The Rational Clinical Examination

Does This Patient Have Infectious Mononucleosis?
The Rational Clinical Examination Systematic Review

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IMPORTANCE Early, accurate diagnosis of infectious mononucleosis can help clinicians target treatment, avoid antibiotics, and provide an accurate prognosis.

OBJECTIVE To systematically review the literature regarding the value of the clinical examination and white blood cell count for the diagnosis of mononucleosis.

DATA SOURCES The databases of PubMed (from 1966-2016) and EMBASE (from 1947-2015) were searched and a total of 670 articles and abstracts were reviewed for eligibility.

STUDY SELECTION Eleven studies were included that reported data sufficient to calculate sensitivity, specificity, or both for clinical examination findings and white blood cell count parameters compared with a valid reference standard.

DATA EXTRACTION AND SYNTHESIS Data were abstracted from each article by at least 2 reviewers, with discrepancies reconciled by consensus. Clinical findings evaluated in only 1 study are reported with sensitivity, specificity, likelihood ratio (LR), and 95% confidence interval, which were calculated from the available data. Findings evaluated in only 2 studies were summarized with their range, findings evaluated in 3 studies were summarized with a univariate random-effects summary, and findings evaluated in 4 or more studies were summarized with a bivariate random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Sensitivity, specificity, and LRs for the diagnosis of mononucleosis.

RESULTS Mononucleosis is most commonly present among patients aged 5 to 25 years (especially those aged 16-20 years, among whom approximately 1 in 13 patients presenting with sore throat has mononucleosis). The likelihood of mononucleosis is reduced with the absence of any lymphadenopathy (summary sensitivity, 0.91; positive LR range, 0.23-0.44), whereas the likelihood increases with the presence of posterior cervical adenopathy (summary specificity, 0.87; positive LR, 3.1 [95% CI, 1.6-5.9]), inguinal or axillary adenopathy (specificity range, 0.82-0.91; positive LR range, 3.0-3.1), palatine petechiae (specificity, 0.95; positive LR, 5.3 [95% CI, 2.1-13]), and splenomegaly (specificity range, 0.71-0.99; positive LR range, 1.9-6.6). Symptoms are of limited value for the diagnosis of mononucleosis; sore throat and fatigue are sensitive (range, 0.81-0.83) but nonspecific. The presence of atypical lymphocytosis significantly increases the likelihood of mononucleosis (summary LR, 11.4 [95% CI, 2.7-35] for atypical lymphocytes ≥10%, 26 [95% CI, 9.6-68] for those with 20%, and 50 [95% CI, 38-64] for those with 40%). The combination of a patient having greater than 50% lymphocytes and greater than 10% atypical lymphocytes also is useful (specificity, 0.99; positive LR, 54 [95% CI, 8.4-189]).

CONCLUSIONS AND RELEVANCE In adolescent and adult patients presenting with sore throat, the presence of posterior cervical, inguinal or axillary adenopathy, palatine petechiae, splenomegaly, or atypical lymphocytosis is associated with an increased likelihood of mononucleosis.

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Clinical Scenario

A 17-year-old boy presents with 5 days of sore throat and adenopathy. The patient has a measured oral temperature of 38.6°C and a mild, persistent headache but denies having significant fatigue. He has purulent tonsils bilaterally, enlarged anterior and posterior cervical nodes, and several axillary nodes. There is no evidence of hepatomegaly or splenomegaly. A rapid test for group A β-hemolytic streptococcal bacteria is negative. An automated office laboratory test reveals a white blood cell (WBC) count of 18 × 10^9/L and WBC differential counts of 40% for segmented neutrophils, 51% for lymphocytes, 12% for atypical lymphocytes, 4% for monocytes, and 3% for eosinophils. A rapid heterophile antibody test (mononuclear spot test) for infectious mononucleosis was negative. Does this patient have infectious mononucleosis despite the negative result on the mononuclear spot test?

Why Is This Question Important?

Initially described as a "mononuclear leukocytosis in reaction to acute infection (infectious mononucleosis),"[1] it was also formerly called glandular fever. Infectious mononucleosis is caused by the Epstein-Barr virus (EBV) and is characterized by fever, sore throat, adenopathy, and malaise.[2] Splenomegaly, jaundice, and hepatomegaly may occur. Symptoms may persist for 6 months or longer, and serious complications, such as splenic rupture, rarely occur.[3] The differential diagnosis includes cytomegalovirus infection, toxoplasmosis, adenovirus infection, human immunodeficiency virus infection, and acute leukemia, although all of these are much less common. Being able to accurately diagnose mononucleosis in the outpatient setting using the clinical examination and office-based laboratory tests is important because it will allow physicians to better advise patients regarding limits on activity and overall prognosis, and might avoid inappropriate use of antibiotics for this viral disease. This is especially true early during the course of the illness when antibody tests for mononucleosis are more likely to produce false-negative results, and in younger children in whom false-negative results are more common.[4-6]

Infectious mononucleosis typically occurs in children and young adults aged 5 to 25 years, but is not limited to this age group. Rates of infections are highest among those aged 15 to 24 years with about 6 to 8 cases/1000 persons per year.[7] The disease is uncommonly diagnosed in infants and young children, although most cases probably go undetected because symptoms are generally milder in this age group (age <5 years).[7] It is most commonly diagnosed in adolescents and young adults,[8-10] especially those in communal living situations, such as military barracks.[11] Additional evidence comes from a population-based study[12] conducted in Rochester, Minnesota, that identified all serologically confirmed cases of mononucleosis between 1950 and 1969. The annual incidence of mononucleosis for persons aged 15 to 19 years living in that community[12] was 2.7%, among those aged 20 to 24 years it was 1.3%, and among all other age groups it was 0.2% or lower. There was no clear seasonal variation with 24% of cases occurring during winter, 23% during spring, 26% during summer, and 26% during fall.[12] Even though these rates of infections apply to a particular population of patients,[12] they do not represent the prevalence of disease among all patients with symptoms.

An Australian study[13] of patients treated in a primary care network reported that the annual incidence of mononucleosis was highest among those aged 16 to 20 years (14.3 episodes/1000 persons per year). A proportion of all episodes of sore throat was caused by mononucleosis (2.1% among those aged 5-15 years; 7.9%, aged 16-20 years; 3.2%, aged 21-25 years; and 1.7%, aged 26-35 years).[13] In all other age groups, 1% or fewer of patients presenting with sore throat were diagnosed as having mononucleosis.[13]

How to Examine a Patient for Infectious Mononucleosis

Signs and Symptoms

The history of a patient with sore throat should include the onset, duration, and presence or absence of fever, chills, sweats, myalgias, and fatigue, which cannot be explained by sleep deficit or usual activities. Often this presentation will prompt consideration for infectious mononucleosis. Patients with these signs and symptoms also should be asked about close contact with a person who received a confirmed diagnosis of mononucleosis; however, many will not recall such contact.

Inspect the face and exposed body surfaces for evidence of rash. A fine maculopapular rash (viral exanthem) may be present. Patients with mononucleosis who have been treated with a β-lactam, especially ampicillin or amoxicillin, may have a pruritic, morbilliform rash occurring within days to 1 week. A study of 173 children with serologically confirmed mononucleosis[14] found this hypersensitivity rash in 30% of patients who had received at least 1 dose of amoxicillin. However, another study of 184 children[15] found that the incidence of rash was similar between patients who did and did not receive a penicillin derivative. Jaundice is an uncommon finding in patients with mononucleosis.

Examine the patient for adenopathy in the anterior and posterior cervical chains. Almost all patients with mononucleosis have anterior cervical adenopathy, but this location is nonspecific and occurs in other common conditions as well. Posterior cervical adenopathy is more specific for mononucleosis, as are axillary and inguinal adenopathy. Therefore, these regions should be palpated if symptoms persist or remain unexplained, or if more serious alternative diagnoses, such as lymphoma, are being considered. Evaluate the pharynx for tonsillar enlargement, palatine petechiae, and pharyngeal and tonsillar exudates. Even though mononucleosis can cause these symptoms, they can also be caused by viral or group A β-hemolytic streptococcal pharyngitis. In addition, examine the patient's abdomen for splenomegaly or hepatomegaly.[16,17]

WBC Count

The WBC count can be a useful adjunct to the history and physical examination in the outpatient setting, and can be abnormal in patients with mononucleosis before antibody-based rapid tests, such as the heterophile test (mononuclear spot), yield positive test results. The EBV infects B lymphocytes, which leads to activation of a T-cell–mediated response. These cells are often immature and atypically formed. Thus, increases in the total number of

lymphocytes, the percentage of WBCs that are lymphocytes, and the percentage that are atypical lymphocytes are suggestive of mononucleosis.

Methods

Search Strategy

We conducted a systematic review of studies published between 1945 and August 2015 that reported data regarding the accuracy of symptoms, signs, or WBC count among patients with either a sore throat, or those for whom the clinical presentation prompted testing for infectious mononucleosis. We searched the Database of Abstracts of Reviews of Effectiveness using the search term *mononucleosis* and found no previous systematic reviews of diagnosis. Next, we searched PubMed (from 1966-February 10, 2016) using a broad strategy for diagnostic accuracy studies with the search terms *mononucleosis* AND (*specificity* or *predictive value* or *likelihood ratio* or *sensitivity* or *accuracy*), limited to studies with an abstract and conducted in humans. We also searched EMBASE (from 1947-2015) using a similar strategy.

The PubMed search returned 339 abstracts, of which 69 were deemed potentially relevant and were examined in detail. Ultimately, 5 of these studies were selected for inclusion. We reviewed the bibliographies of all identified articles for any relevant studies not returned with this search strategy and found 6 additional studies for inclusion. An EMBASE search yielded 622 abstracts, of which 38 were considered potentially relevant. However, all were ultimately excluded. Google Scholar was searched with a variety of search terms and strategies but failed to return any new studies for possible inclusion. This left 11 studies for our analysis. A summary of the literature search appears in the eFigure in the Supplement.

Inclusion Criteria and Quality Assessment

Studies were included if (1) data were provided regarding the accuracy of the medical history, the physical examination, or the WBC count for EBV-related mononucleosis, (2) a consecutive or convenience sample were enrolled (ie, no case-control studies of patients with mononucleosis vs healthy controls), and (3) the data reported were sufficient to calculate the sensitivity, specificity, likelihood ratios (LRs), or a mix of these. For evaluating the sensitivity of elevated WBC count or lymphocytes, studies with an incorporation bias were excluded when the finding was also part of the case definition. Studies were included that compared the index test with an adequate reference standard, which we defined as the EBV viral capsid antigen immunoglobulin M test or a heterophile antibody test. The latter relies on agglutination of heterophile antibodies in the presence of sheep red blood cells (Paul-Bunnell test) or horse red blood cells (Monospot test).

Studies were included that had enrolled patients with undifferentiated sore throat, as well as case series of patients with mononucleosis. However, the latter could only be used to determine the sensitivity of clinical findings. Studies were excluded that had only enrolled hospitalized patients because our focus was on evaluation in primary care and emergency department settings (an exception was some older studies in which the criteria for hospitalization were much looser, such as in the military or in a college infirmary). When the reference standard was a laboratory test performed after the patient encounter, or when the index test was also a laboratory test, masking (blinding) was assumed to have occurred.

For each included study, Rational Clinical Examination quality levels[18] were determined. Only studies with quality levels 1 through 3 were used to create summary measures for the symptoms, signs, and WBC count parameters. The Quality Assessment of Diagnostic Accuracy Studies criteria were used to describe sources of bias.[19,20] Case series of consecutive patients were not assigned a quality level because they were not studies of diagnostic accuracy; however, these studies were used to describe the sensitivity of the clinical findings.

Data Extraction and Analysis

Each study was reviewed and data extracted in parallel by 2 of the authors (which 2 authors varied depending on the study). Any discrepancies between reviewers were resolved by discussion until consensus could be achieved. If necessary, a third author (M.H.E.) was involved to achieve consensus. Similar signs and symptoms were grouped together when possible. For example, sore throat, pharyngeal erythema, and pharyngeal inflammation were combined into a single parameter termed *pharyngitis*. When an individual finding was part of the entrance criteria for an individual study (eg, sore throat), that study was excluded from the data analysis because 100% of the patients would have had the finding. We retained findings when they were 1 of several qualifying features for inclusion.

Studies reporting lymphocytosis (lymphocytes >50%) were grouped with those describing a lymphocyte to WBC count ratio of 0.5 or higher. When a single study reported 2 closely related variables, we included only 1 of the variables. Studies in which less than 5 patients had a finding were not included in the analyses of diagnostic accuracy. Clinical findings evaluated in only 1 study are reported with sensitivity, specificity, LR, and 95% confidence interval, which were calculated from the available data. Findings evaluated in only 2 studies were summarized with their range, findings evaluated in 3 studies were summarized with a univariate random-effects summary (Comprehensive Meta-Analysis version 2.2046, Biostat), and findings evaluated in 4 or more studies were summarized with a bivariate random-effects meta-analysis (MADA procedure, R version 3.2.2, R Project for Statistical Computing). For findings evaluated in at least 3 studies, the I^2 statistic was used to describe the heterogeneity of the LRs.[21]

Results

Study Characteristics

The study characteristics of the 11 included studies are summarized in **Table 1**. The quality assessment characteristics of the included studies appear in eTables 1 and 2 in the Supplement. There were 3 studies that included a total of 1388 patients with sore throat or clinically suspected mononucleosis, of whom 320 had mononucleosis[22-24]; 3 retrospective studies that used only laboratory data for 2088 patients, of whom 732 had mononucleosis[25-27]; and 5 studies that enrolled 1293 patients with typical symptoms of mononucleosis, which had been serologically confirmed.[2,3,12,28,29]

Table 1. Characteristics of Included Studies on Infectious Mononucleosis

Source	Description of Population	Age of Cohort	No. With Mononucleosis/ Total No. (%)	Reference Standard	Level of Evidence[a]
Prospective cohort studies of patients with sore throat or clinically suspected mononucleosis					
Aronson et al,[22] 1982	Consecutive patients presenting with a chief concern of sore throat at an adult internal medicine practice	Range, 16-73 y	15/709 (2.1)	Mononuclear spot test or Paul-Bunnell test	I
Fleisher et al,[23] 1983	Consecutive students at a college health service presenting with "illnesses suggestive of mononucleosis"	Not reported	190/500 (38)	High titer of IgG to VCA, IgM to VCA, detection of antibody to the early antigen diffuse component, and absence of low titers to the EBNA antibody	I
Grotto et al,[24] 2003	Military personnel with clinically suspected mononucleosis presenting at a military hospital during a 4-y period	Range, 18-23 y	115/179 (64)[b]	Concordant findings from EBV IgM and elevated heterophile antibody titer (both positive or negative)	III
Retrospective laboratory-based studies without other clinical or demographic information					
Lennon et al,[25] 2013	Outpatients and inpatients with tonsillitis who had a mononuclear spot test ordered	Not reported	500/1000 (50)	Mononuclear spot test	I
Brigden et al,[26] 1999	Patients with a clinical diagnosis of infectious mononucleosis who had a mononuclear spot test ordered	Not reported	181/362 (50)	Monosticon Dri-Dot test for heterophile antibody	I
Biggs et al,[27] 2013	Patients of any age presenting with sore throat, fever, and lymphadenopathy undergoing both lymphocyte count and mononuclear spot test	Means of 21 y (positive result on mononuclear spot test) and 30 y (negative result on mononuclear spot test)	51/726 (7.0)	Mononuclear spot test	I
Case series of patients with laboratory-confirmed mononucleosis[c]					
Rea et al,[3] 2001	Patients with clinical signs of mononucleosis and serological confirmation of the disease; approximately three-quarters of patients presented with sore throat and fatigue	Mean, 21 y (minimum of ≥16 y)	150/150 (100)	IgM to VCA	
Sumaya and Ench,[28] 1985	Patients with clinical signs and symptoms consistent with mononucleosis (≥3 of the following: fever, tonsillopharyngitis, cervical adenopathy, hepatomegaly, splenomegaly) and serological confirmation	Range, 6 mos-16 y	113/113 (100)	IgM to EBV-VCA, 4-fold increase in IgG, response to D component of EBV early antigen, or early IgG to EBV-VCA plus later antibody to EBNA	
Hoagland,[2] 1960	Military recruits at an army facility in Germany; most were hospitalized with "typical signs and symptoms of mononucleosis," lymphocytosis, and serological confirmation[d]	Range, 6 to 35 y	200/200 (100)	Abnormal heterophile antibody titer	
Lofsness et al,[29] 1987	College students presenting with clinical symptoms of mononucleosis and serological confirmation	Median, 21 y (range, 18-30 y)	60/60 (100)	Atypical lymphocytes present plus positive test result on rapid heterophile antibody test	
Henke et al,[12] 1973	Retrospective chart review of patients with clinical symptoms of mononucleosis and serological confirmation during a 20-y period in Rochester, Minnesota	Range, 0-≥25 y[e]	770/770 (100)	Heterophile antibody titer >1:64	

Abbreviations: EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

[a] Level I defined as an independent, blind comparison of sign or symptom results with a criterion standard of anatomy, physiology, diagnosis, or prognosis among a large number of consecutive patients suspected of having the target condition; level II, same as level I except among a small number of consecutive patients (vs large number in level I); level III, same as level I except among nonconsecutive patients (vs consecutive patients in level I); level IV, dependent comparison of signs and symptoms with a criterion standard of anatomy, physiology, diagnosis, or prognosis among grab samples of patients who obviously have the target condition plus individuals without the target condition; level V, dependent comparisons of signs and symptoms with a standard of uncertain validity (may incorporate sign or symptom result in its definition) among grab samples of patients with or without the target condition.

[b] Data only available for 179 of 938 patients with clinically suspected mononucleosis.

[c] This type of study cannot be used to describe diagnostic accuracy, which requires an assessment of specificity in addition to sensitivity. Therefore, a diagnostic accuracy quality level cannot be described. These studies of consecutive patients with mononucleosis can only be used to describe the sensitivity of clinical findings.

[d] It was common practice in the military or at universities at that time to confine most patients with mononucleosis to the infirmary; however, these patients would be treated as outpatients in contemporary practice. Lymphocytosis was not evaluated from this study.

[e] Distribution by age group: 0 to 4 years, 3.1%; 5 to 14 years, 12.1%; 15 to 18 years, 38.2%; 19 to 24 years, 36.2%; 25 years or older, 11.2%.

Table 2. Accuracy of Signs, Symptoms, and White Blood Cell Count for the Diagnosis of Infectious Mononucleosis

	No. of Studies and Reference No.					
	Only Sensitivity[a]	Sensitivity and Specificity	Sensitivity (95% CI)[b]	Specificity (95% CI)[b]	Positive LR (95% CI)[b]	Negative LR (95% CI)[b]
Symptoms						
Headache	1[3]	2[22,24]	0.66 (0.39-0.86)	0.27-0.55	1.1-1.3	0.63-0.73
Loss of appetite	0	2[22,24]	0.47-0.74	0.24-0.64	0.97-1.3	0.83-1.1
Malaise or fatigue	1[3]	2[22,24]	0.83 (0.73-0.89)	0.08-0.23	0.93-1.2	0.29-1.8
Sore throat	2[2,3]	2[22,24]	0.81 (0.74-0.86)	0.06-0.27	1.0-1.1	0.51-0.62
Nausea or vomiting	1[3]	1[24]	0.27-0.41	0.54 (0.41-0.67)	0.90 (0.64-1.3)	1.1 (0.82-1.4)
Myalgia or arthralgia	1[3]	1[24]	0.28-0.32	0.59 (0.46-0.71)	0.79 (0.53-1.2)	1.2 (0.90-1.5)
Signs						
Palatine petechiae	1[2]	1[22]	0.25-0.27	0.95 (0.93-0.97)	5.3 (2.1-13)	1.0 (0.57-1.0)
Lymphadenopathy						
Posterior cervical	2[3,28]	1[22]	0.64 (0.40-0.83)	0.87 (0.84-0.89)	3.1 (1.6-5.9)	0.69 (0.46-1.0)
Axillary, inguinal, or both	2[3,28]	1[22]	0.23 (0.08-0.51)	0.82-0.91	3.0-3.0	0.57-0.81
Anterior cervical	2[3,28]	1[22]	0.67 (0.59-0.73)	0.43 (0.39-0.47)	1.2 (0.81-1.7)	0.78 (0.38-1.6)
Any	3[2,3,28]	2[22,24]	0.91 (0.70-0.97)	0.25-0.58	1.2-2.1	0.23-0.44
Hepatomegaly	2[3,12]	2[22,24]	0.15 (0.07-0.30)	0.73-0.99	1.4-2.9	0.87-0.98
Rash	4[2,3,12,28]	1[24]	0.11 (0.05-0.20)	0.86 (0.75-0.92)	1.2 (0.56-2.4)	0.97 (0.85-1.1)
Fever	2[2,3]	2[22,24]	0.72 (0.35-0.93)	0.12-0.84	0.90-1.7	0.87-1.7
Jaundice	1[2]	1[24]	0.08-0.17	0.79 (0.67-0.89)	0.81 (0.43-1.5)	1.0 (0.90-1.2)
Splenomegaly	2[3,12]	2[22,24]	0.26 (0.11-0.49)	0.71-0.99	1.9-6.6	0.65-0.94
Exudate						
Tonsillar	0	1[22]	0.33 (0.12-0.62)	0.84 (0.81-0.87)	2.1 (0.99-4.4)	0.79 (0.55-1.1)
Pharyngeal	0	1[22]	0.13 (0.02-0.41)	0.93 (0.91-0.95)	1.9 (0.51-7.1)	0.93 (0.76-1.1)

Abbreviation: LR, likelihood ratio.

[a] Some of the studies were case series and were not studies of diagnostic accuracy; therefore, the data could only be used to calculate sensitivity.

[b] If there are only data from a single study, the point estimate and a 95% confidence interval are presented. If there are data from 2 studies, ranges are presented. For 3 studies, data from a univariate meta-analysis (calculated using data from Comprehensive Meta-Analysis) are presented. For 4 or more studies, data from a bivariate meta-analysis (using the metandi procedure in Stata version 13.1) are presented.

Six studies[22-27] provided data that could be used to calculate sensitivity, specificity, and LRs, whereas only 5 studies[2,3,12,28,29] could only be used to determine the sensitivity of a clinical finding.

Interrater Reliability of Signs and Symptoms

There are limited data regarding the interrater reliability of the clinical examination for patients presenting with sore throat. One study had 2 primary care physicians independently evaluate each of 126 patients with sore throat.[30] The interrater reliability as measured by the κ score (in which 0 is agreement no better than expected by chance alone and 1.0 is perfect agreement) was 0.24 for palpable anterior lymph nodes, 0.48 for tender anterior lymph nodes, 0.53 for enlarged tonsils, and 0.39 for tonsillar exudates.[30] Use of a standard visual aid showing different degrees of abnormality did not improve the interrater reliability of the physical examination for children with sore throat.[31]

Accuracy of Symptoms and Signs

Symptoms

The accuracy of symptoms and signs is summarized in **Table 2**. Complete data by individual study appear in eTable 3 in the Supplement. Although the presence of individual symptoms and signs prompt consideration for the diagnosis of mononucleosis, in isolation they were of limited value. Patients were typically selected for inclusion in these studies because they had sore throat, fever, fatigue, adenopathy (ie, clinically suspected mononucleosis), or a mix of these symptoms. The study by Aronson et al[22] was an exception because the investigators enrolled consecutive adults with sore throat, of whom 2% were ultimately diagnosed with mononucleosis. The absence of sore throat (sensitivity, 0.81; LR range, 0.51-0.62) or headache (sensitivity, 0.66; LR range, 0.63-0.73) were findings that reduced the likelihood of mononucleosis.

Signs

Among consecutive adolescents and adults with sore throat, the presence of palatine petechiae had the highest LR, but it was only completely evaluated in 1 study (specificity, 0.95; positive LR, 5.3 [95% CI, 2.1-13]). Lymphadenopathy was studied more frequently, with results similar for the presence of posterior cervical adenopathy (summary specificity, 0.87; positive LR, 3.1 [95% CI, 1.6-5.9]) and axillary or inguinal adenopathy (specificity range, 0.82-0.91; positive LR range, 3.0-3.1).[3,22,28]

Splenomegaly was present in 7% to 53% of patients with mononucleosis[3,12,24] compared with only 1% in a single prospective study[22] of 694 adults with sore throat but without mononucleosis. However, the LR for the presence of splenomegaly was only evaluated in 2 studies (specificity range, 0.71-0.99; positive LR range, 1.9-6.6).[22,24]

Table 3. Accuracy of the White Blood Cell Count for the Diagnosis of Infectious Mononucleosis

	No. of Studies and Reference No.					
	Only Sensitivity[a]	Sensitivity and Specificity	Sensitivity (95% CI)[b]	Specificity (95% CI)[b]	Positive LR (95% CI)[b]	Negative LR (95% CI)[b]
Atypical lymphocytosis						
≥40%	0	1[22]	0.25 (0.19-0.32)	1.0 (0.98-1.0)	50 (38-64)	0.75 (0.68-0.81)
≥20%	0	1[22]	0.56 (0.49-0.64)	0.98 (0.94-0.99)	26 (9.6-68)	0.45 (0.38-0.53)
≥10%	0	3[23,24,26]	0.66 (0.52-0.78)	0.92 (0.71-0.98)	11 (2.7-35)[c]	0.37 (0.26-0.51)[d]
≥50% Lymphocytes and ≥10% atypical lymphocytes	0	3[22,23,26]	0.43 (0.23-0.65)	0.99 (0.92-1.0)	54 (8.4-189)[e]	0.58 (0.39-0.77)[f]
Lymphocytosis (≥4 × 10^9/L lymphocytes) by age group, y	0	1[27]	0.84 (0.71-0.93)	0.94 (0.92-0.96)	15 (11-21)	0.17 (0.09-0.32)
≥18	0	1[27]	0.97 (0.82-0.99)	0.96 (0.84-0.98)	26 (17-42)	0.04 (0.01-0.25)
<18	0	1[27]	0.65 (0.43-0.84)	0.88 (0.83-0.93)	5.6 (3.4-9.2)	0.39 (0.22-0.69)
Ratio of lymphocytes to WBC count						
>0.50	0	4[23-26]	0.55 (0.44-0.67)	0.92 (0.81-0.97)	8.5 (2.8-20)[g]	0.49 (0.36-0.64)[g]
>0.45	0	1[25]	0.65 (0.61-0.69)	0.93 (0.90-0.95)	9.3 (6.7-13)	0.38 (0.33-0.43)
>0.40	0	1[25]	0.74 (0.70-0.78)	0.86 (0.83-0.89)	5.3 (4.2-6.6)	0.30 (0.26-0.35)
>0.35	0	1[25]	0.84 (0.80-0.87)	0.72 (0.68-0.76)	3.0 (2.6-3.5)	0.22 (0.18-0.27)
Monocytosis (>1 × 10^9/L monocytes)	0	2[26,27]	0.14-0.33	0.95-0.98	2.9-14	0.69-0.90
Leukocytosis (>10 × 10^9/L WBC count)	1[29]	3[24,26,27]	0.40 (0.28-0.53)	0.87 (0.62-0.96)	2.7 (1.2-5.7)[c]	0.79 (0.73-0.85)[h]

Abbreviations: LR, likelihood ratio; WBC, white blood cell.

[a] Some of the studies were case series and were not studies of diagnostic accuracy; therefore, the data could only be used to calculate sensitivity. Heterogeneity (I^2 statistic) is only reported for LRs when there are at least 3 studies providing data.

[b] If there are only data from a single study, the point estimate and a 95% confidence interval are presented. If there are data from 2 studies, ranges are presented. For 3 studies, data from a univariate meta-analysis (calculated using data from Comprehensive Meta-Analysis) are presented. For 4 or more studies, data from a bivariate meta-analysis (using the metandi procedure in Stata version 13.1) are presented.

[c] I^2 = 88%.

[d] I^2 = 80%.

[e] I^2 = 71%.

[f] I^2 = 76%.

[g] I^2 = 100%.

[h] I^2 = 0%.

Because mononucleosis has been studied in several case series, the sensitivity of signs are easier to evaluate. The absence of any lymphadenopathy is the finding that reduces the likelihood of mononucleosis the most (summary sensitivity, 0.91; LR range, 0.23-0.44).[2,3,22,24,28] The absence of other findings did not reduce the LR below 0.50. Most patients with mononucleosis will not have splenomegaly (summary sensitivity, 0.26; 95% CI, 0.11-0.49) or hepatomegaly (summary sensitivity, 0.15; 95% CI, 0.07-0.30).[3,12,22,24]

There have been no published studies attempting to develop and validate a clinical decision rule for combinations of findings or a clinical judgment for mononucleosis.

Accuracy of WBC Count

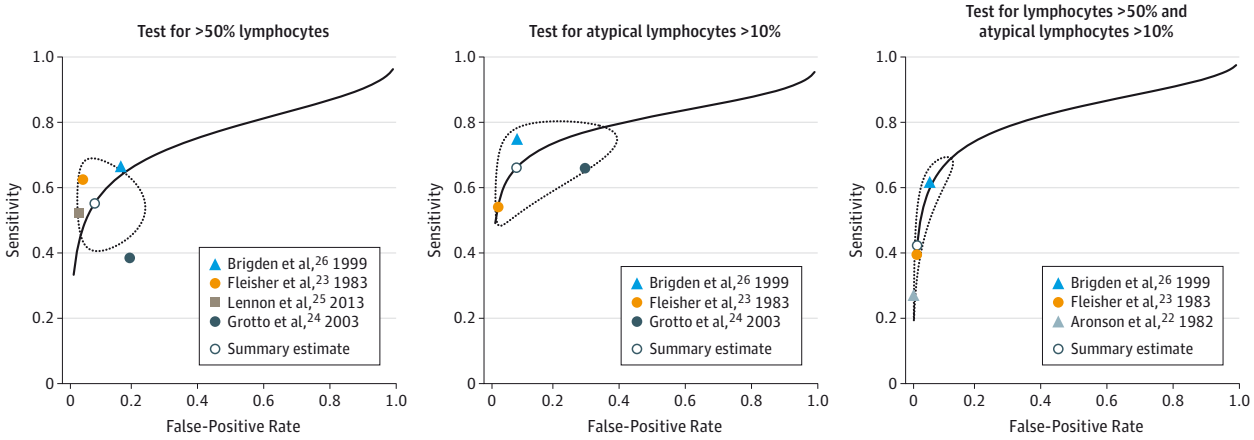
The accuracy of the WBC count and associated parameters are summarized in **Table 3**. The individual study data appear in eTable 3 in the Supplement. Several easily and quickly obtainable hematologic parameters are helpful for diagnosing mononucleosis among patients with clinically suspected disease. The presence of atypical lymphocytosis significantly increases the likelihood of mononucleosis (summary LR, 11 [95% CI, 2.7-35] for patients with atypical lymphocytes ≥10%, 26 [95% CI, 9.6-68] for those with 20%, and 50 [95% CI, 38-64] for those with 40%).[23,24,26] For diagnostic purposes, a high percentage of lymphocytes also is helpful when combined with atypical lymphocytosis. For example, patients with greater than 50% lymphocytes and greater than 10% atypical lymphocytes had a specificity of 0.99 and a positive LR of 54 (95% CI, 8.4-189).[22,23,26]

An absolute lymphocyte count at a threshold of 4 × 10^9/L or greater is helpful in diagnosing adolescents and adults (positive LR, 26 [95% CI, 17-42]; negative LR, 0.04 [95% CI, 0.01-0.25]); however, this observation is based on data from a single study.[27] Four studies[23-26] provided data regarding ratios of lymphocytes to WBC counts greater than 0.5, which made it more likely that mononucleosis is present (positive LR, 8.5; 95% CI, 2.7-20). The presence of monocytosis (monocytes >1 × 10^9/L) increases the likelihood of mononucleosis as well (positive LR range, 2.9-14).[26,27]

The presence of less than 10% atypical lymphocytes (summary sensitivity, 0.66; negative LR, 0.37 [95% CI, 0.26-0.51]) was the most frequently studied normal finding and the most efficient in lowering the likelihood of mononucleosis.[23,24,26] The presence of less than 35% lymphocytes had a negative LR of 0.22 (95% CI, 0.18-0.27), but was only evaluated in a single study.[25] The accuracy of atypical lymphocytosis (lymphocytes >50%), greater than 10% atypical lymphocytes, and the combination (>50% lymphocytes and >10% atypical lymphocytes) appear in the **Figure** as separate summary receiver operating characteristic curves. The curves in the Figure confirm the modest sensitivity but excellent specificity for patients having greater than 50% lymphocytes, greater than 10% atypical lymphocytes, or both.

The presence of atypical lymphocytosis or lymphocytosis among adolescents and adults with sore throat has the biggest effect on the probability of disease. Using the baseline prior probability estimate of 7% for mononucleosis among adolescents and young adults presenting with sore throat, the presence of greater than 10% atypical

Figure. Summary Receiver Operating Characteristic Curves



A bivariate random-effects model[32] that accounts for the inverse relationship between sensitivity and specificity was used to identify a summary estimate of sensitivity and specificity (indicated by the open circle), a 95% confidence interval around that point (dotted line), and a best fit receiver operating characteristic curve (the line). Tests that better discriminate between patients with and without infectious mononucleosis will have a greater area under the curve, with a summary estimate closer to the upper left corner of the plot. A smaller area within the confidence interval plot indicates a more precise estimate around the summary point.

lymphocytes has a positive predictive value of 39% and a negative predictive value of 97%. When a patient has greater than 10% atypical lymphocytes and greater than 50% lymphocytes each time the WBC count is measured, the positive predictive value is even higher at 73%.

Discussion

Our findings are limited by the age and quality of the literature. For example, older studies may not clearly describe their inclusion or exclusion criteria,[2] and most studies did not specify at what point patients were enrolled during the course of illness (ie, unknown duration of symptoms prior to presentation). Because the clinical and laboratory findings vary considerably at different stages of the disease,[3] it would be useful to stratify the accuracy of clinical findings and tests from the onset of symptoms (eg, <1 week, 1-2 weeks, or >2 weeks).

Another limitation was that several laboratory-based studies were included and these studies provided no clinical information.[25-27] In addition, many studies only included patients with laboratory-confirmed mononucleosis, and only report sufficient information to calculate the sensitivity. Thus, a large, prospective study of patients presenting within 7 days of the onset of sore throat would help to clarify the role of the medical history, physical examination, and office-based tests in the diagnosis of mononucleosis.

Scenario Resolution

The patient is in a high-risk age group for mononucleosis, and the pretest probability of infectious mononucleosis is approximately 8% based on data from an Australian primary care research network.[13] Heterophile antibody tests are approximately 75% sensitive early during the course of mononucleosis caused by EBV so it is correct for a physician to wonder whether the test may represent a false-negative result.[4-6,33] The tests are also less sensitive in young children (especially those aged <5 years).[5,6] The presence of fever, headache, anterior cervical lymphadenopathy, and the absence of fatigue, splenomegaly, and hepatomegaly do not appreciably change the likelihood of mononucleosis.

The presence of a tonsillar exudate (positive LR, 2.1), posterior cervical adenopathy (positive LR, 3.1), and axillary adenopathy (positive LR range, 3.0-3.1) modestly increase the likelihood of mononucleosis. Because these findings may not be independently useful, the presence of posterior cervical adenopathy is the single most important diagnostic finding, increasing the probability of mononucleosis from 8% to 21% after the clinical examination. From this revised probability estimate of 21%, the presence of lymphocytes of 51% and atypical lymphocytes of 12% (positive LR, 54) increases the probability of mononucleosis to 93%. The diagnosis of mononucleosis should be made and the patient should be given advice regarding symptomatic therapy and restriction of activities involving physical contact.

Clinical Bottom Line

Mononucleosis is a relatively common cause of sore throat among patients between the ages of 5 and 25 years, and particularly in those between the ages of 16 and 20 years, but is uncommon in younger children (age <5 years) and adults older than 25 years. Most patients have sore throat and adenopathy; fever, headache, and fatigue are common but nonspecific symptoms. Posterior cervical, axillary, and inguinal adenopathy significantly increase the likelihood of mononucleosis, as do splenomegaly and palatine petechiae. The presence of greater than 10% atypical lymphocytes significantly increases the likelihood of mononucleosis, especially when accompanied by lymphocytosis. If mononucleosis is clinically suspected, a WBC count can provide useful guidance regarding the diagnosis

early during the course of illness when serological testing has a higher false-negative rate. Another option is a test for the EBV viral capsid antigen.

Although mononucleosis is a common condition, well-designed prospective studies for the diagnosis of this disease are uncommon in the literature, and there is a need for studies that develop and validate a clinical decision rule (perhaps in combination with WBC count) to help clinicians make the diagnosis early during the course of the disease. In addition to helping clinicians provide a more accurate prognosis and better advice regarding symptomatic treatment, this would help to avoid the inappropriate use of antibiotics in patients with this viral illness.

ARTICLE INFORMATION

Author Contributions: Dr Ebell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ebell.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Ebell.
Statistical analysis: Ebell, Gardner.
Administrative, technical, or material support: Ebell.
Study supervision: Ebell.

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