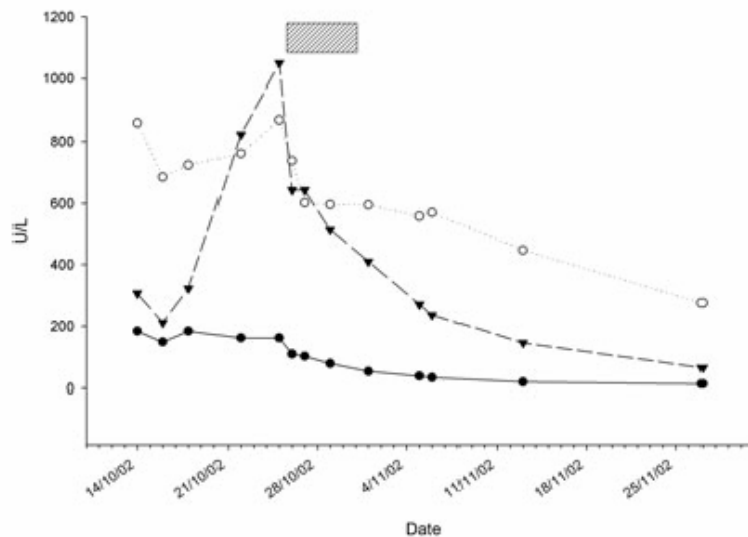


Figure 1 Liver function of patient 1 over time. (●) Bilirubin; (○) ALP; (▼) ALT; (▨) ganciclovir administration.

Epstein-Barr virus hepatitis

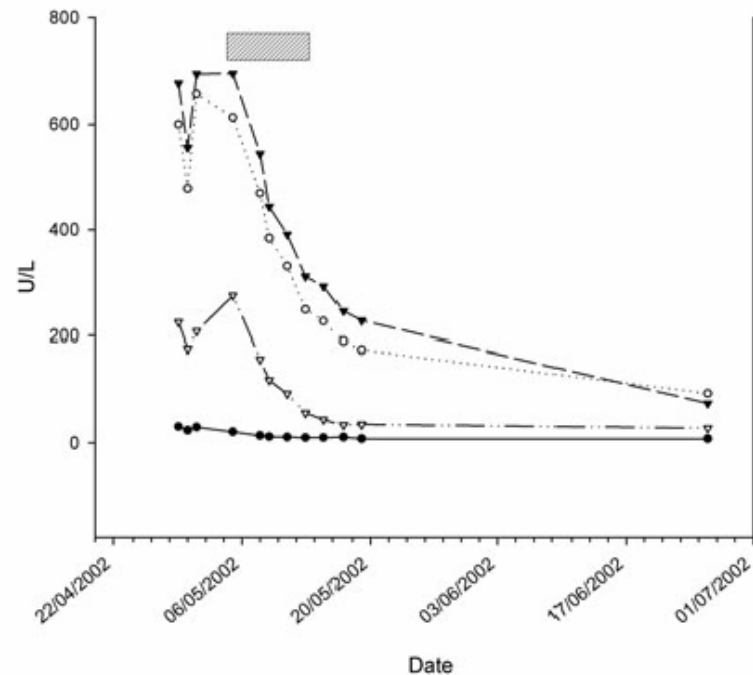


Figure 2 Liver function of patient 2 over time. (●) Bilirubin; (○) ALP; (▼) GGT; (△) ALT; (▨) ganciclovir administration.



Steroid

- Steroid is not recommended therapy for routine cases of IM.
- A trial of corticosteroids is warranted in individuals with impending airway obstruction and should be considered in those suffering from severe overwhelming life-threatening infection (eg, liver failure) or other severe complications such as aplastic anemia.
- Data supporting the benefit of corticosteroids in the last two settings are lacking (Uptodate, April 6, 2007)



END
