

# Beyond the Classic Mononucleosis: A Multidisciplinary Review of Epstein-Barr Virus-Induced Splenic Rupture from Pediatrics to Adulthood

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## Abstract

Epstein-Barr virus (EBV)-induced infectious mononucleosis (IM) is a common clinical syndrome characterized by fever, pharyngitis, and lymphadenopathy. Although IM is typically self-limiting, splenic rupture represents its most catastrophic and life-threatening complication, accounting for the majority of EBV-related mortality. To consolidate multidisciplinary evidence on the epidemiology, pathophysiologic mechanisms, diagnostic challenges, evolving management strategies, and return-to-play protocols for EBV-induced splenic rupture across the pediatric, adolescent, and adult age spectrum. Pathologically, profound lymphoid proliferation expands the splenic red pulp, attenuating the organ's capsule and trabecular architecture. Remarkably, up to 90% of ruptures occur atraumatically, often provoked by routine physiological exertion or mild Valsalva maneuvers rather than blunt trauma. Clinical presentations vary across the lifespan: young children frequently exhibit subclinical or nonspecific symptoms, while adolescents and young adult males experience the highest incidence of rupture. Contrast-enhanced computed tomography remains the diagnostic reference standard in hemodynamically stable patients, whereas focused assessment with sonography for trauma (FAST) is critical during resuscitation of unstable individuals. Modern treatment paradigms prioritize organ preservation via nonoperative management (NOM) and splenic artery embolization (SAE) to mitigate the lifelong hazard of overwhelming post-splenectomy infection (OPSI). Most splenic ruptures manifest within the initial three weeks of symptom onset, though heightened vulnerability persists for up to eight weeks. Because baseline splenic dimensions do not reliably predict rupture risk, return-to-play clearance demands individualized shared decision-making rather than isolated imaging thresholds. Interdisciplinary collaboration is imperative to improve outcomes and guide evidence-based prevention across all ages.

**Keywords:** Epstein-Barr Virus; Splenic Rupture; Infectious Mononucleosis

**Abbreviations:** EBV: Epstein-Barr virus; IM: Infectious mononucleosis CD8+: Cluster of differentiation 8 positive; FAST: Focused assessment with sonography for trauma; CT: Computed tomography; DNA: Deoxyribonucleic acid; IgM: Immunoglobulin M; IgG: Immunoglobulin G; HIV: Human immunodeficiency virus; NOM: Nonoperative management; SAE: Splenic artery angioembolization; AAST: American Association for the Surgery of Trauma; OPSI: Overwhelming post-splenectomy infection; MenACWY: Meningococcal groups A, C, W, and Y; AMSSM: American Medical Society for Sports Medicine; AAP: American Academy of Pediatrics

## Introduction

Epstein-Barr virus (EBV), also designated human herpesvirus 4, is a gamma-herpesvirus and one of the most ubiquitous human pathogens, with more than 90% of adults worldwide demonstrating serologic evidence of prior infection [1]. Transmitted primarily through saliva and, less commonly, blood, the virus establishes lifelong latency in memory B lymphocytes following primary infection [2]. While most primary infections in infants and young children are asymptomatic or produce nonspecific illness, primary infection in adolescents and young adults frequently manifests as infectious mononucleosis (IM), the major clinical syndrome of symptomatic EBV disease [2,3]. The clinical symptoms of IM are largely immune-mediated, driven by a vigorous CD8<sup>+</sup> cytotoxic T-lymphocyte response directed against EBV-infected B cells, accompanied by elevated levels of pro-inflammatory cytokines [2].

Infectious mononucleosis classically presents with the triad of fever, pharyngitis, and posterior cervical lymphadenopathy, most often affecting individuals between 15 and 24 years of age [4]. Additional features may include profound fatigue, palatal petechiae, tonsillar exudate, periorbital edema, and hepatosplenomegaly, while laboratory evaluation frequently reveals atypical lymphocytosis and elevated hepatic aminotransferases [3,5]. Diagnosis is usually clinical, supported by a complete blood count with differential and a heterophile antibody test, with EBV-specific serology reserved for atypical or unconfirmed cases [4]. In the overwhelming majority of immunocompetent patients, IM is a benign, self-limiting illness with an excellent prognosis, and treatment remains supportive, as antivirals and corticosteroids are not routinely recommended [4,6].

Splenic involvement is an intrinsic feature of EBV mononucleosis rather than an incidental one. Splenomegaly is clinically detectable in a substantial proportion of patients and, when assessed by ultrasound, splenic enlargement can be demonstrated in essentially all cases, with the spleen commonly enlarging to three to four times its normal size [1]. Splenomegaly is reported in approximately half of patients with IM and typically begins to regress by the third week of illness [6]. The underlying pathology is instructive: dense lymphocytic infiltration stretches the splenic capsule, weakens the trabeculae, and expands the medullary volume, collectively increasing organ fragility, while progressive enlargement diminishes the protective coverage of the rib cage-together predisposing the spleen to rupture [1]. Against this background, splenic rupture stands out as the most feared complication of IM. Although it occurs in only an estimated 0.1% to 0.5% of cases, it is the most common cause of death attributable to EBV infection, with reported mortality figures ranging from roughly 5% to as high as 9% across case series [1,7,8]. The rarity of the event, coupled with its potentially catastrophic consequences, creates a clinical paradox: the complication is uncommon enough to be easily overlooked yet lethal enough that

a missed or delayed diagnosis can prove fatal. Notably, the risk of rupture does not correlate with the severity of the underlying mononucleosis, meaning that even mildly symptomatic patients remain vulnerable [1].

Of particular importance is the recognition that most cases of EBV-associated splenic rupture are atraumatic, or so-called spontaneous, occurring in the absence of any significant precipitating injury. Across systematic reviews, a preceding history of trauma is documented in only a small minority of cases-on the order of 9% to 14%-so that the great majority arise without an obvious mechanical inciting event, with everyday movements such as bending, turning in bed, or straining potentially sufficient to breach the friable capsule [1,7,8]. Because abdominal pain is the presenting complaint in the vast majority of these patients and may be the first indication of the diagnosis, clinicians must maintain a high index of suspicion for splenic rupture in any young patient with EBV infection and new abdominal symptoms, even without a history of trauma [1,7]. Failure to consider this entity risks misdiagnosis and delayed intervention. The temporal window of risk is also relevant: rupture typically occurs within the first three weeks of symptom onset-approximately 80% of cases-but has been documented up to eight weeks out, and injuries continue to occur beyond the traditionally cited three-week interval, informing ongoing debate about the appropriate duration of activity restriction and return-to-play guidance [7-9]. Contemporary management increasingly emphasizes splenic preservation through nonoperative approaches in hemodynamically stable patients, thereby avoiding the lifelong risk of post-splenectomy sepsis, a consideration that is especially pertinent in children [8,10].

This review adopts a multidisciplinary and lifespan perspective on EBV-induced splenic rupture, spanning the pediatric through adult populations. Although IM affects patients across age groups, its clinical expression differs substantially between children and adults-younger children more often experience nonspecific or subclinical infection and distinct complication profiles, whereas adolescents and young adult men appear to bear the highest burden of splenic rupture [5,7,11]. By integrating the virology, clinical presentation, epidemiology, diagnostic approach, and evolving surgical and nonoperative management of this complication across the age spectrum, this review aims to consolidate current evidence, highlight the diagnostic pitfalls of atraumatic rupture, and inform practical, age-appropriate strategies for recognition, risk stratification, and management from pediatrics to adulthood.

## Epidemiology and Pathophysiology

EBV is one of the most common viruses in humans, with more than 90% of adults worldwide having evidence of previous infection [12,13]. The age at primary infection varies according to geographic and socioeconomic factors. In settings characterized by crowded living conditions and lower

socioeconomic status, primary EBV infection is generally acquired earlier in childhood, whereas improved hygiene and higher socioeconomic conditions are associated with delayed acquisition into adolescence or young adulthood [15,16]. Consequently, the vast majority of adults eventually become EBV-seropositive [14]. The clinical manifestations of primary EBV infection vary with age at acquisition. In young children, primary infection is usually subclinical and therefore frequently goes unrecognized. In contrast, primary infection acquired during adolescence and young adulthood is more likely to manifest as infectious mononucleosis, with the incidence of clinically apparent disease peaking in adolescents and young adults [15,16].

Splenomegaly is a common manifestation of infectious mononucleosis, occurring in nearly half of affected patients. Although infectious mononucleosis is generally self-limiting, splenic rupture is a rare but potentially life-threatening complication, with a reported incidence of approximately 0.1–0.5%. Most cases of splenic rupture occur within the first three weeks of illness [17,18]. Splenic enlargement during EBV infection is thought to result from marked infiltration by lymphocytes and mononuclear cells within the splenic parenchyma. This cellular infiltration disrupts the normal splenic architecture, contributing to increased splenic volume and structural vulnerability, thereby predisposing the spleen to rupture [19]. Several mechanisms have been proposed to explain the progression from splenic enlargement to rupture, including elevated portal venous pressure and abrupt compression by diaphragmatic or abdominal wall contraction, which may increase mechanical stress on the splenic capsule and lead to spontaneous rupture [19]. Both traumatic and spontaneous splenic ruptures have been reported in athletes. However, among individuals with infectious mononucleosis, most splenic ruptures occur spontaneously rather than as a consequence of contact trauma [18].

### Clinical Presentation and Risk Factors

Abdominal pain is the most common presenting symptom of splenic rupture, accounting for approximately 88% of reported cases [20]. When localized, the pain is typically described in the left upper quadrant or upper abdomen and may be epigastric; referred left shoulder pain (Kehr sign) may also occur. Other manifestations of hemoperitoneum and peritoneal irritation include abdominal distension, rebound tenderness, and guarding [20]. Patients may have preceding symptoms of infectious mononucleosis, including sore throat, fever, fatigue, and malaise. Although splenomegaly is a characteristic feature of infectious mononucleosis-associated splenic injury, splenic rupture has been reported in patients whose spleen was normal in size on imaging, indicating that spleen size alone cannot reliably exclude the risk of rupture [20,24]. Bilateral periorbital or palpebral edema (Hoagman sign) is an uncommon but characteristic early manifestation of infectious mononucleosis and may be observed particularly in children and adolescents [23]. It may precede the more typical manifestations of fever,

pharyngitis, and cervical lymphadenopathy. Other manifestations of hemoperitoneum and peritoneal irritation include abdominal distension, rebound tenderness, and guarding [20].

Patients with significant splenic hemorrhage may develop features of hypovolemic or hemorrhagic shock, including tachycardia, hypotension, pallor, orthostasis, syncope, and diaphoresis. A declining hemoglobin or hematocrit, particularly when accompanied by abdominal pain or hemodynamic instability in a patient with infectious mononucleosis, should heighten suspicion for intra-abdominal hemorrhage and prompt appropriate imaging and/or resuscitation [25]. Importantly, splenic rupture can occur in the absence of recognized trauma. Indeed, most reported splenic injuries associated with infectious mononucleosis are atraumatic. In a systemic literature review of 186 cases of EBV-associated splenic rupture, only 17 of the cases (9.1%) had documented preceding trauma [22]. The inflamed and enlarged spleen may therefore rupture following relatively minor increases in intra-abdominal pressure or seemingly trivial or unrecognized trauma.

Reported risk factors include male sex, men under 30 years (with a mean of 22), participation in contact or high-intensity sports during acute illness, greater degrees of splenomegaly, and the early weeks of illness [20,21]. Although the risk is greatest during the first several weeks, it does not disappear immediately when systemic symptoms improve. A retrospective analysis of 42 cases of infectious mononucleosis-associated splenic injury reported a mean time to injury of  $15.4 \pm 13.5$  days. Approximately 73.8% of injuries occurred within 21 days and 90.5% within 31 days of symptom onset [21]. These findings are clinically important because they challenge the assumption that clinically significant splenic injuries are confined to the earliest phase of illness. Although most injuries occur within the first three weeks, clinical improvement does not necessarily indicate complete resolution of splenic vulnerability. The risk appears to decline progressively with time rather than disappearing abruptly. Approximately 9.5% of injuries in the retrospective series occurred after 31 days, and case reports have described rupture as late as eight weeks after symptom onset [20,21]. Consequently, while the absolute risk of splenic rupture decreases as infectious mononucleosis resolves, a patient who feels clinically better should not automatically be considered free of splenic risk.

### Pediatric, Adolescent, and Adult Considerations

The clinical behavior of Epstein-Barr virus (EBV) infection, and by extension the recognition of its splenic complications, varies substantially across the human lifespan, such that a diagnosis considered “classic” in one age group may be atypical, easily missed, or dangerously delayed in another. Understanding these age-dependent differences in presentation, diagnostic reliability, management priorities, and prognosis is essential to timely identification of infectious mononucleosis (IM) and its most feared complication, splenic rupture.

In young children, primary EBV infection is frequently asymptomatic, unrecognized, or clinically nonspecific, and the classic triad of fever, pharyngitis, and lymphadenopathy is often absent [1]. Infections in infants and young children are typically subclinical or mimic ordinary upper respiratory tract infections, which contributes to a high rate of misdiagnosis and missed diagnosis [26]. The insidious, complex, and varied clinical picture in children makes timely and accurate diagnosis particularly challenging [26]. Diagnostic testing is also less reliable in this group: the heterophile (Monospot) antibody test frequently yields false-negative results in children younger than four to five years because of an immature immune system, delayed IgM production, and interference from heterophile antibodies, so EBV-specific serology or EBV-DNA quantification is often required for confirmation [4,26]. Compounding the diagnostic difficulty, young children have limited ability to communicate or localize symptoms such as sore throat, fatigue, or abdominal discomfort, meaning that early warning signs of splenic involvement may go unreported. Notably, IM is a relatively common cause of sore throat in patients between 5 and 25 years of age but is uncommon in children younger than 5 years [27], and airway obstruction—rather than splenic rupture—is the most frequent cause of IM-related hospitalization in the pediatric population.

Adolescents and young adults, particularly those aged 15 to 24 years, experience the highest incidence of symptomatic IM and most reliably manifest the classic syndrome of fever, pharyngitis, and posterior cervical lymphadenopathy, with up to roughly 70% presenting with the symptomatic triad plus lymphocytosis [2,4,26]. The more robust and clinically more symptomatic-cytotoxic T-cell response seen in this age group, possibly related to a higher viral inoculum from close personal contact, explains why illness is more overt than in children [2]. This is also the population in which sports participation and return-to-play decisions dominate management, because splenomegaly is nearly universal early in illness and physical exertion or contact during this window raises the risk of splenic rupture. Current guidance recommends avoiding athletic activity for at least three weeks from symptom onset, with contact or collision sports and heavy exertion withheld for a minimum of three to four weeks [4,28]. Because physical examination and single-time-point imaging of the spleen have poor sensitivity and do not reliably correlate with rupture risk, return-to-sport decisions are individualized through shared decision-making that weighs the athlete's age, sport, timing within the season, symptom resolution, and psychological readiness [28,29].

Young adults share the typical, well-defined presentation of the adolescent group and represent the demographic in which most reported cases of atraumatic splenic rupture occur; in a systematic review of IM-associated splenic complications, the mean age of affected patients was approximately 22 years, and the majority of ruptures were spontaneous and atraumatic [8].

Physical activity considerations therefore remain central in this group, as the same three-week window of heightened rupture risk applies, with roughly 80% of ruptures occurring within three weeks of symptom onset [8]. As in adolescents, management centers on supportive care, counseling on activity restriction, and specific guidance about symptoms that may herald splenic rupture rather than blanket advice to simply rest.

In older adults, IM is uncommon because of near-universal prior EBV exposure, and when it does occur it frequently presents atypically, broadening the differential diagnosis and increasing the risk of diagnostic delay [30]. Older patients are more likely to present without the hallmark lymphadenopathy, pharyngitis, splenomegaly, or atypical lymphocytosis and instead show fever, jaundice, and hepatomegaly, which can mimic lymphoma, leukemia, biliary obstruction, or fever of unknown origin [31]. Diagnostic closure is a particular hazard in this group: severe fatigue, thrombocytopenia, elevated liver enzymes, and atypical lymphocytosis in an older patient should prompt consideration of IM and immunologic confirmation with EBV-DNA quantification and EBV-specific serology even when the presentation is not classic [30]. Older adults are also more prone to a severe or complicated disease course and clinical decompensation, underscoring the importance of maintaining IM in the differential across the full age spectrum [30].

Taken together, these age-related patterns highlight clinically important differences in diagnosis, management, and prognosis. Diagnostically, heterophile testing is least reliable at the extremes of age—falsely negative in young children and confounded by atypical presentations and comorbidity in older adults—so serologic and molecular testing carry greater weight in these groups [27,32]. From a management standpoint, activity restriction and return-to-play counseling are the defining concern in adolescents and young adults, whereas prompt diagnostic vigilance and a broad differential are the priorities in children and older adults. Prognostically, most patients across all ages recover fully, but young children face the greatest risk of airway obstruction, adolescents and young adults bear the highest absolute burden of splenic rupture, and older adults are at elevated risk of severe, complicated disease. A lifespan-oriented awareness of these distinctions is therefore critical to recognizing EBV-induced splenic rupture wherever it occurs along the age continuum.

## Diagnosis and Imaging

The diagnostic approach to suspected splenic rupture in infectious mononucleosis begins at the bedside, where the first and most consequential determination is hemodynamic stability. Because the spleen is highly vascular and mononucleosis-associated rupture is frequently atraumatic, patients may present anywhere along a spectrum from mild left upper quadrant discomfort to frank hemorrhagic shock, and the initial evaluation should prioritize vital signs, evidence of ongoing blood

loss, and peritoneal signs [33]. Any patient with worsening or acute abdominal pain in the setting of confirmed or suspected mononucleosis-particularly pain radiating to the left shoulder (Kehr sign) or accompanied by hypotension and tachycardia-must be assumed to have a splenic injury until proven otherwise [1,4,34]. The presence of hemodynamic instability or peritonitis fundamentally changes the diagnostic pathway, shifting the emphasis away from detailed imaging and toward immediate resuscitation and surgical evaluation [33,34]. Approximately 80% of mononucleosis-associated ruptures occur within three weeks of symptom onset, so a recent or concurrent diagnosis of mononucleosis should heighten clinical suspicion in the appropriate window [8].

Laboratory evaluation serves two purposes: confirming the underlying diagnosis of EBV mononucleosis and characterizing the severity of hemorrhage. A complete blood count with differential is central to both, typically demonstrating lymphocytosis with greater than 40% lymphocytes and more than 10% atypical lymphocytes, alongside the leukocytosis characteristic of primary EBV infection [4,32,35]. Serial hemoglobin and hematocrit measurements are the most important laboratory parameters for detecting and monitoring intra-abdominal hemorrhage; a progressive decline in hemoglobin, rather than a single value, signals ongoing bleeding and may prompt transfusion or escalation of care [1]. Elevated hepatic aminotransferases are common in mononucleosis and, in the setting of a negative heterophile antibody test, increase clinical suspicion for the diagnosis [4,5]. Confirmation of EBV can be pursued with a rapid heterophile (Monospot) antibody test, though false-negative results occur in roughly 10% of patients and are especially common in young children and during the first week of illness; EBV-specific viral capsid antigen IgM and IgG serology provides greater sensitivity and specificity when the heterophile test is negative but suspicion remains high [4,32]. Coagulation studies, including prothrombin time, activated partial thromboplastin time, fibrinogen, and platelet count, are important in any patient with suspected active hemorrhage, both to identify a coagulopathy that may aggravate bleeding-thrombocytopenia is itself a recognized hematologic complication of mononucleosis-and to guide correction before any operative or interventional procedure [5,35].

Ultrasound is often the first imaging modality employed because it is rapid, portable, radiation-free, and can be performed at the bedside in an unstable patient. It reliably detects and characterizes splenomegaly and can identify free intraperitoneal fluid, making it well suited to the focused assessment with sonography for trauma (FAST) examination in the hemodynamically unstable patient [4,36,37]. On ultrasound, splenic laceration and subcapsular hematoma appear as an inhomogeneous splenic texture with irregular hypoechoic or hyperechoic areas, and free abdominal fluid with internal echoes is typical of hemoperitoneum

[36]. However, ultrasound has important limitations: because splenomegaly occurs in nearly all patients with mononucleosis, an enlarged spleen alone is nonspecific, and conventional B-mode ultrasound has relatively low sensitivity for detecting the parenchymal injury itself [4,36]. Contrast-enhanced ultrasound substantially improves accuracy-approaching that of CT in some series-and can identify active bleeding, pseudoaneurysms, and the extent of laceration in stable patients, but it is operator-dependent and not universally available [37].

In the hemodynamically stable patient, contrast-enhanced CT of the abdomen and pelvis is the preferred imaging modality and the reference standard for diagnosing splenic injury [4,33,34]. CT allows precise grading of the injury, characterization of subcapsular versus parenchymal hematoma, quantification of hemoperitoneum, and-critically-identification of active contrast extravasation ("blush") or contained vascular injury, findings that directly influence whether nonoperative management, angioembolization, or surgery is pursued [34]. CT also enables evaluation for alternative or coexisting splenic pathology such as infarction, which appears as a wedge-shaped, non-enhancing, typically subcapsular defect [38]. The imaging findings most suggestive of splenic rupture include splenomegaly with loss of capsular integrity, an irregular or rough splenic contour, a subcapsular or perisplenic hematoma, and perisplenic and pelvic free fluid consistent with hemoperitoneum [36-39]. On contrast-enhanced CT, a laceration appears as a linear or branching non-enhancing defect, and active hemorrhage manifests as extravasation of contrast material; weakened or heterogeneous parenchymal enhancement may accompany these findings [38,39]. In reported EBV cases, CT has demonstrated diminished splenic parenchymal enhancement, a rough splenic outer edge, and perisplenic and pelvic hematomas, with ultrasound confirming splenic laceration, subcapsular hematoma, and peritoneal effusion [1]. The distribution of free fluid-perisplenic, in the paracolic gutters, and in the pelvis-helps estimate the volume of hemoperitoneum and the acuity of bleeding [39].

In the hemodynamically unstable patient, imaging must never delay definitive treatment. Patients with hemodynamic instability and evidence of intraperitoneal hemorrhage, or with peritonitis, warrant immediate resuscitation and prompt surgical intervention rather than transfer for CT [33,34]. In this setting, a bedside FAST examination confirming free intraperitoneal fluid is sufficient to justify proceeding directly to the operating room, and time spent obtaining cross-sectional imaging in a decompensating patient may be fatal [34,37]. CT and detailed characterization are reserved for patients who are stable or who stabilize with resuscitation and are being considered for nonoperative or angiographic management [33,34].

The differential diagnosis of acute left upper quadrant pain and abdominal hemorrhage in a patient with mononucleosis

includes splenic infarction, which-unlike rupture-typically occurs in patients with an underlying hematologic condition and appears as a wedge-shaped non-enhancing lesion without significant hemoperitoneum [8,38]. Other considerations include EBV-associated splenic pathology such as inflammatory pseudotumor and EBV-related lymphoproliferative disease or lymphoma, particularly in immunocompromised patients or when focal splenic lesions are present [38]. Non-EBV causes of atraumatic splenic rupture and spontaneous intra-abdominal hemorrhage-including other infections, hematologic malignancies, sickle cell disease, anticoagulation, and ruptured splenic cysts or neoplasms-should also be weighed, since the imaging appearance of subcapsular hematoma or hemoperitoneum is not specific to EBV [38,39]. Finally, the broader differential for the underlying viral syndrome itself includes cytomegalovirus, acute HIV infection, toxoplasmosis, and streptococcal pharyngitis, which is relevant when the diagnosis of mononucleosis has not yet been established [4,38].

### Management and Outcomes

The management of Epstein-Barr virus (EBV)-associated splenic rupture begins with rapid assessment of hemodynamic status, because the initial physiologic response to intraperitoneal hemorrhage dictates the entire treatment pathway. Patients should be approached according to standard trauma-resuscitation principles: two large-bore intravenous catheters, crystalloid and balanced blood-product resuscitation, serial measurement of hemoglobin and hematocrit, and continuous monitoring of pulse pressure, heart rate, and peripheral oxygen saturation [33]. In hemodynamically normal patients, this stabilization creates the window in which contrast-enhanced computed tomography (CT) can grade the injury and identify active bleeding, whereas in patients who remain unstable despite resuscitation, ongoing hemorrhage mandates immediate operative control rather than further imaging [33]. Because atraumatic ruptures in mononucleosis tend to present with higher-grade lacerations than blunt traumatic injuries, a lower threshold for escalation is prudent, and interdisciplinary evaluation-emergency medicine, surgery, and interventional radiology-should be engaged early [38].

Conservative, or nonoperative, management (NOM) has become the preferred strategy in the hemodynamically stable patient, mirroring the paradigm shift that has occurred in blunt traumatic splenic injury. NOM is appropriate for patients who respond to and maintain stability after resuscitation, who lack peritonitis, and in whom serial hemoglobin measurements and vital signs remain reassuring; it entails admission to a monitored or intensive-care setting, serial abdominal examinations, laboratory surveillance, activity restriction, and readiness to convert to intervention should deterioration occur [8,39]. In blunt splenic trauma, NOM succeeds in 80% to 95% of carefully selected patients across all injury grades [40]. Outcomes in atraumatic rupture are more guarded: because these spleens are diffusely

diseased and lacerations are often higher grade, the clinical success rate of conservative management is lower (approximately 75% versus 94.5% in traumatic injury) and the conversion-to-surgery rate is higher, underscoring the need for vigilant monitoring and early reassessment [38].

Splenic artery angioembolization (SAE) is an important adjunct that can extend splenic salvage in hemodynamically stable patients with evidence of ongoing arterial bleeding. Contemporary guidance recommends SAE as a first-line adjunct when a contrast blush, pseudoaneurysm, arteriovenous fistula, or other vascular injury is identified on CT, and in high-grade injuries even absent a demonstrable blush, provided the patient is stable and institutional expertise is available [41,42]. Meta-analytic data in blunt injury show that SAE significantly reduces NOM failure in high-grade (AAST grade IV-V) injuries but adds little benefit in grade I-III injuries, and that proximal and distal embolization are broadly equivalent in efficacy [42,43]. The role of embolization has grown over time, and in contemporary series of spontaneous splenic rupture, angioembolization now accounts for roughly 11% of treatments as splenectomy rates have correspondingly declined [44]. In atraumatic injury specifically, the clinical success rate of SAE is somewhat lower than in trauma (approximately 87% versus 97%), again reflecting the underlying splenic pathology [38].

Surgical intervention remains indicated when the patient is hemodynamically unstable, when there is diffuse peritonitis, or when NOM or embolization fails with continued bleeding or physiologic deterioration [33,40]. In these settings, the priority is rapid hemorrhage control, and total splenectomy is frequently the definitive procedure. Historically, some authors advocated emergent splenectomy for all mononucleosis-associated ruptures given the unpredictability of the diseased spleen [4]. The modern goal, however, is to preserve splenic tissue whenever the patient's physiology permits, thereby avoiding the lifelong risk of post-splenectomy infection [8,39]. In the EBV-specific literature, the likelihood of splenectomy correlates with rupture severity: in the largest systematic review, splenectomy was performed in 84% of cases with a severe World Society of Emergency Surgery score versus 58% of moderate or minor cases [8]. Spleen-preserving operations such as splenorrhaphy are technically possible but are performed in only a small minority of spontaneous ruptures [44].

Management differs meaningfully between children and adults, driven largely by the disproportionate risk of overwhelming post-splenectomy infection (OPSI) in young patients. In the pediatric population, nonoperative management is favored even more strongly, and successful conservative treatment of spontaneous mononucleosis-associated rupture in hemodynamically stable children and adolescents has been well documented [39]. Notably, embolization has not been shown to be efficacious in children and is generally reserved for those with demonstrated ongoing bleeding and a vascular blush on CT, so pediatric management relies more heavily on observation and, when necessary, spleen-preserving surgery [41]. Adults tolerate splenectomy with lower

absolute OPSI risk, but the contemporary emphasis on salvage applies across all ages, and advanced age (over 50–55 years) and neoplastic etiology are independently associated with higher mortality, warranting a more cautious approach in older patients [38,44].

Complications and mortality remain clinically significant despite the rarity of the event. Splenic injury complicates only 0.1% to 0.2% of infectious mononucleosis cases, but reported mortality from mononucleosis-associated rupture ranges up to about 5% to 9% across systematic reviews, and splenic rupture is the most common cause of death in infectious mononucleosis [1,7,8,45]. Approximately 80% of ruptures are atraumatic, and most occur within three weeks of symptom onset (about 74% by day 21, 90% by day 31), although ruptures have been described up to eight weeks after illness onset [1,7,45]. In broader spontaneous-rupture cohorts, overall mortality is approximately 8.7% and has decreased over time in parallel with declining splenectomy rates and increasing use of embolization [44]. Delay in recognition is a principal driver of adverse outcome, so patients with mononucleosis should be explicitly counseled about the warning symptoms of rupture—sudden abdominal or left shoulder-tip pain, dizziness, and syncope—rather than being given activity restriction alone [45,46].

When splenectomy cannot be avoided, structured post-splenectomy care is essential to prevent OPSI, which carries lifelong risk and can occur decades after surgery [47]. Prevention rests on three pillars: immunization, antibiotic prophylaxis, and patient education [15]. Vaccination should cover the encapsulated organisms responsible for fulminant sepsis—*Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b—together with annual inactivated influenza vaccine [47–49]. In the emergency (unplanned) splenectomy that characterizes traumatic rupture, vaccines should be administered at least two weeks after surgery to optimize the antibody response, whereas in any elective setting they are given at least two weeks (ideally four to six weeks) beforehand [48,49]. Pneumococcal protection uses a conjugate vaccine followed by the polysaccharide vaccine with appropriate boosters, and both quadrivalent (MenACWY) and serogroup B meningococcal vaccines are recommended; the live attenuated influenza vaccine is contraindicated in asplenic patients [47–49]. Antibiotic prophylaxis is directed at the highest-risk periods—young children, the interval shortly after splenectomy, and immunocompromised patients—and all patients require durable education, ideally reinforced through dedicated asplenia clinics or care pathways that have been shown to improve vaccine coverage and reduce infection [47].

Reported outcomes from the published case literature support these principles. Pooled analyses of mononucleosis-associated rupture describe a predominantly young, male population (mean age approximately 22 years, 60% to 70% male), with abdominal pain as the near-universal presenting symptom and a preceding

history of trauma in only 9% to 14% of cases [1,8]. Across the historical case literature, roughly one-third of patients were managed nonoperatively and two-thirds underwent splenectomy, though this balance continues to shift toward splenic preservation and embolization in more recent series [1,44]. Individual reports, including contemporary cases of spontaneous atraumatic rupture, reinforce that early recognition and prompt, physiology-guided treatment are the principal determinants of survival [46].

### Prevention, Activity Restriction, and Return to Play

The rationale for restricting physical activity during acute EBV infectious mononucleosis rests on the near-universal splenic enlargement that accompanies the illness. Some degree of splenomegaly develops in essentially all patients within days of symptom onset, with rapid early enlargement peaking approximately 1 to 3 weeks later [28]. The enlarged spleen extends below the protective rib cage, becomes more friable, and is therefore vulnerable to rupture from even minor increases in intra-abdominal pressure or direct impact—the feared complication that drives all activity-restriction recommendations [8,28]. Because physical examination has poor sensitivity and specificity for detecting relative splenomegaly, and because virtually all patients have some enlargement regardless of examination findings, restriction is applied empirically to all patients rather than being reserved for those with a palpable spleen [28,50].

The principal danger is splenic rupture during contact or collision sports and strenuous exertion, an event estimated to complicate roughly 0.1% to 0.5% of mononucleosis cases, although the true incidence is likely lower given that many infections are subclinical or under-reported [1,28]. Notably, most ruptures are atraumatic rather than the result of an identifiable blow: in a systematic review of 85 cases, approximately 86% were spontaneous, and in a military retrospective series roughly 80% were atraumatic, underscoring that ordinary exertion, Valsalva maneuvers, and even routine activity—not only collision—can precipitate rupture [1,28]. Splenic rupture is the most common cause of death in mononucleosis, with reported mortality around 9% in one case-based systematic review, which is why counseling and restriction are emphasized despite the rarity of the event [1,28].

Current recommendations converge on avoiding strenuous activity and contact/collision sports for a minimum period after symptom onset, though the exact thresholds differ by society. The American Medical Society for Sports Medicine (AMSSM) recommends that athletes may begin a trial of supervised, nonimpact, low-intensity aerobic activity as early as 2 weeks from symptom onset if they are afebrile with adequate energy and an improving clinical examination, while contact and collision sports should be avoided for at least 3 to 4 weeks from symptom onset given the risk of splenic rupture [28]. The American Academy of Pediatrics Red Book advises avoiding strenuous

activity and contact sports for at least 21 days after symptom onset, permitting limited noncontact aerobic activity thereafter if the patient is asymptomatic without overt splenomegaly, and reserving clearance for contact sports until 4 to 7 weeks after symptom onset [1]. The American Academy of Family Physicians rapid review similarly recommends no athletic activity for three weeks following symptom onset, beginning with light noncontact exercise and returning only when the patient feels clinically well and is afebrile [9]. Across all guidelines, the return-to-play decision is explicitly individualized and grounded in shared decision-making between clinician, athlete, and family, accounting for the sport's contact risk, the athlete's age, timing within the competitive season, and psychological readiness [5,28].

Evidence on the duration of splenic vulnerability supports these windows but also raises concern that the traditional 3-week cutoff may be too short. Ultrasonographic natural-history data show that peak splenic enlargement is reached at a mean of about 12 days (range 6–23 days) after symptom onset, after which spleen size decreases at a fairly predictable rate of roughly 1% per day, with resolution in most athletes by 4 to 6 weeks [4,28]. A military retrospective series of 42 laboratory-confirmed cases found a mean time from symptom onset to splenic injury of 15.4 days, but only 73.8% of injuries occurred within 21 days and 90.5% within 31 days—leading the authors to suggest extending restriction to 31 days [1]. Ruptures have been reported beyond even this window, and some authors, citing a maximum reported interval of up to 8 weeks, argue that vigorous activity should be avoided for no less than 8 weeks [1,50]. This spread of estimates is the central source of guideline discordance: recommendations range from 21 days to 4 weeks to as long as 7–8 weeks depending on the source and the weight given to late ruptures.

The role of follow-up ultrasound in clearing patients for return is limited and contested. Because normal splenic dimensions vary widely across individuals—and because a substantial proportion of tall collegiate athletes have baseline splenic lengths that would be classified as “enlarged” by standard thresholds—a single spleen measurement at one time point is unreliable and can lead to both under- and over-diagnosis of splenomegaly. There is also no established correlation between spleen size and the risk of rupture, so a “normal” measurement does not guarantee safety [28]. Routine imaging is therefore not recommended in the uncomplicated athlete; when imaging is pursued, serial ultrasound to document a decreasing or stable spleen size is more meaningful than an isolated reading, particularly for an athlete considering early return before the 3-to-4-week mark, whereas CT is preferred when actual splenic injury or rupture is suspected. Guidelines note that imaging can raise costs without proven improvement in patient-oriented outcomes [1,28].

Patient counseling should be explicit rather than a generic instruction to “take it easy.” Patients—and, for minors, their parents and coaches—must be educated about the probability and time course of splenic rupture, advised to avoid maneuvers that

compress or strain the abdomen (heavy lifting, straining, Valsalva), and counseled to prevent constipation and to use caution with medications such as aspirin that may promote bleeding. Critically, patients should be taught the warning signs that warrant immediate emergency evaluation: sudden or severe left upper quadrant or diffuse abdominal pain, left shoulder pain (Kehr sign) from diaphragmatic irritation, lightheadedness, syncope, or other signs of hemodynamic compromise. Because rupture is frequently atraumatic and the diagnosis of mononucleosis is often made only after the rupture in athletes, clear anticipatory guidance about these red-flag symptoms is as important as the activity restriction itself [4,28,51].

### Multidisciplinary Perspective and Current Knowledge Gaps

EBV-associated splenic rupture sits at the intersection of numerous specialties, and its optimal recognition and management depend on coordinated, multidisciplinary care that spans the entire patient trajectory from initial diagnosis to definitive treatment and long-term follow-up. Pediatrics occupies a central role because infectious mononucleosis is the most common symptomatic presentation of primary EBV infection, and children frequently present with unrecognized or nonspecific illness; the pediatrician must therefore maintain awareness of hematologic complications such as splenic rupture and counsel families on activity restriction, as codified in the American Academy of Pediatrics Red Book [5]. Emergency medicine is often the point of first contact when rupture occurs, since these patients may present acutely with abdominal pain, hemodynamic instability, or shock; rapid recognition, resuscitation, and triage of the unstable patient are the domain of the emergency clinician [52]. Internal medicine and family medicine clinicians manage the majority of uncomplicated infectious mononucleosis cases, provide supportive care, and are responsible for the counseling and follow-up that reduce the risk of catastrophic complications, as emphasized in family medicine rapid reviews and splenomegaly management guidance [4,50].

Infectious diseases expertise underpins the accurate diagnosis of primary EBV infection and the distinction of infectious mononucleosis from other causes of splenomegaly and febrile illness, as well as the recognition of the broader spectrum of severe EBV complications [4]. Radiology provides the imaging that confirms splenic injury and hemoperitoneum, with CT preferred when actual rupture is suspected and ultrasound reserved for selected situations, though the discipline also defines the important limitations of imaging in this setting [50]. Surgery—including trauma and acute care surgery—delivers definitive management when rupture occurs, weighing splenic preservation against splenectomy; the contemporary shift toward spleen-conserving strategies, including nonoperative management and angioembolization, reflects the goal of eliminating the risk of post-splenectomy sepsis [50]. Finally, sports medicine integrates all of these considerations into the return-to-play decision, applying

shared decision-making that balances the athlete's clinical status, the sport's contact risk, and the unpredictable risk of rupture; the American Medical Society for Sports Medicine explicitly describes itself as a multidisciplinary organization whose members bridge primary care and athlete care in exactly this way [28].

Despite this breadth of involvement, the current evidence base is strikingly limited. The literature is dominated by case reports, retrospective case series, and systematic reviews of those cases rather than prospective, controlled data; the largest systematic review identified 186 cases of rupture accumulated across more than 50 years of publications, and the most-cited timing data derive from a single retrospective military chart review of 42 patients [8,50]. There are no well-designed, large clinical trials to guide sports medicine providers in return-to-sport decisions, a gap the AMSSM itself acknowledges [28]. This reliance on retrospective and case-based evidence introduces publication and selection bias and limits the ability to generate reliable incidence estimates—indeed, the frequently cited rupture risk of 0.1% to 0.5% is likely an overestimate given that infectious mononucleosis is often subclinical or under-reported [28].

Predictors of which patients will rupture remain poorly defined. There is no established correlation between the severity of infectious mononucleosis and the risk of rupture, and no demonstrated relationship between absolute splenic size and rupture risk, which undermines the use of a single imaging measurement to stratify risk [6,50]. The wide inter-individual variability of normal splenic dimensions further confounds attempts to identify a threshold above which rupture becomes likely [50]. The duration of splenic vulnerability is similarly uncertain. While most ruptures occur within the first three weeks, the retrospective military data showed that only 73.8% occurred within 21 days and 90.5% within 31 days, and ruptures have been reported as late as 7 to 8 weeks after symptom onset—prompting some authors to argue for extending restriction well beyond the traditional window [4,8,9]. These uncertainties translate directly into a lack of standardized return-to-play recommendations. Guidance ranges from the AAP's advice to avoid contact sports for 4 to 7 weeks, to the AMSSM's recommendation of at least 3 to 4 weeks with individualized shared decision-making, to proposals to extend restriction to 31 days or longer—reflecting genuine, unresolved disagreement rather than a settled standard [5,8,28]. The role of imaging in clearance likewise remains contested, with serial ultrasound offered only as an option of uncertain value for athletes considering early return [50].

Priorities for future research follow directly from these gaps. The AMSSM has specifically called for studies establishing whether changes in relative spleen size correlate with rupture risk, whether earlier return to sport is safe in the clinically well athlete, and how to advance evaluation and treatment toward positive patient-oriented outcomes, as well as addressing health

inequities in access to diagnosis and care [1]. Beyond these, prospective multicenter registries capturing the true incidence of rupture, validated risk-stratification tools, prospective data defining the actual duration of splenic vulnerability across age groups, and comparative studies of nonoperative management, embolization, and splenectomy are all needed to move the field beyond its current dependence on retrospective and anecdotal evidence [8,50,52].

## Conclusion

EBV-induced splenic rupture represents a rare yet perilous clinical paradox: it is an uncommon occurrence that carries disproportionately high mortality, frequently arising atraumatically and independently of underlying mononucleosis severity. As demonstrated across the human lifespan, clinical presentation and diagnostic reliability differ fundamentally among young children, competitive adolescent athletes, and older adults. Optimal patient outcomes hinge on an integrated, multidisciplinary pathway uniting emergency physicians, internists, pediatricians, radiologists, trauma surgeons, and sports medicine specialists. Over recent decades, management paradigms have successfully shifted away from universal surgical ablation toward physiology-guided organ salvage through nonoperative observation and transcatheter arterial embolization, significantly diminishing the lifelong burden of overwhelming post-splenectomy infection. Nevertheless, critical knowledge gaps remain regarding the true incidence of rupture, the precise temporal window of structural splenic vulnerability, and the utility of serial sonographic clearance. Expanding prospective, multicenter registries and validating objective risk-stratification metrics will be vital to moving return-to-play guidance and clinical management beyond retrospective observation into definitive, evidence-based care.

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