



Systematic Review

Hemolytic Anemia Linked to Epstein–Barr Virus Infectious Mononucleosis: A Systematic Review of the Literature

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Abstract: Background: In Epstein–Barr virus infectious mononucleosis, hemolytic anemia occasionally occurs. **Methods:** To characterize hemolytic anemia linked to Epstein–Barr virus infectious mononucleosis, we performed a systematic review (PROSPERO CRD42024597183) in the United States National Library of Medicine, Excerpta Medica, and Web of Science with no restrictions on language. Only reports published since 1970 were included. Eligible were reports describing hemolytic anemia in subjects with clinical signs and microbiological markers of Epstein–Barr virus mononucleosis. **Results:** In the literature, we detected 56 reports released between 1973 and 2024, documenting 60 individuals (32 females and 28 males; 27 children and 33 adults) with hemolytic anemia linked to Epstein–Barr virus infectious mononucleosis. The mechanism underlying anemia was categorized as cold-antibody-mediated (N = 31; 52%), warm-antibody-mediated (N = 18, 30%), mixed warm- and cold-antibody-mediated (N = 4; 6.7%), or paroxysmal cold hemoglobinuria (N = 2; 3.3%). The remaining 5 cases (8.3%) remained unclassified. Observation alone was the chosen approach in 23% of cases (N = 14). Steroids (67%; N = 40) and blood transfusions (38%; N = 23) were the most commonly used treatment, while plasma exchange, intravenous polyclonal immunoglobulin, rituximab, and splenectomy were used less frequently. Observation was slightly but significantly ($p = 0.032$) more common in cases of cold-antibody-mediated anemia compared to all other cases combined. Patients recovered a median of 28 [interquartile range 21–39] days after disease onset. Two patients with warm-antibody-mediated hemolytic anemia died. **Conclusions:** This literature review points out that Epstein–Barr virus, like *Mycoplasma pneumoniae*, cytomegalovirus, or