



**Review Article**

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# The Dark Side of MONO



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## Abstract

Infectious mononucleosis is a well-known disorder in adolescents and young adults due to the Epstein-Barr virus that can present with fever, fatigue, sore throat and cervical lymph node enlargement for several weeks. Though often considered benign with a self-limiting course, a minority of patients who are considered immune competent can develop severe, even deadly, complications from this virus. Causes of death for these patients include splenic rupture, sepsis and airway obstruction. Clinicians must evaluate their patients with infectious mononucleosis carefully and aggressively manage those whose course is worsening. Assuming that all patients with this infection will have an uneventful recovery increases the annual death toll of this viral infection.

## Introduction

Infectious mononucleosis is a well-known disorder in adolescents and young adults due to the Epstein-Barr virus (EBV) that can present with fever, fatigue, sore throat and cervical lymph node enlargement for several weeks [1]. A wide variety of features can be seen and some experts note that infectious mononucleosis is more likely in patients with a sore throat who also have lymphadenopathy (posterior cervical, inguinal or auxiliary), palatine petechiae, splenomegaly or atypical lymphocytosis [2].

German physician Emil Pfeiffer (1846-1921) described this condition in 1889 as “glandular fever” (“Drüsenfieber”) with fever, pharyngitis, lymphadenopathy, hepatomegaly and splenomegaly [3]. The term, infectious mononucleosis, was coined by Thomas Peck Sprunt (1884-1955) and Frank Alexander Evans (1889-1956) in 1920 in an article in the Bulletin of the Johns Hopkins Hospital in Baltimore, Maryland [4-6]. The 1964 finding of the Epstein-Barr virus in Burkitt’s lymphoma cells was by Sir Michael Epstein (born 1921), Yvonne Barr (1932-2016) and Bert Achong (1928-1999) at the University of Bristol (Bristol, United Kingdom) [7,8]. Werner and Gertrude Henle linked the EBV with infectious mononucleosis in 1968 at the Children’s Hospital of Philadelphia [9].

Infectious mononucleosis (IM) is often described as a self-limiting and benign infectious disorder. Such a description can lull clinicians into a “benign” view of IM that only needs supportive care. Unfortunately, there is a dark side to IM that can haunt a minority of persons who are infected with the Epstein-Barr virus (EBV).

One must remember that there are many potential complications to EBV infection—both acute, chronic and potentially fatal [10,11].

The Epstein-Barr virus (EBV) is a  $\gamma$ -herpesvirus that is estimated to infect 90% or more of all Homo sapiens in the world [1]. In addition to causing IM the EBV also is linked to various dangerous epithelial and lymphocytic cancers including 10% of gastric cancers [12]. Another dark side of EBV infection and IM is that the infected person may die if clinicians are not vigilant to this possibility and provide assiduous evaluation, management, and follow-up—especially for those individuals who are not having a “benign” course of what is sometimes euphemistically called “the kissing disease.” It is not a “kissing” disease but IM may be a “deadly” disease for some [10].

## Dark & Deadly Side of IM

Clinicians have been recording deaths from glandular fever or disorders similar to this disorder since the 1890s [13]. Clinicians became more aware of the potential dangers of IM in the 1940s which included a classic review by Bernstein on IM warning of dangers from severe infection (sepsis) [14], a report by Ziegler of death in IM in 1944 from splenic rupture [15], discussion of IM complications by Berg in 1945 [16], report of a death in a 23 year old from IM from generalized infection by Allen and Kellner in 1947 [17], the death of a 23 year old from liver disease in 1949 by Ainley [18], and the warning by Houck in the American Journal of Medicine in 1949 that IM “frequently incapacitates and occasionally kills [19].”

Leibowitz provided a review in 1953 of 38 deaths attributed to IM and Albuquerque published a report in 1966 of 50 deaths attributed to IM [20,21]. A comprehensive and critical review of deaths from IM was published in 1970 by pathologist H.G. Penman from the University of Otago medical school in Dunedin, New Zealand [22]. In this landmark review he looked at 87 reported cases of death by IM up to 1969, discussed the difficulties in verifying that each case was truly IM (or mono-like), and concluded that 20 were IM.

He noted that 9 died from neurologic complications, 2 from secondary infection with splenic rupture, 2 from hepatic failure, 1 possible death from myocarditis (1942), and others has unclear causes [22]. He wrote about 6 annual deaths from IM in a population of 48 million and calculated a mortality rate of under 1 per 3,000 cases; however, he acknowledging the difficulty in such calculations since so many IM cases are asymptomatic and unreported [22].

Based on his work and addition reports, it became more evident that death from IM complications was a rare but known possibility and should be considered in ill persons having IM [22]. As the 20th century entered its last decade, death from IM complications were identified as being most commonly from splenic rupture, sepsis and severe respiratory obstruction; other causes were identified neurologic complications (as meningoencephalitis), hepatic failure, cardiac conditions and immunocompromised status [10,22,23]. Death in IM from three of causes are considered: splenic rupture, sepsis and airway obstruction.

### Splenic Rupture in IM

The 20th century established that the most common cause of death from IM was splenic rupture starting perhaps with a Norwegian article by Andersen in 1939 [24]. As reports were entered into the literature of spontaneous splenic rupture in persons with IM it slowly became clear in the middle of the 20th century that death was possible from this event unless rapid emergency care was offered to this vulnerable patient [21,25,26]. Two reports in the 1980s reminded the medical community that death from IM due to spontaneous splenic rupture is a major tragedy of a condition (i.e., IM) often considered to be a benign and self-limiting disorder [27,28].

Further research suggests that 0.1% to 0.5% of patients with IM develop spontaneous splenic rupture and that persons with splenomegaly should avoid trauma such as seen with sports play [29-31]. Persons of any age who present with tachycardia and abdominal pain with or without know IM should be evaluated for potential splenic rupture and continuous case reports are seen in the 21st century [31-38]. This condition may also be seen in a patient with multi-organ failure in which splenic rupture is only part of the generalized complications of EBV-IM [39].

### Death by Sepsis in IM

As clinicians have focused on observing for splenomegaly and potential splenic rupture in those with IM, some are not concerned

that this condition, described as being benign and self-limiting, can kill rare patients from other causes; a leading contender in this regard, after a ruptured spleen, is death by sepsis. This possibility was noted in 1905 by Korsakoff [40], considered by Bernstein in 1940 [14] and detailed further by the classic 1970 Penman review that included a case of death due to streptococcal retrotonsillar abscess in 1951 [22].

Other case reports were published in the last half of the 20th century about infections complicating IM such as death via beta hemolytic streptococcal infection in 1979 [41] in addition to cases of IM complicated by *Mycoplasma pneumonia* [42] and postanginal sepsis [43]. Some may die from IM complicated by immunological conditions [44] while others appear to be healthy but are unable to deal with sepsis induced by the IM infection.

Clinicians must be aware of this deadly potential for infection with IM even in healthy persons and be vigilant in aggressively caring for those with IM whose course is worsening-deviating from the benign, self-limiting descriptor often assigned to IM infections. Some reports note an increase in peritonsillar, retropharyngeal and parapharyngeal abscess rate possibly related to a decrease in tonsillectomy and continuing the long-lasting debate on the indications for tonsillectomy [45-49].

An important example in this regard is patients having IM who develop the Lemierre syndrome or postanginal septicemia that is characterized by acute infection of the oropharynx (with fevers and tenderness to the lateral aspect of the neck) and secondary septic thrombophlebitis of the internal jugular vein [50-54]. It was described in 1936 by the French bacteriologist, Dr. André-Alfred Lemierre (1875-1956) [55].

The microbiologic cause is *Fusobacterium necrophorum*, an anaerobic bacterium of oropharyngeal flora that can worsen the pharyngitis due to IM and lead to emboli pulmonary abscesses as well as other metastatic infections [56]. The most prevalent pathogen in peritonsillar abscesses in some areas is *Fusobacterium necrophorum* [57]. It is important for clinicians to have a high index of suspicion for this condition in patients have severe pharyngitis with a course that is worsening and not appearing to be self-limiting. Early diagnosis with antibiotic treatment will save lives while failure to do this will result in more deaths from mono complications.

The use of penicillin for pharyngitis led to fewer cases of this condition in the 1960s and 1970s and it became known as the "forgotten disease [55]" later in the 20th century. However, the deadly combination of being a forgotten disease and the current antibiotic era has led to its occurrence in seemingly healthy teenagers and young adults who develop severe pharyngitis and die from lack of aggressive management.

### Airway obstruction

Death from airway obstruction was noted by Bellotti in 1896 and Moir in 1930 when various infections occurred in the upper respiratory tract [13,22]. In 1984 Johnsen and colleagues pointed

out that airway obstruction is the most frequent fatal complication of IM and emphasized the need for very close observation and management of anyone with even mild respiratory difficulty with pharyngitis due to IM [58]. In 1986 Carrington and Hall reported on death by airway obstruction in a 20 year old male with IM [59]. Experts have continued to warn clinicians to watch for and aggressively manage patients with IM who are not progressing well and to be on the lookout for upper airway obstruction as an emergency situation [60-63]. One group estimates that 1% to 3.5% of those with IM develop significant airway compromise [64]. Patients can also develop pneumonia after an EBV infection whether they are identified as being immune competent or having known immune deficiency [65,66].

### Conclusion

Though infectious mononucleosis from Epstein-Barr virus infection is often described in the literature as a benign and self-limiting illness, clinicians must always understand that this infection can represent a very serious illness for a minority of patients. Death from mono can occur in various manifestations and three of the most common causes of death in pediatric patients (children, adolescents and young adults) are considered: splenic rupture, sepsis, and airway obstruction. Clinicians must always remember that a few patients will take a deadly course when infected with the Epstein-Barr virus and assiduous evaluation as well as comprehensive management is necessary for these individuals who are getting worse. Those with splenic rupture, sepsis, or airway obstruction should be emergently managed with published protocols and principles [67-70]. Such an approach will save these precious lives and prevent infectious mononucleosis from claiming even more unnecessary victims in the 21st century.

*"Infectious mononucleosis is no longer properly regarded as a diagnostic*

*Curiosity or as a benign and unimportant disorder. The disease always impairs*

*Vital organs, frequently incapacitates and occasionally kills."*

**GEORGE H. HOUCK MD (1949) [19]**

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