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Infectious Mononucleosis

In this Issue...

Although the cause of infectious mononucleosis (IM) has now been known for nearly 40 years, the management of acute infection with Epstein-Barr virus (EBV) still can be confusing for both clinicians and patients. Frequently-asked questions include: How did I get mono? How is the infection best diagnosed? What are the best recommendations for recovery? Why is fatigue such a common problem?

In this issue, we review recent articles that, though by no means definitive, begin to provide some answers.



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1.0 hours Physicians

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April 29, 2010

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Guest Faculty Disclosures

Paul G. Auwaerter, MD has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough and Genzyme. He is on the Speaker Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson and Johnson.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe to colleagues how primary Epstein-Barr virus infection is acquired
- Discuss with colleagues expectations for recovery after infectious mononucleosis, especially regarding recovery from fatigue
- Provide colleagues with recommendations regarding when athletes may safely return to practice after infectious mononucleosis

COMMENTARY

Infectious mononucleosis (IM) has been described as a disease of the industrialized 20th century, whereby acute infection with Epstein-Barr virus (EBV) in susceptible adolescents and adults can yield the typical triad of fever, severe pharyngitis, and lymphadenopathy, often accompanied by profound fatigue. Whereas acquiring EBV infection in early childhood most often yields subclinical infection, the hygiene of developed societies means that up to 30%-50% of individuals develop infection in later years when vigorous immune responses controlling infection appear to cause disease.^{1,2} Other features suggestive of IM include splenomegaly, elevations in liver transaminase levels, and increased percentages of both typical and atypical lymphocytes. Diagnosis in North American is usually secured through the use of the Monospot™ test that detects characteristic heterophile antibodies. In approximately 10% of cases, the Monospot™ may be negative. In such cases, when suspicion of IM is high, the Monospot™ may be repeated or EBV-specific antibodies (EBV capsid IgM and IgG antibodies) should be ordered. The term "infectious mononucleosis" should only properly be applied to acute EBV infection, whereas "mononucleosis-like" syndromes can be due to a number of pathogens, including acute human immunodeficiency virus (HIV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), herpes simplex virus (HSV), adenovirus, *Toxoplasma gondii*, and *Streptococcus pyogenes*.³

More than 20 years ago, EBV was proposed as an explanation for chronic fatigue syndrome, although there is as yet no compelling information that this is indeed the case. Consequently, healthcare practitioners are not advised to assess EBV titers as part of a general evaluation for persistent fatigue.⁴ Although fatigue can be an unremitting consequence of IM in a small minority of patients, there remains little understanding of this process. As reviewed herein, the papers by Vollmer-Conna and Cameron explore the basis of fatigue, while the Cochrane analysis by Candy and Hotopf deals with the practical topic of symptom control, although the authors report not finding enough convincing evidence that corticosteroids reliably shorten the duration of IM-related fatigue (or other symptoms for that matter).

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Infectious mononucleosis is sometimes called the "kissing disease", as acquisition of EBV has been thought for years to be entirely transmitted through virus shed in saliva. A number of studies have now concluded that EBV can also be found in genital secretions, and the study from Thomas et al makes the case that sexual intimacy may be a risk factor for acquiring IM (although whether EBV can be spread genitally remains unproven). Interest in prevention has received some increased attention now that IM has been linked to increased risk for developing Hodgkin's lymphoma and multiple sclerosis,^{5,6} and a vaccine for the prevention of IM has been successfully studied by Sokal et al in a phase II trial. Lastly, a number of papers have been written wrestling with the topic of when athletes may safely resume sport after IM, mainly because of the fear that activities begun too soon may precipitate splenic rupture. Many sports medicine practitioners rely upon imaging studies to document a spleen that has returned to normal size in these circumstances. The ultrasonographic study of Division I college athletes by Hosey and colleagues, unfortunately, only lends confusion to this arena, as they document that 7% of their cohort appear to meet criteria for splenomegaly without a prior history of IM.

Although none of the studies reviewed herein provide definitive answers, this snapshot of the on-going research helps shed some light on these less well-defined areas.

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IS INFECTIOUS MONONUCLEOSIS A STD?

Thomas R, Macsween KF, McAulay K, et al. **Evidence of shared Epstein-Barr viral isolates between sexual partners, and low level EBV in genital secretions.** *J Med Virol.* 2006;78(9):1204-1209.

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This 2006 study attempts to determine whether EBV can be transmitted through genital contact. Thirty patients with infectious mononucleosis (IM) were enrolled from a university health clinic, along with non-IM patients from a regional sexually transmitted disease (STD) clinic and an infertility clinic (all located in Edinburgh, Scotland). The IM case patients also had their close contacts approached if they consented to join the study. Peripheral blood mononuclear cells and throat washings were all analyzed for recovery of EBV. Virus isolated from IM cases and their contacts were compared by polymerase chain reaction (PCR) amplification of two regions (EBNA 3C and LMP1) and sequencing.

A total of 29 IM/contact pairs were fully analyzed. EBV viral isolates were found to be identical in 41% of the pairs, with those having sexual contact having a far higher rate (82%) of identical isolates than those who had non-sexual relations (17%) [Table 1].

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Table 1: Comparison of Sequence Similarity Between Sexual and Non-Sexual IM Contacts, in University Students

	IM/contact pairs	Amplified EBNA 3C and/or LMP1 sequence similarity between IM case and contacts	
		Identical (%)	Non-Identical (%)
Total	29	12 (41)	17 (59)
Type of contact			
Sexual	11	9 (82)	2 (18)*
Non-Sexual	18	3 (17)	15 (83)*

*Fisher's exact *P*-value 0.0012.

Adapted from Thomas R, et al. *J Med Virol.* 2006;78(9):1204-1209.

The second part of the study examined the recovery of EBV in specimens obtained from STD and infertility clinic patients [Table 2]. These samples were not from patients known to have IM.

Sample	Total EBV positive (%)
Cervical swabs	6/84 (7)
Male urethral swabs	3/55 (5)
Semen	1/33 (3)

Adapted from Thomas R, et al. *J Med Virol.* 2006; 78(9):1204-1209.

Most transmission of EBV is thought to occur through oral secretions, as the virus has been easily demonstrated in salivary samples in IM patients.¹ This oral route of acquisition makes sense, especially since most EBV is acquired during childhood when it usually yields a subclinical infection.² Challenging this conventional wisdom, epidemiological studies of British students suggested that sexual activity correlated significantly with EBV seropositivity as well as reported IM.^{3,4} The biological plausibility has been reinforced by a number of studies finding evidence of EBV in both female and male genital secretions.^{5,6} The difficulty has been proving a genital source of acquisition, since virus could also be acquired through other activities associated with sexual intercourse, such as deep kissing.

This small study lends further support to the concept of genitally acquired EBV by showing that partners with sexual contact were far more likely to display identical EBV DNA sequences than those who had non-sexual contact. These results provide indirect support at best, because partners reporting sexual contact might still have acquired infection by oral means, and prior relationships were not well accounted for in this study.

The second part of the study adds to the literature that shows a small (3%-7%) percentage of individuals shed EBV in genital secretions. When these positive cases were further investigated by semi-quantitative PCR, the investigators found only low levels of virus (<10 EBV copies/μg of DNA) in this study population. Others have found higher levels in genital samples, but amounts of up to 10⁶ EBV copies/μg DNA have been described in salivary secretions in asymptomatic individuals shedding virus.^{7,8}

Overall, sexual activity appears to be a risk factor for acquiring both EBV and probably IM in the uninfected; however, the exact contribution of genitally shed EBV remains unclear.

As an aside, EBV has been rarely associated with causing female genital ulcerations as an initial manifestation of primary infection. Recent reports review the several dozen cases in the literature, but many are in young girls with no history of sexual exposure,^{9,10} hence providing additional caution before considering acute EBV a routine STD.

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CAN INFECTIOUS MONONUCLEOSIS BE PREVENTED?

Sokal EM, Hoppenbrouwers K, Vandermeulen C, et al. **Recombinant gp350 vaccine for infectious mononucleosis: phase 2 randomized, double-blind, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of an Epstein-Barr virus vaccine in healthy young adults**. *J Infect Dis*. 2007;196(12):1749-1753.

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This phase II vaccine study sought to determine whether acute EBV infection or IM could be prevented through the immunization of naive young adults. This was a randomized, double-blind trial using a recombinant gp350 vaccine that prompts antibody development against a key viral antigen that facilitates EBV entry into B lymphocytes. Immunizations were carried out at initiation, and at 1 month and 5 months, with follow-up for a total of 18 months.

The authors found that immunization with the gp350 vaccine yielded detectable antibody response in 98.7% of subjects (95% CI, 85.5-97.9%). By the end of the 18 month study period, the primary end point of preventing IM showed an efficacy of 78% (95% CI, 1-96%), but did not halt asymptomatic acquisition of EBV. Adverse side effects were no different between the vaccine and placebo groups.

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Case Presentation Category	Placebo	Vaccine
Infectious mononucleosis	9	2*
Definite	8	2
Probable	1	0
Asymptomatic infection	9	11
Total	18	13

*Difference is significant ($\alpha = 0.05$, by 1-sided Fisher's exact test).

Adapted from Sokal E, et al. *J Infect Dis.* 2007; 196(12):1749-1753.

The group receiving the gp350 vaccine had no cases of IM once the three series of immunizations were completed, compared to the placebo group that continued to develop IM.

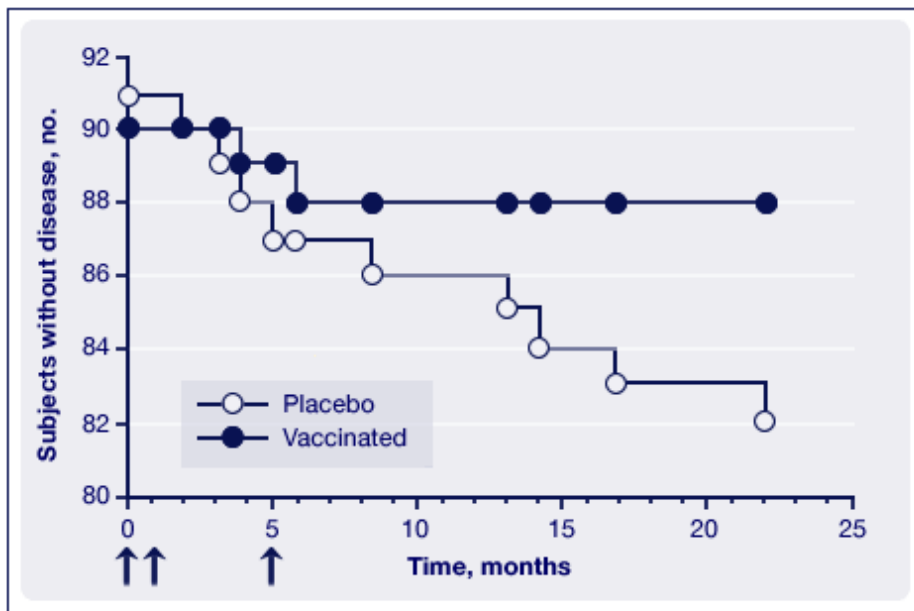


Figure 1: Timing of occurrence of infectious mononucleosis in vaccine and placebo recipients (an intention-to-treat cohort). Arrows denote the times of vaccination. After completion of the study, 1 additional case of infectious mononucleosis was reported in the placebo group.

Used with permission from The University of Chicago Press; Sokal E, et al. *J Infect Dis.* 2007;196(12):1749-1753.

Although IM is usually a self-limiting illness, some patients experience prolonged and debilitating fatigue that can last months after acute infection.¹ Also, IM may rarely cause death or severe morbidity through complications, such as airway obstruction, splenic rupture, and neurological sequelae.² A preventative vaccine strategy may further be appealing for adolescent and young adult populations who wish to avoid missing significant time from school and work. Heightened interest has also come about due to the recent epidemiological association suggesting that the risk of Hodgkin's lymphoma may be 40-fold higher in those who have experienced IM.³ Since EBV is also directly responsible for serious malignancies such as Burkitt's lymphoma, nasopharyngeal carcinoma, and post-transplant lymphoproliferative disorder, a separate question not addressed by this trial is whether a vaccine may affect these routinely life-threatening cancers.

This trial suggests that in the intent-to-treat analysis, the gp350 vaccine was protective against the development of IM — although the small study design guaranteed wide confidence intervals. Immunization appeared to be safe and it generated reliable seroconversion, suggesting that the vaccine is a candidate for study in larger populations. Whether such a vaccine can interrupt the malignancy potential of EBV depends on whether the significant immune dysregulation as a consequence of IM is a leading driver. If, instead, oncogenic potential is related to viral infection alone, then this vaccine is unlikely to yield this specific benefit, since it does not appear to halt acquisition of the EBV virus.

Regardless, since there is no reliable medical therapy for IM that shortens illness or post-infectious fatigue duration, a vaccine strategy could well be worthwhile in industrialized countries where there is some evidence suggesting that IM is increasing in incidence as well as severity.^{4,5} Given the immunological complexity of EBV infection, the question of whether a vaccine strategy can be safely employed will not be quickly answered, as long-term studies will likely be needed.

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SHOULD CORTICOSTEROIDS BE USED FOR ROUTINE SYMPTOMS OF INFECTIOUS MONONUCLEOSIS?

Candy B, Hotopf M. **Steroids for system control in infectious mononucleosis**. *Cochrane Database Syst Rev*. 2006;19;3:CD004402.

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Candy and Hotopf performed an evidence-based review to examine whether corticosteroids assist in the resolution of infectious mononucleosis with demonstrable safety. The authors utilized the typical Cochrane protocol search strategy of looking for randomized control trials (RCT). Seven studies were identified; however, these studies varied so tremendously in a number of attributes (such as dosing schemes of corticosteroids, primary outcomes, and study numbers), that the researchers were unable to determine data sufficient enough to make any recommendations regarding symptom control for IM. In the 7 examined studies, the authors found the following regarding corticosteroids versus placebo:

- Two trials finding a benefit of 12 hours in the resolution of throat soreness
- One trial suggesting that fatigue was reduced at 4 weeks (although the benefit was confounded by combination with antiviral therapy)
- Two trials reporting severe complications in the corticosteroid group (symptomatic ketoacidosis, peritonsillar infection)

Corticosteroids have long been employed by some practitioners to help provide immediate improvement and perhaps speed resolution of profound constitutional symptoms due to IM.¹ In one recent study of 206 IM patients treated at a tertiary care center, 45% received

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corticosteroids, though upon review of these cases, only 8% met the usually recommended criteria for use such as impending airway obstruction or profound hemolytic anemia.² This practice remains controversial, since the 2 largest studies examining the role of glucocorticoids in the treatment of IM failed to find significant improvement in pharyngeal symptoms or a faster return to work or school.^{3,4} Additional concern has also been raised because of evidence that acute EBV infection appears to be linked to increased risks of developing multiple sclerosis, EBV-related Hodgkin's lymphoma, and perhaps systemic lupus erythematosus.^{5,6,7} Whether using corticosteroids impacts on these potential associations is completely unknown, although 1 retrospective study of corticosteroid use in IM found no short-term complications.⁸ This is in contradistinction to the study reviewed here that identified at least 2 serious complications ascribed to corticosteroid use.

Although this evidenced-based Cochrane review found insufficient literature to derive any recommendations for the use of corticosteroids to control common symptoms of IM, it should be noted that available RCTs were few in number, heterogeneous in design, and frequently underpowered to reach conclusions. Where this report leaves clinicians is less than clear: the use of corticosteroids for symptom control remains in the "art" rather than the science of medicine. Further, practitioners need to consider that most individuals will be improved in less than four weeks regardless of interventions, and that corticosteroids could abet the transformative fires stoked by EBV, leading to future health problems.

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FATIGUE AFTER INFECTIOUS MONONUCLEOSIS: ARE WE ANY CLOSER TO AN EXPLANATION?

Vollmer-Conna U, Cameron B, Hadzi-Pavlovic D, et al. Dubbo Infective Outcomes Study Group. **Postinfective fatigue syndrome is not associated with altered cytokine production**. *Clin Infect Dis*. 2007;45(6):732-735. Epub 2007 Aug 6.

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Cameron B, Galbraith S, Zhang Y, et al. Dubbo Infective Outcomes Study Group. **Gene expression correlates of postinfective fatigue syndrome after infectious mononucleosis**. *J Infect Dis*. 2007;196(1):55-66. Epub 2007 May 24.

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Prolonged fatigue is a well-known and well-feared complication that afflicts a certain subset of individuals who have IM. Although fatigue is a common component of the acute infection, fatigue that persists beyond one month affects only a small minority for a year or more, with female gender and pre-existing affective disorders described as increasing this risk.¹⁻³ The explanation for this persistent fatigue is far from clear, although the use of molecular methods by investigators has identified a menu of candidate genetic transcriptional changes impugning mitochondrial dysfunction, cell-cycle dysregulation, myogenic changes, and neuronal disturbance.^{4,5}

These 2 studies looked for possible mechanisms to account for the persisting fatigue following IM. In the investigation by Cameron et al, 7 subjects with significant fatigue at 6 months after IM were compared to 8 control patients with IM who recovered promptly. Over 30,000 genes were studied by microarray analysis from peripheral blood samples between the 2 groups. The report by Vollmer-Conna et al used cytokine analysis of peripheral blood mononuclear cells to compare 22 patients with IM-related fatigue to 44 controls by cytokine analysis of peripheral blood mononuclear cells.

Cameron's group et al found 234 genes differentially expressed in individuals with significant fatigue, and 180 genes in those who reported chronic musculoskeletal symptoms. When using multiple sample points longitudinally, the authors find a total of 35 genes with increased expression compared to the group with quick resolution of IM symptoms. In comparison, Vollmer-Conna et al could not discriminate between the prolonged fatigue group and the recovery group when testing for a total of 8 pro-inflammatory cytokines.

Samples for both studies came from the landmark prospective Dubbo study that concluded that about 11% of individuals met criteria for chronic fatigue syndrome 6 months after an acute infection, regardless whether they suffered from infectious mononucleosis, acute Q fever (*Coxiella burnetii*), or Ross River virus infection.⁶ The study has been cited by many as evidence that a variety of infections may trigger a uniform post-infectious fatigue syndrome, perhaps through a common pathway(s).

Evidence for a measurable cytokine response driving infection was not identified in the study by Vollmer-Conna and colleagues. Although the immune response to acute EBV is extensive and perhaps long-lasting, a simple measure such as cytokine profiles in the blood does not seem to be an easy explanation for persistent fatigue.^{7,8} In contrast, the study by Cameron et al hints at the beginnings of an exciting approach to understanding the mechanisms of post-infectious fatigue through changes in transcriptional function of certain genes. Whether these genes will hold the key to understanding IM-related fatigue remains unclear, but this approach holds at least the glimmer of hope that science may be able to shed light on a problem of immense frustration to both the patient and the physician alike.

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SPLEEN SIZE AND ATHLETES: IMPLICATIONS FOR RETURN TO PLAY AFTER INFECTIOUS MONONUCLEOSIS

Hosey RG, Mattacola CG, Kriss V, et al. **Ultrasound assessment of spleen size in collegiate athletes.** *Br J Sports Med.* 2006;40(3):251-254.

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Splenomegaly is a common feature of typical infectious mononucleosis, as up to 50% of patients may develop this finding within 2 weeks of symptom onset. Splenic rupture causing massive hemorrhage is among the most rare but feared complications of IM – occurring spontaneously or resulting from trauma.^{1,2} For competitive athletes recovering from IM, a common question is when sports, especially contact sports, may be safely resumed. This is difficult to answer, as no prospectively performed studies exist. Using observational information, expert recommendations have varied between 3 weeks to 6 months as timeframes that athletes should avoid training and competition.^{2,3}

Splenic rupture due to IM mostly occurs within 2 to 21 days of symptom onset; however, there are descriptions of occurrences thereafter, with 7 weeks as one of the latest descriptions in the medical literature.^{4,5} A common approach taken by clinicians faced with this difficulty is to recommend waiting an average of 4 weeks for contact supports, and 3 weeks for non-contact supports, with the assumption that the spleen has returned to normal size. Since physical examination of the spleen is unreliable, for an earlier return to sport, obtaining an ultrasound to document the absence of splenomegaly has been thought to offer some confidence that activities may be safely resumed.⁶

To test the adequacy of this measurement, Hosey et al evaluated spleen size by ultrasound evaluation in a college-aged, athletic population without evident illness. Both male and female athletes were examined, with a total of 631 splenic measurements taken. Using standard ultrasonographic definitions, the investigators found that 7% of this population met the criteria for splenomegaly. Interestingly, a prior history of IM did not correlate with splenic enlargement.

This study adds to that existing literature documenting a subset of patients who may have a "normal" spleen that is enlarged. One study of 2200 healthy college freshman found that 3% met criteria for an enlarged spleen by physical examination.⁷ It is perhaps not unreasonable to surmise that an even larger percentage of individuals who are Division I competitive athletes, as in Hosey's study, may have larger physiques and therefore have a higher percentage (7%) of increased spleen size.

Unfortunately, this information only makes decision-making for an athlete's return-to-play even more difficult, as ultrasonographic evidence of splenomegaly in an athlete may be a normal finding in some, rather than continued evidence of risk from EBV-driven processes. As there is no clear ability to distinguish between normal and abnormal spleen enlargement, the advice to wait for at least 7 weeks after onset of IM (regardless of ultrasound findings) before initiating contact sports may be prudent when encountering this scenario

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CME INFORMATION

Accreditation Statement — [back to top](#)

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Credit Designations — [back to top](#)

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Post-Test — [back to top](#)

To take the post-test for eInfections Review you will need to visit [The Johns Hopkins University School of Medicine's CME website](#). If you have already registered for another Hopkins CME program at these sites, simply enter the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post-test/evaluation is required to receive CME credit.

Statement of Responsibility — [back to top](#)

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Intended Audience — [back to top](#)

This activity has been developed for the Primary Care Physician, Internist, and Infectious Disease Specialist.

Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Describe to colleagues how primary Epstein-Barr virus infection is acquired
- Discuss with colleagues expectations for recovery after infectious mononucleosis, especially regarding recovery from fatigue
- Provide colleagues with recommendations regarding when athletes may safely return to practice after infectious mononucleosis

Internet CME Policy — [back to top](#)

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Step 3.

Complete the post-test and course evaluation.

Step 4.

Print out your certificate.

PHYSICIAN
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- **John G. Bartlett, MD** has disclosed that he has served on the HIV Advisory Board for GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Pfizer and Tibotec. He is also on the Policy Board for Johnson & Johnson.
- **Paul G. Auwaerter, MD** has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme. He is on the Speakers' Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson & Johnson.
- **Sara E. Cosgrove, MD, MS** has disclosed that she has received grants or research support from Merck and served on the Advisory Boards for Ortho-McNeil, Cadence Pharmaceuticals, and Theravance/Astellas.

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