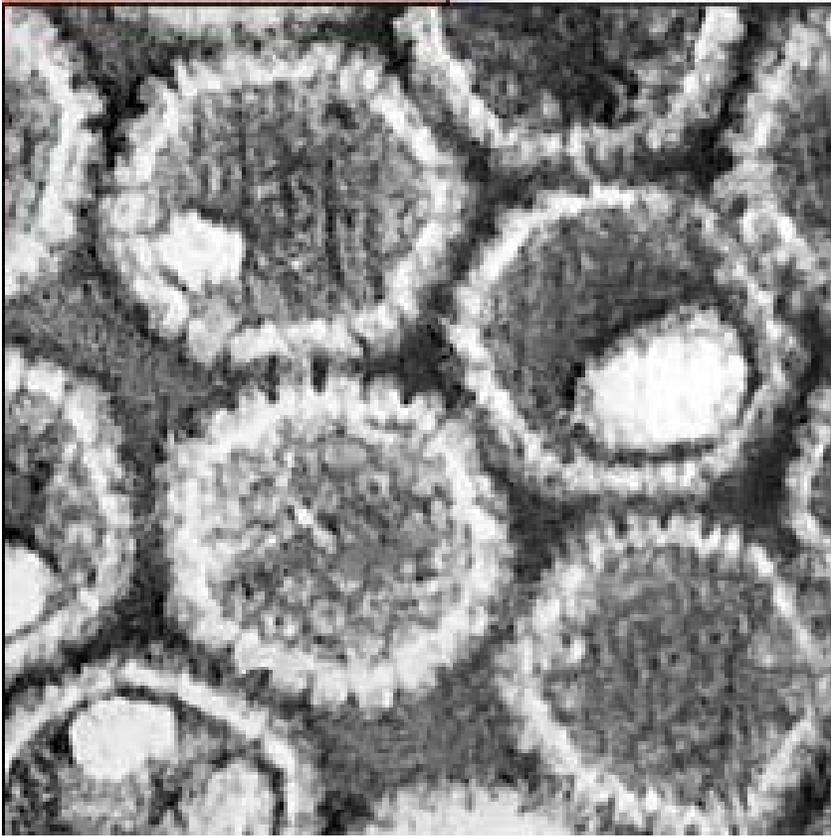


Pediatric Herpes Virus Infections

C. Buddy Creech, MD, MPH

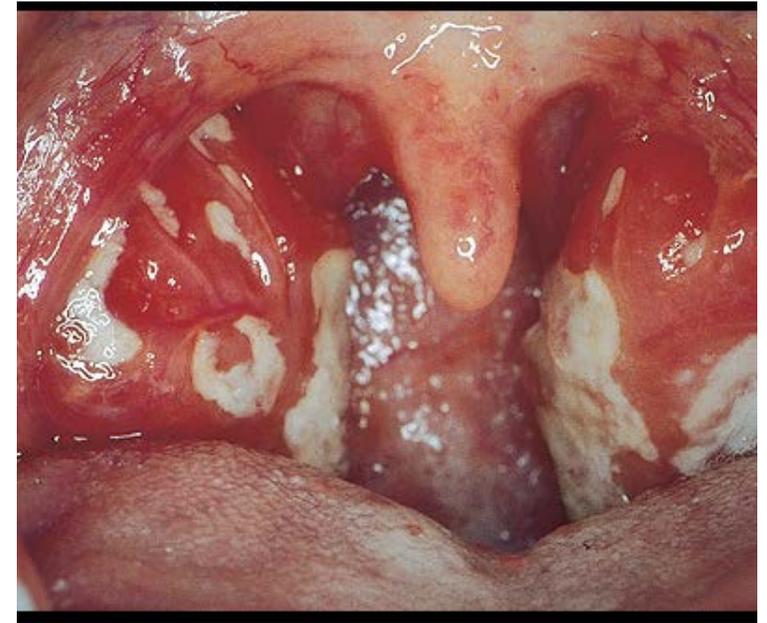
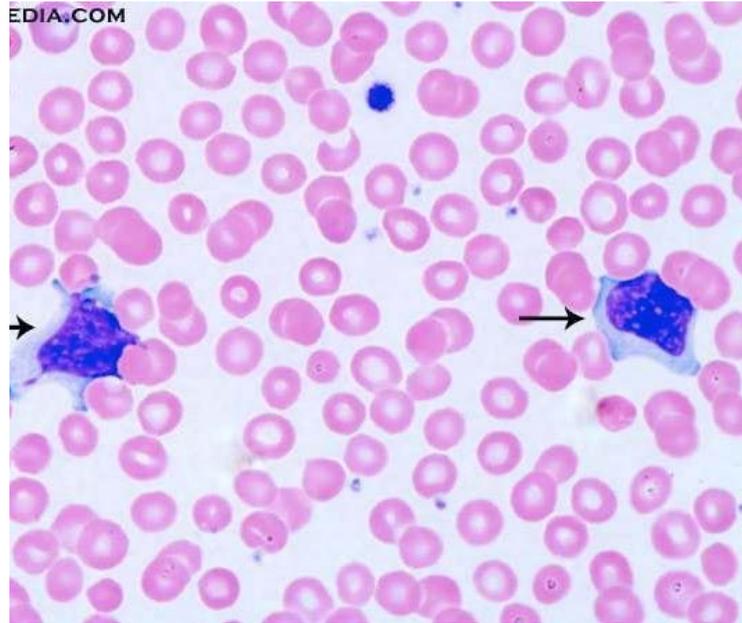


Herpes are Like Diamonds: They're Forever

C. Buddy Creech, MD, MPH

Overview

- Epstein Barr Virus
- Herpes Simplex Virus



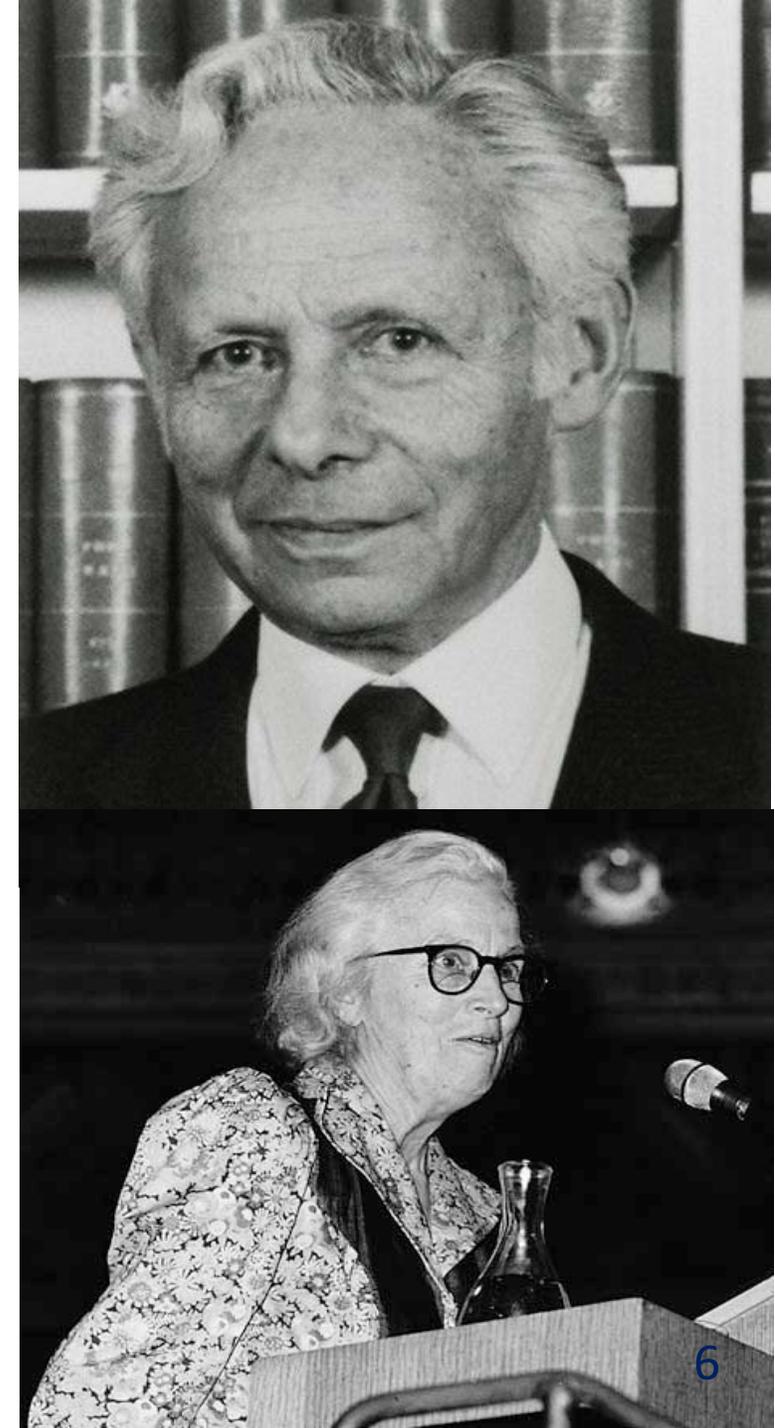
Infectious Mononucleosis

Roadmap

- Review the epidemiology of mononucleosis in adolescents and young adults
- Discuss diagnosis, including role of Monospot
- Opportunities for treatment
- Discuss issues related to return to play

Historical perspective of EBV

- Epstein Barr virus is named after Sir Michael Anthony Epstein (Professor) and Yvonne Barr (PhD, Research Assistant).
- In 1961, Epstein attended a lecture on Children's Cancer in Africa led by Denis Burkitt, a surgeon practicing in Uganda.
- In 1963, a specimen was sent from Uganda to Epstein's laboratory, and in 1964, the original article demonstrating virus particles was published in Lancet.
- Werner and Gertrude Henle (CHOP) developed serological markers, which were made easier in 1967 when a technician developed infectious mononucleosis and serum samples were obtained.



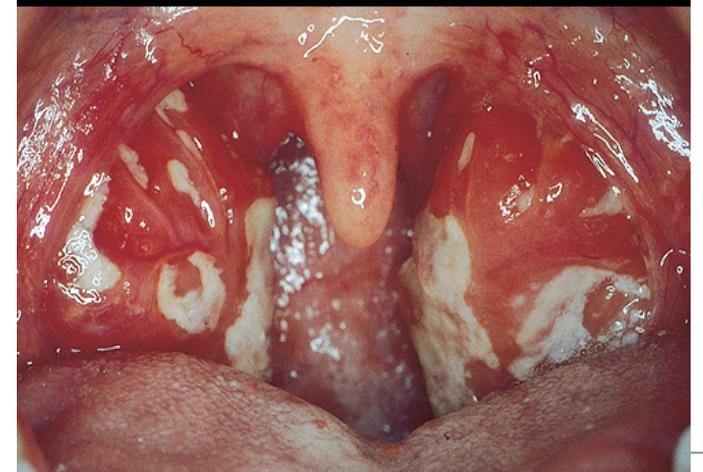
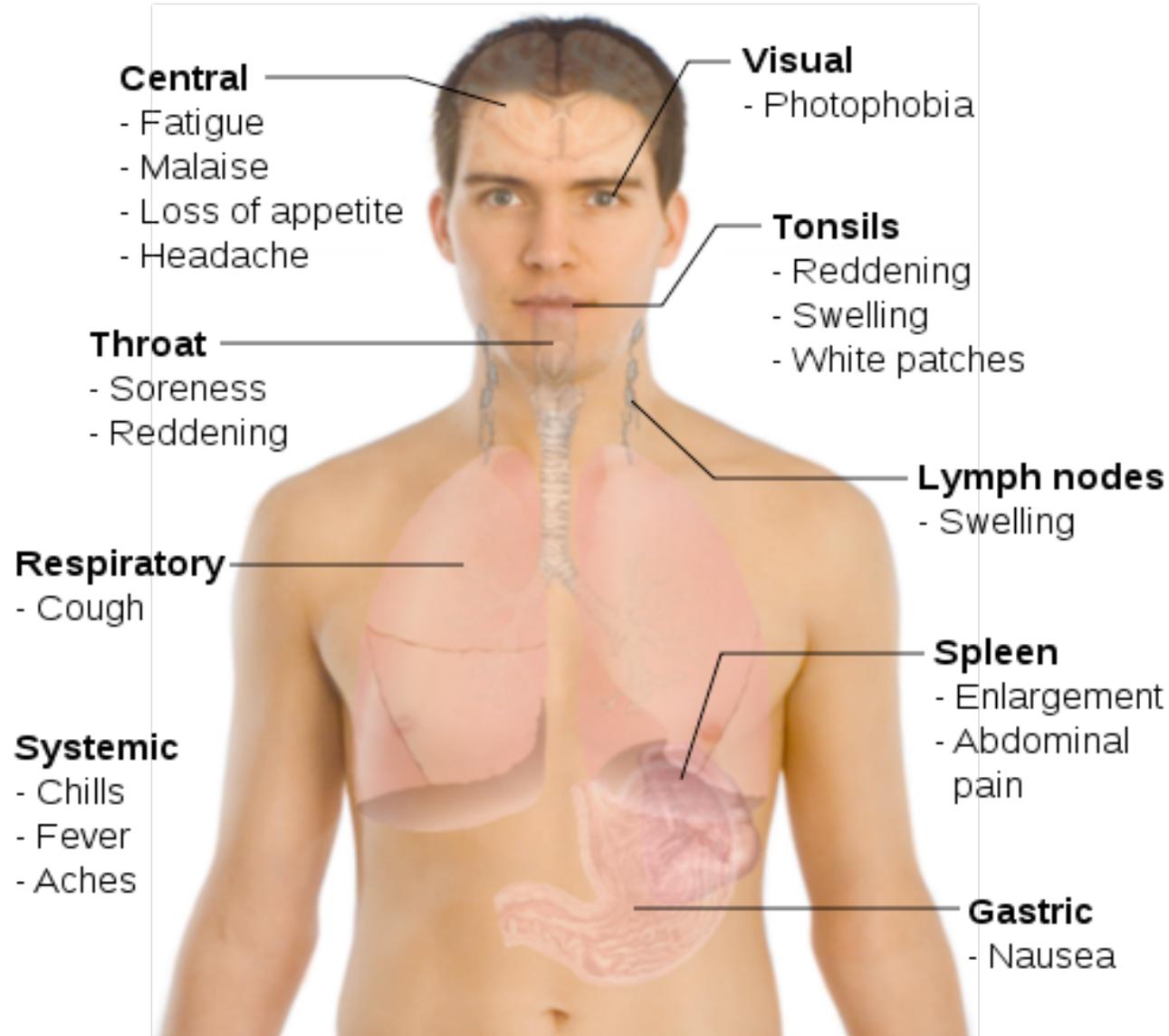
Epidemiology

- Incubation period can be quite long, on the order of 1-2 months.
- Typically a disease of the young, with those of lower socioeconomic status being infected at a younger age.
- Symptoms vary in severity and usually resolve within 1-2 months

Clinical characteristics

- Classic triad is fever, pharyngitis, and cervical adenopathy
- At least 50% will have some degree of splenomegaly
- Rash occurs in as many as 25-50% of patients in some series, primarily those exposed to beta-lactams.
- Additional pearls
 - Subclinical hepatitis occurs in as many as 80%, and should be considered a part of the initial disease, not a complication.
 - Eyelid edema can sometimes be seen and is unique to EBV

Main symptoms of
Infectious mononucleosis

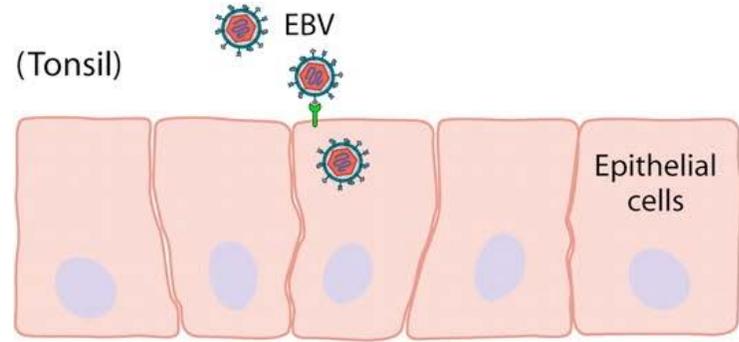


Clinical features of EBV in young adults and adolescents

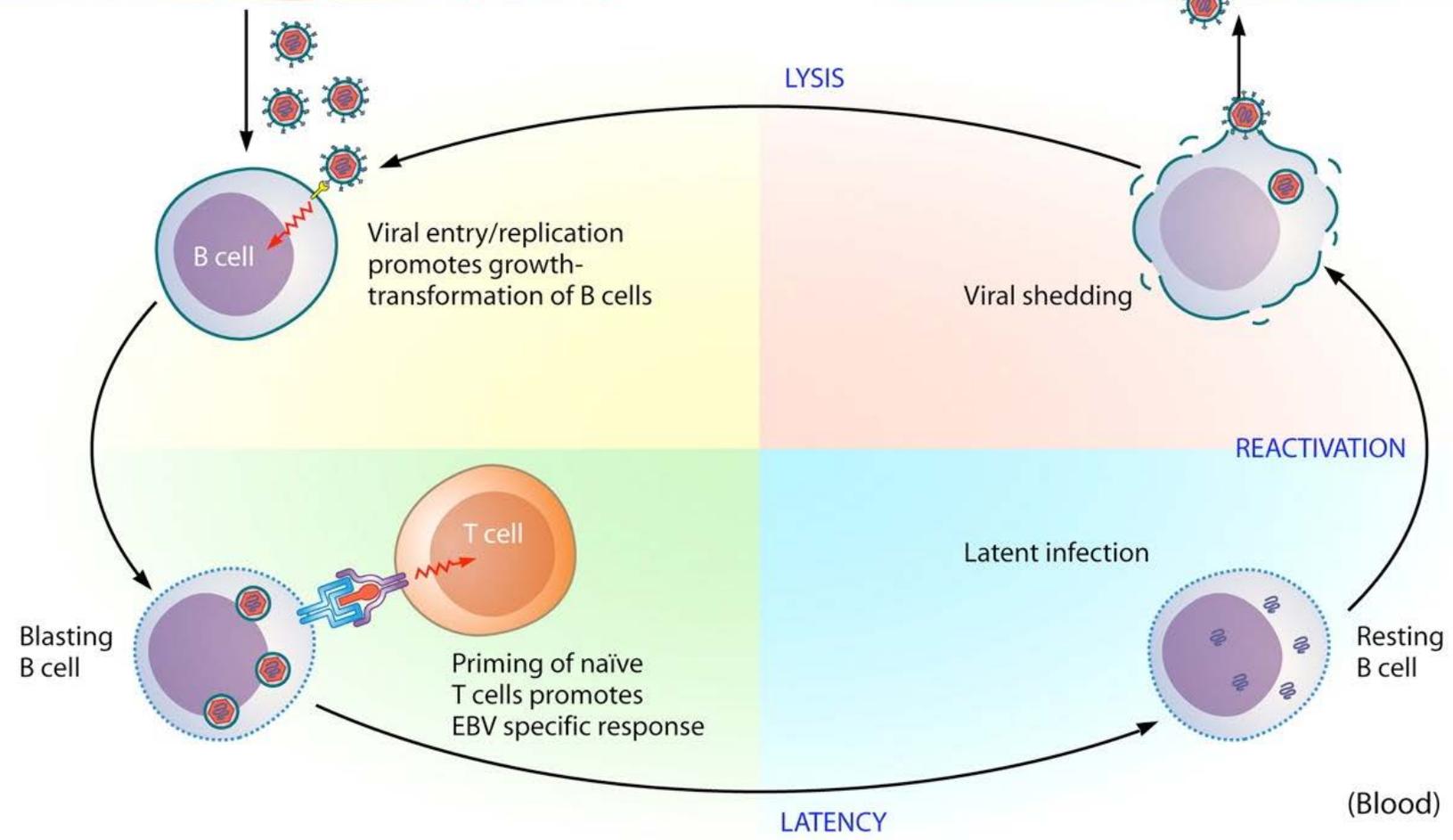
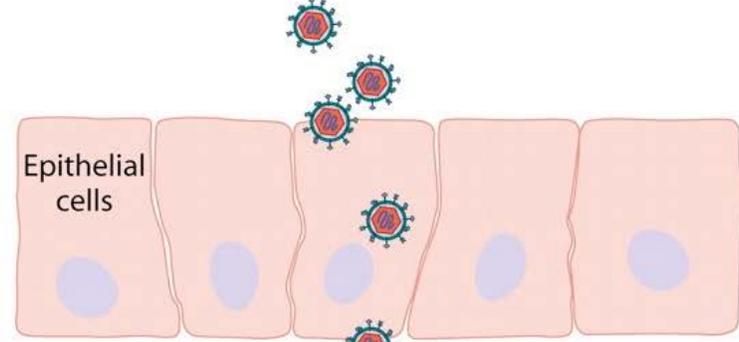
Complication	Comment
Airway Obstruction	Due to oropharyngeal swelling/edema
Meningoencephalitis	Other CNS complications can occur, but are rare
Hemolytic Anemia	Autoimmune
Thrombocytopenia	Autoimmune
Rash	Uncommon when due to EBV alone, majority of patients with PCN treatment will get rash

Complications of EBV (occurring in >1%)

Primary infection

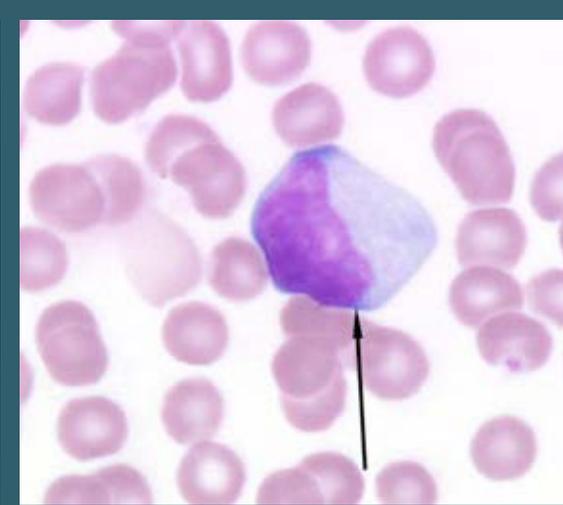


Persistent infection



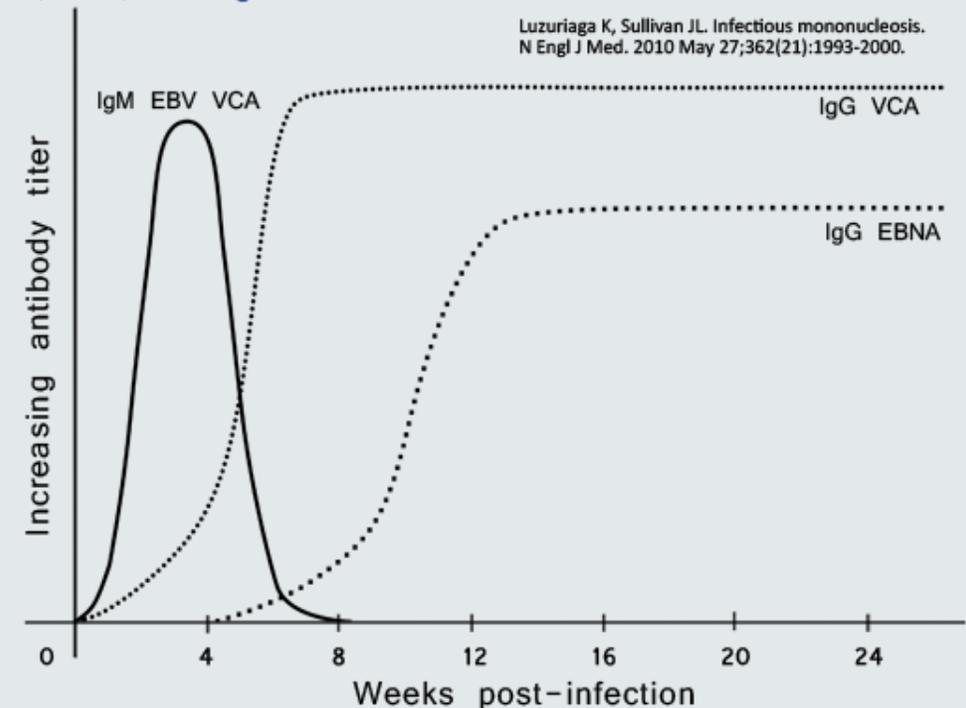
Diagnosis of EBV

- **Atypical Lymphocytes** (Hogland's Criteria of 10% atypicals in the setting of fever, pharyngitis, and adenopathy)
- **Monospot**
(Reasonable specificity, poor sensitivity)
- **EBV-specific titers**



Levels of antibodies specific to Epstein-Barr Virus (EBV) during Infectious Mononucleosis and Convalescence

Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med. 2010 May 27;362(21):1993-2000.

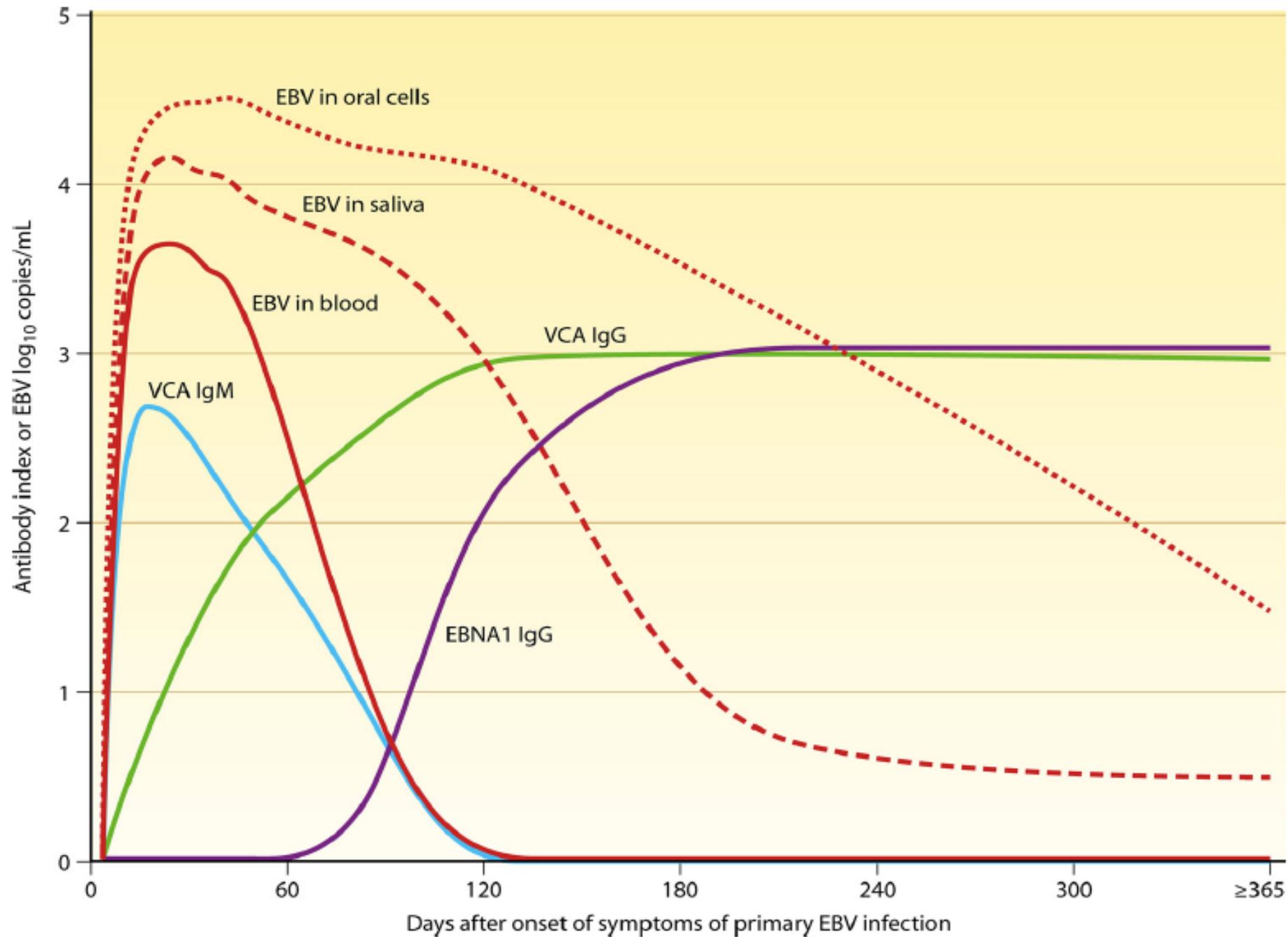


Serological markers (antibodies):

IgM EBV VCA - immunoglobulin G antibodies against EBV viral capsid antigen;

IgG EBV VCA - immunoglobulin G antibodies against EBV viral capsid antigen;

IgM EBV CA - immunoglobulin M antibodies against EBV nuclear antigen;

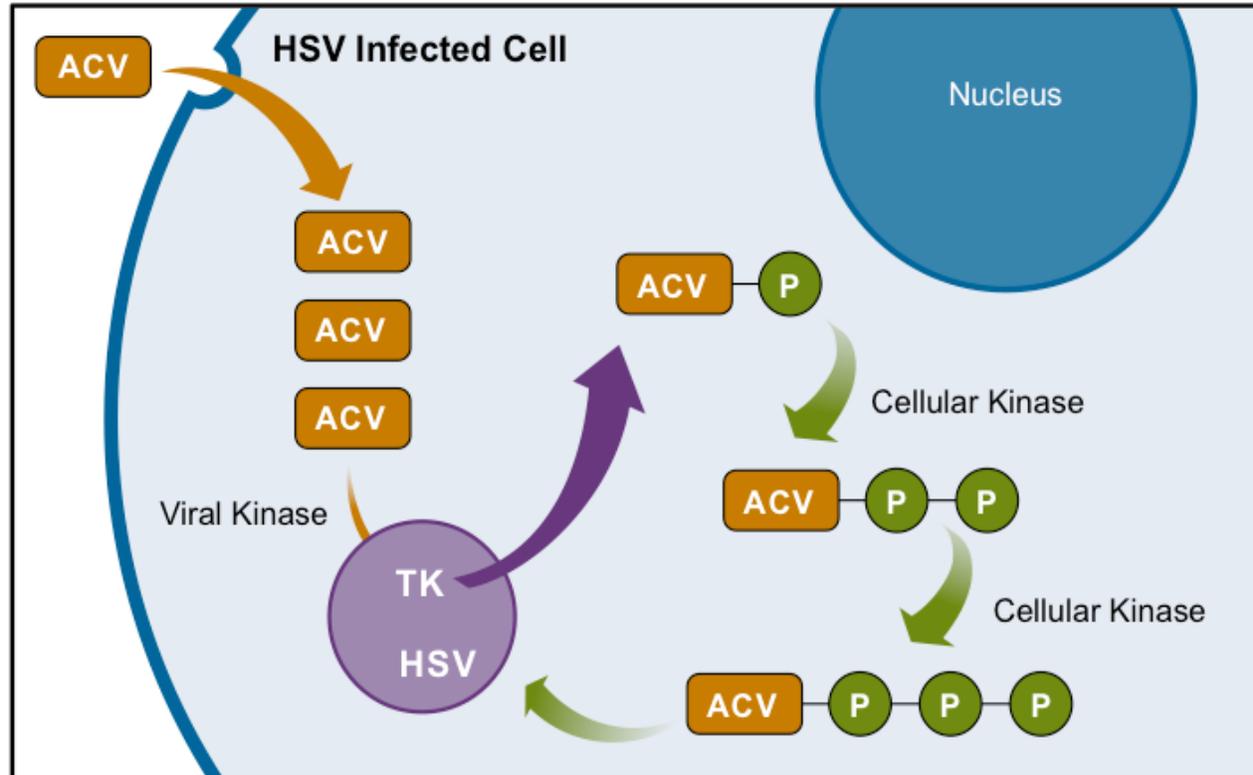


Primary Management of EBV

- Supportive care is indicated for all patients.
 - hydration
 - graded return to activities
 - monitoring for complications
- Corticosteroids should not be routinely administered.
- Clinical trials of acyclovir have been disappointing.

Why doesn't acyclovir work?

- Acyclovir is inactive until phosphorylated to its active form by a viral-encoded thymidine kinase (TK).
- Rather than a TK, EBV has a less efficient protein kinase (PK).
- Thus, ACV can reduce EBV shedding to some degree, but no clinical efficacy is seen.



What about valacyclovir?

- Valacyclovir is a prodrug of acyclovir.
- Studies in a small number of undergraduate students suggest that there may be some benefit to valacyclovir in regards to severity of clinical symptoms, but these findings have yet to be confirmed in larger, controlled studies.

Role of corticosteroids in primary EBV

- Steroids may be helpful in specific situations
 - obstructive symptoms due to excessive tonsillar hypertrophy
 - hemolytic anemia
 - autoimmune thrombocytopenia
- Steroids are not recommended in routine EBV infections
 - one primary consideration is the immunosuppressive effects of steroids, in the context of a virus that transforms and immortalizes B-cells

Management of athletes with EBV

- Goals of management may be slightly different
 - return to play sooner due to practical reasons of physical fitness, team performance
 - avoidance of 'lost time'
 - patient safety due to risk of secondary complications, most notably splenic rupture

Mononucleosis and Athletic Participation: An Evidence-Based Subject Review

Margot Putukian, MD,† Francis G. O'Connor, MD, MPH,‡ Paul R. Stricker, MD,§
Christopher McGrew, MD,¶ Robert G. Hosey, MD,||** Steven M. Gordon, MD,††
James Kinderknecht, MD,‡‡ Vesna M. Kriss, MD,§§ and Gregory L. Landry, MD¶¶|||*

- Major highlights:
 - Splenic imaging, if done, must be done soon in illness and repeated somewhat frequently in order to accurately assess change from baseline
 - Since the majority of splenic rupture occurs in the first 3 weeks of illness, most athletes may return to play after the first month of illness.

The Spleen and EBV

- Detectable splenomegaly develops in up to 50% of patients with primary EBV
 - ~1/1000 adults with primary EBV may experience a splenic rupture
 - Rates in children are lower
- Rupture occurs during the 1st - 3rd week of illness and is heralded by abdominal pain
 - Pain in the left shoulder (Kehr sign) is caused by diaphragmatic irritation from blood and is seen in ~50% of patients.

Role of Imaging in Athletes with EBV

- Imaging *could* be helpful in patients with significant splenomegaly at the baseline evaluation, but data are lacking.
 - Ultrasound and CT are highly correlative, thus U/S should be chosen
 - Literature standards define the ULN as 12-14 cm longitudinally

Normative Spleen Size in Tall Healthy Athletes: Implications for Safe Return to Contact Sports After Infectious Mononucleosis

Ryan McCorkle, MD, MPH, Brittany Thomas, MD,† Heidi Suffaletto, MD,*
and Dietrich Jehle, MD, RDMS**

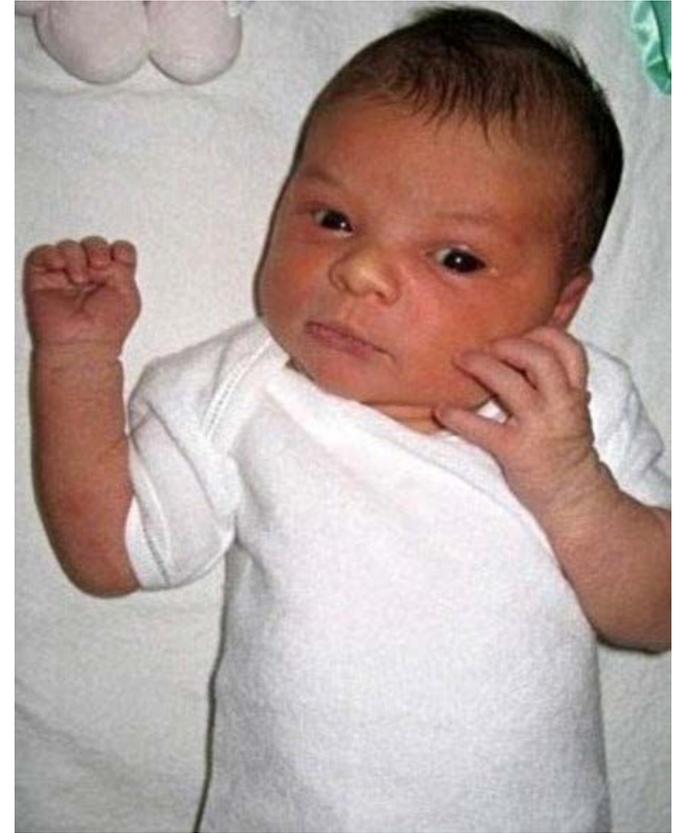
- Healthy males (>6'2") and females (>5'7") were enrolled.
- Athletes were excluded if <18 years, had pre-existing splenomegaly, EBV in the past 3 months, or history of splenectomy
- Mean splenic length for males was 12.8 cm and for females was 11.3 cm.
- More than 30% of subjects would have met criteria for 'splenomegaly' should they have developed EBV.

Imaging Recommendations

- Typical mononucleosis with palpable splenomegaly (mild)
 - no imaging is required
- Mononucleosis with moderate-severe splenomegaly based on clinical examination
 - ultrasound at baseline, then at repeated intervals throughout the first month (approximately) of recovery
 - serial imaging allows for comparisons to a patient's baseline
- There appears to be no role for ultrasound-guided return to play guidelines, particularly if baseline imaging was not obtained.

EBV Summary

- EBV is remarkably common in adolescents and young adults.
- Symptomatology is similar between teens and young adults, with fever, pharyngitis, and adenopathy predominating.
- Splenic rupture, a dreaded complication of contact sports, is rare and usually occurs within the first month of illness.
- Care must be individualized, but return to play is reasonable once acute symptoms resolve.



Neonatal Herpes Simplex Virus

HSV Epidemiology and Pathogenesis

- Two key components of HSV disease include:
 - neurovirulence/neurotropism
 - latency
- During HSV infection, virions undergo retrograde axonal transport.
- Viral replication occurs in a sensory neurons and latency is established in dorsal root ganglia.
- Reactivation then occurs when virus is transported distally to the site of original inoculation.

Epidemiology and Pathogenesis

- Two major serotypes, HSV-1 and HSV-2
 - Both can cause stomatitis and both can cause genital ulcers, but HSV1 disease is a more common cause of oral lesions and HSV2 is the more common cause of genital lesions.
- Both establish latency and both are inhibited by acyclovir.
- Both can be devastating to the newborn baby, though HSV1 may have slightly less morbidity/mortality.

Importance to Neonatal Health

- Babies born to women experiencing their first outbreak of HSV2 disease at delivery will have no HSV antibodies and are therefore at highest risk.
 - About 50% of these babies will acquire HSV and are considered extremely high risk for disease.
- This is in contrast to those with recurrent disease where <2% will acquire disease due to maternal antibody transfer.
- More than 75% of infants who contract HSV have been born to women with no history or clinical findings suggestive of genital HSV infection during or preceding pregnancy

Management of Perinatal HSV

- Recognition of risk factors
 - rupture of membranes >6 hours
 - scalp electrodes
 - vaginal delivery
 - cervicitis
 - primary infection
- Recognition of time-frame
 - Birth to 6 weeks
 - Most occur in the first 28 days.

Management of HSV Exposure

- For mothers with a current outbreak of genital HSV, most experts recommend:
 - C-section delivery
 - Careful monitoring of the baby, including HSV cultures of the skin, eyes, and mucus membranes.
- It is critical that these HSV cultures be performed after 36-48 hours of birth; otherwise transient contamination of the skin, without risk for subsequent development of disease, may be captured.
- If these culture are positive, most would then treat for skin/eye/mucus membrane form of neonatal HSV.

Types of Neonatal HSV

- **Skin-Eye-Mucus Membranes (~45%)**
 - disease is limited
 - diagnosed by SEM cultures, blister fluid PCR
 - treatment is acyclovir for 14 days
- **Disseminated (20%)**
 - disease is widespread, affecting the liver, CNS, lungs
 - diagnosed by serum HSV PCR, liver enzyme elevation in setting of HSV+
 - treatment is acyclovir for 21 days
- **CNS (35%)**
 - CNS involvement, including encephalitis and seizures
 - diagnosed by HSV PCR in the spinal fluid with CSF pleocytosis
 - treatment is at least 21 days; repeat LP must document negative PCR before completing therapy.

Neonatal HSV Pearls

- HSV virions are heavily cell associated; therefore, samples taken from vesicles should be from the base of the vesicle, not the vesicle fluid.
- The classic 'bloody tap' of HSV is rarely encountered in the neonatal population.
 - Most common CSF findings is a lymphocytic pleocytosis
- Temporal lobe seizures are the classic finding, including PLEDS (paroxysmal lateralizing epileptiform discharge spikes)

New developments in Neonatal HSV

- It has been well established that frequent HSV recurrences in the first 6 months of life negatively impact neurocognitive development.
- About 50% of infants experience at least one recurrence.
- Therefore, all infants with neonatal HSV disease should be offered prophylactic acyclovir (300 mg/m²/dose, administered 3 times daily for 6 months)
 - absolute neutrophil counts should be assessed at 2 and 4 weeks after initiating suppressive therapy and then monthly during the treatment period.

HSV and Wrestlers (Herpes Gladiatorum)

- All lesions must be scabbed over, with no new lesions in the preceding 48 hours.
- If treated with anti-viral medications:
 - During the first episode of herpes gladiatorum, athletes are not allowed to compete for a minimum of 10 days because they are highly contagious.
 - For recurrent outbreaks, the amount of virus in saliva and on the skin is often less. The athlete should refrain from competition for a minimum of five days. No new lesions while on antiviral medications for 48 hours.

Final Comments

- The rise in use of immunomodulating agents and in those receiving chemotherapy will most certainly have an impact on our patients' ability to control latent herpesvirus infections.
- Get to know your local laboratory offerings and the turn around times for EBV serologies and HSV PCR, in particular.
- Be on the lookout for new vaccine approaches, particularly for CMV.