CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 5-2007: A 53-Year-Old Man with a Prosthetic Aortic Valve and Recent Onset of Fatigue, Dyspnea, Weight Loss, and Sweats

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PRESENTATION OF CASE

Dr. Julie E. Myers (Department of Medicine): A 53-year-old man with a prosthetic aortic valve was admitted to this hospital because of the recent onset of fatigue, dyspnea, weight loss, and sweats.

Approximately 4 years earlier, severe aortic insufficiency had developed. Echocardiography revealed a calcified, bicuspid aortic valve. Aortic-valve replacement was performed elsewhere, with a Medtronic Hall tilting-disk valve. Three months later, aortic insufficiency recurred, and the aortic valve was replaced with another Medtronic Hall valve at the same hospital. During the second operation, there was partial dehiscence of the prosthesis along a portion of the annulus, and although there was no abscess, inflammatory tissue was present at the surgical site. Pathological examination of the excised tissue disclosed a foreign-body giant-cell reaction; no organisms were identified.

Approximately 4 months before admission, the patient began to have anorexia, fatigue, and dyspnea on exertion, which gradually worsened, causing him to avoid climbing stairs. He reported profuse sweating during the day but no night sweats, fevers, or chills. He saw his primary care physician, who prescribed escitalopram for depression.

During the next 2 months, his symptoms continued, and he lost more than 22.7 kg in weight. He noticed that his mechanical heart sounds were less crisp than usual. One month before admission, he again saw his primary care physician. The results of laboratory tests are shown in Table 1. Orally administered iron supplementation was begun.

Two weeks before admission, the patient saw his cardiologist for a regularly scheduled visit and transthoracic echocardiography. The echocardiogram showed severe aortic insufficiency, with a poorly seated valve and a moderately enlarged aortic root. The ejection fraction was 40%, and there was diffuse hypokinesis. Two specimens of blood were sent for culture the next day; there was no bacterial growth after 5 days, at which time the cultures were discarded. A transesophageal echocardiogram, obtained at another hospital 3 days later, showed an echolucent area near the

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N Engl J Med 2007;356:715-25.

Table 1. Results of Laboratory Tests.*

Variable	Normal Range	1 Month before Admission	1 Week before Admission	Day 1	Day 2	Day 4
White-cell count (per mm^3)	4500–11,000	2700	2500	3100	2800	
Erythrocyte sedimentation rate (mm/hr)	0–17		75	63		
Haptoglobin (mg/dl)	16–199				<6	
Hematocrit (%)	41.0–53.0	31.0	26.0	29.5	28.8	
Hemoglobin (g/dl)	13.5–17.5	9.9	8.3	9.6	9.5	
Mean corpuscular hemoglobin (pg/red cell)	26.0–34.0		24.4	24.6	24.7	
Mean corpuscular volume (μm^3)	80–100		76.5	76	75	
Platelet count (per mm^3)	150,000–350,000	161,000	131,000	155,000	172,000	
Partial thromboplastin time (sec)	22.1–35.1			50.6	53.9	
Prothrombin time (sec)	11.1–13.1			16.8	16.4	
Reticulocyte count (%)	0.5–2.5			5.5		
Ferritin (ng/ml)	30–300	41		52		
Iron (μg/dl)	50–150	36		87		
Iron-binding capacity (μg/dl)	250–370	311		313		
Iron-binding capacity, saturation (%)	20–45	12		27.8		
Vitamin B_{12} (pg/ml)	>250		373			
Sodium (mmol/liter)	136–145		140	130	133	131
Chloride (mmol/liter)	98–106		109	100	100	96
Glucose (mg/dl)	75–115		122	127	130	
Aspartate aminotransferease (U/liter)	0–35		60	45		
Alanine aminotransferase (U/liter)	0–35		39	21		
Calcium (mg/dl)	9.0–10.5		8.1	9.1		8.9
Lactate dehydrogenase (U/liter)	100–190					557
Alkaline phosphatase (U/liter)	30–120		134	129		
Protein (g/dl)						
Total	5.5–8.0		8.2	8.4		
Albumin	3.5–5.5		3.3	3.4		
Globulin	2.0–3.5			5.0		

* To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791. To convert the values for vitamin B_{12} to picomoles per liter, multiply by 0.7378. To the convert values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and who do not have medical conditions that could affect the result. These ranges may therefore not be appropriate for all patients.

left coronary cusp that raised concern about the possibility of an annular abscess. The aortic root was dilated, at 48 mm, with a normal left atrium. Additional laboratory test results are shown in Table 1.

The patient declined immediate admission to the hospital because of business issues; instead, for 1 week vancomycin (1.5 g) was administered intravenously every 12 hours, and gentamicin (500 mg) and ceftriaxone (2 g) were given intravenously every day through a peripherally inserted central catheter. One day before admission, he was admitted briefly to another hospital, and on the next day he was transferred to this hospital.

The patient had a history of obstructive sleep apnea and used continuous positive airway pressure by face mask nightly. He had not had dental work in the past year. He was allergic to acet-

aminophen–propoxyphene and codeine. He had no family history of valvular heart disease or rheumatologic disease. His mother was alive and well; his father had died of complications from alcohol-induced liver disease at the age of 56 years.

The patient lived in Maine, was married, and had 8 children and 13 grandchildren. The family owned three cats but had no other pets; the patient had hunted in the past, but not for many years. He owned and operated a junkyard and tow-truck service. He had not traveled outside the country and had had no contact with ill persons. He had used alcohol and tobacco in the past, but had ceased using both approximately 30 years earlier. He did not use illicit drugs. Medications taken on a daily basis included warfarin, escitalopram, furosemide (20 mg, administered intravenously), folic acid, cobalamin, aspirin, and ferrous sulfate; he took hydroxyzine occasionally for allergy symptoms.

On examination, the temperature was 37.2°C, the pulse 99 beats per minute, and the blood pressure 115/57 mm Hg; the respirations were 18 per minute. The oxygen saturation was 95% while the patient was breathing ambient air. He appeared well. He was obese, with a protuberant abdomen. He had a ruddy facial complexion, and he was perspiring. Dentition was poor, with no abscesses or gingival tenderness. The conjunctivas were pale. There was no cervical lymphadenopathy. A well-healed sternotomy scar was noted. Auscultation of the chest revealed bibasilar rales. There was a mechanical second heart sound, a grade 2/6 systolic murmur, heard best at the apex, and a grade 2/4 diastolic murmur, heard best at the base. The point of maximal impulse was not displaced. The jugular venous pressure was 8 cm H_2O. There were no Osler's nodes, Janeway's lesions, splinter hemorrhages, or peripheral edema. No erythema or drainage was evident at the catheter site.

The antibiotics were continued, and anticoagulation therapy with heparin was begun. A urine specimen was positive for proteinuria (1+) and blood (2+) but negative for nitrite. The sediment contained 10 to 20 red cells and 5 to 10 white cells per high-power field, many bacteria, and a few squamous cells. A culture of the urine showed no growth. Specimens of blood were sent for cultures for bacteria, mycobacteria, and fungi; the results were pending. Serum protein electrophoresis showed a moderate, diffuse increase in gamma globulin. No Bence Jones protein was detected, but trace amounts of albumin, alpha and beta globulin, and intact immunoglobulin were present. Serum levels of electrolytes, calcium, phosphorus, and bilirubin were normal, and renal function was also normal. The differential white-cell count was normal. An electrocardiogram showed normal sinus rhythm without prolongation of the PR interval but with ST-segment depressions in leads V_3 through V_6.

On the second hospital day, a chest radiograph showed evidence of a previous sternotomy and a slightly unusual position of the aortic valve, without other abnormalities. Computed tomographic (CT) scanning of the abdomen showed an enlarged spleen with focal abnormalities that were suggestive of tiny septic emboli and multiple small, low-density lesions in both kidneys. There were sigmoid diverticula and prominent retroperitoneal lymph nodes up to 1.6 by 1.0 cm in diameter, with minimal retroperitoneal stranding. CT scanning of the chest showed emphysema and paratracheal, prevascular, and subcarinal lymphadenopathy; the largest node in the right paratracheal region was 2 cm in diameter. The aortic valve appeared malpositioned, and there were several small pockets of contrast material adjacent to the aortic-valve annulus, between the aortic root and the pulmonary artery. Examination of a specimen from a bone marrow biopsy showed hypercellular bone marrow with trilineage hematopoiesis, erythroid predominance, and a reactive plasmacytosis.

Cardiac catheterization on the third day revealed a right-dominant system with normal coronary arteries. An aortogram showed preserved left ventricular function but severe aortic insufficiency. The prosthesis was noted to be rocking, tethered only on the left. The presence of an aortic-root abscess could not be ruled out. The two sets of blood culture specimens obtained on admission still exhibited no growth.

Carotid Doppler studies showed no stenosis. CT angiography of the chest on the fourth hospital day revealed an enlarged aortic root but a normal-size distal ascending aorta and aortic arch. Results of laboratory tests are shown in Table 1. A panoramic dental film obtained on the fifth day showed no evidence of periapical abscess, although many teeth were absent. A dental consultant noted the presence of a fractured tooth and two teeth containing caries.

On the sixth hospital day, transesophageal echocardiography showed that the mechanical aortic valve rocked excessively and moved into the left ventricular outflow tract during diastole. The valve was partly detached from the annulus; the detachment involved more than half the circumference of the valve. There was a large paravalvular leak, with severe aortic insufficiency. Although the left coronary sinus was dilated, there was no continuous flow into the left ventricular outflow tract. The left ventricle was dilated, with a normal ejection fraction.

A procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Didier Raoult: May we see the imaging studies?

Dr. Suhny Abbara: A chest radiograph shows a subtle abnormality of the position of the tilting-disk aortic valve (Fig. 1A). A contrast-enhanced, nongated CT angiogram shows several small pockets of contrast material within the connective tissue superior and adjacent to the aortic annulus (Fig. 1B), findings that are suggestive of small pseudoaneurysms or inflammatory tissue. Coronal reformation through the left ventricular outflow tract demonstrates a gap between the inferior aortic annulus and the inferior margin of the artificial valve. A continuous column of contrast material can be followed from the left ventricular cavity into the aortic root (Fig. 1C). These findings suggest dehiscence of the aortic valve.

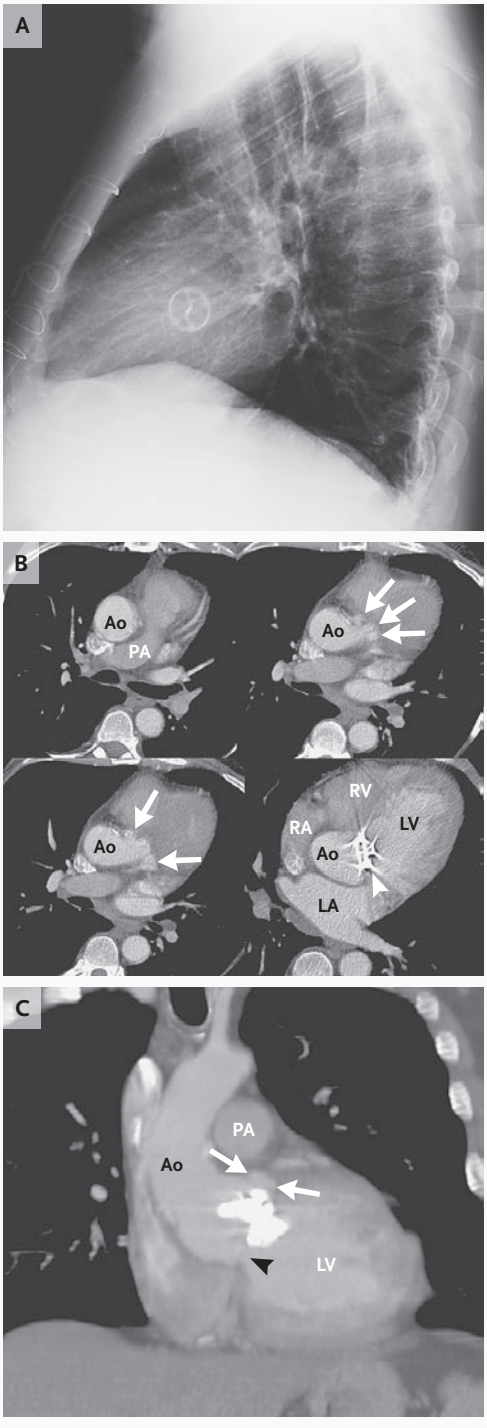


Figure 1. Chest Radiograph and CT Studies.
A lateral radiograph of the chest (Panel A) shows a slightly unusual position and angulation of the tilting-disk aortic valve. The angulation of the valve suggests that the left ventricular outflow tract and aortic root are in a horizontal orientation rather than the more usual upward angulation. A contrast-enhanced, nongated, multidetector-row CT angiogram at four levels through the aortic root (Panel B) shows several small pockets of contrast material adjacent to the aortic annulus and left sinus of Valsalva (arrows). The arrowhead indicates the artificial aortic valve. Coronal reformation of the multidetector-row CT through the left ventricular outflow tract (Panel C) shows a paravalvular collection adjacent to the aortic annulus and left sinus of Valsalva and inferior to the pulmonary artery (arrows), suggestive of paravalvular pseudoaneurysm. A gap between the aortic annulus and the implanted valve, inferior to the mechanical valve, indicates dehiscence of the valve (arrowhead). Ao denotes aorta, PA pulmonary artery, LV left ventricle, LA left atrium, RV right ventricle, and RA right atrium.

Dr. Davinder S. Jassal: A transesophageal echocardiogram was obtained. The views of the aorta revealed a mechanical valve with partial dehiscence through at least half of its circumference (Fig. 2A and 2B; and Videos 1 and 2, available

with the full text of this article at www.nejm.org). The valve rocks excessively, moving into the left ventricular outflow tract during diastole. The aorta is slightly dilated at the annulus, sinuses, sinotubular junction, and ascending root. Although the walls of the aorta appear normal, with no suggestion of an abscess, the left coronary sinus appears dilated. A color Doppler image shows a large paravalvular leak (Fig. 2C), a finding consistent with severe aortic insufficiency.

Dr. Raoult: This 53-year-old man with a prosthetic aortic valve had symptoms of fatigue, weight loss, and sweats. There are several features of this case that are unusual, including the early replacement of his first prosthetic valve and the lack of clinical response to broad-spectrum antibiotic therapy. The findings of lymphadenopathy, splenomegaly, an elevated serum lactate dehydrogenase level, and pancytopenia raise the possibility of a systemic process such as human immunodeficiency virus infection, tuberculosis, or lymphoma; the normal findings on bone marrow biopsy make these conditions less likely but do not rule them out.

Any unexplained illness in a patient with underlying cardiac valvular disease should prompt consideration of infectious endocarditis. The presence of fever, a new heart murmur, echocardiographic vegetations, or a combination of these abnormalities is highly suggestive of infectious endocarditis.[1] Echocardiographic evidence of endocardial involvement is one of the major criteria for the diagnosis of infectious endocarditis (Table 2). In patients with a prosthetic valve, transesophageal echocardiography is recommended because it has greater sensitivity for the detection of endocardial involvement than does transthoracic echocardiography.[2] Vegetations may not be present on a prosthetic valve, and infection usually involves the sewing ring, leading to paraprosthetic leaks and ring abscess.[3]

Culture of the blood before antibiotic administration is critical for the diagnosis of infectious endocarditis. Three blood cultures obtained during a 4-hour period are usually adequate to detect most organisms.[4] Highly automated blood-culture systems facilitate identification of fastidious organisms, including bacteria in the HACEK group (haemophilus species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*), which are typically recovered within 5 days of incubation.[5] A longer incubation period may be required for the growth of organisms such as propionibacterium and bartonella. The diagnosis of infectious endocarditis can be extremely difficult when the patient has neither fever nor valvular vegetations and blood cultures are negative, indicating a condition known as blood culture–negative infectious endocarditis.

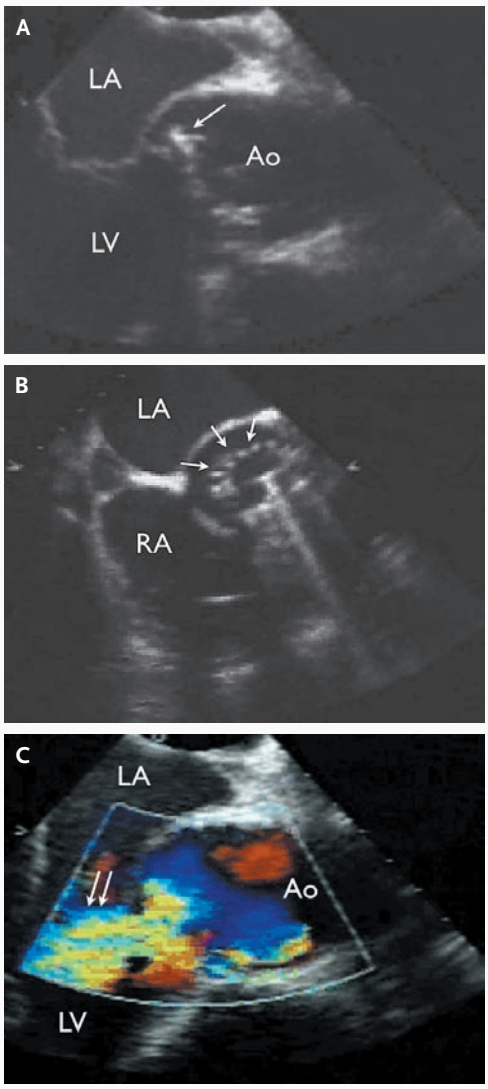


Figure 2. Transesophageal Echocardiograms.
A midesophageal view of the aorta in the long axis (Panel A) shows a partial dehiscence of the mechanical valve (arrow). A short-axis view of the aorta (Panel B) shows partial detachment of the mechanical valve and sutures (arrows) through half its circumference. A Doppler image (Panel C) shows a large paravalvular leak (arrows). Ao denotes aorta, LA left atrium, LV left ventricle, and RA right atrium.

Table 2. Modified Duke Criteria for Endocarditis.*

Major criteria
A positive blood culture for infective endocarditis, as defined by the recovery of a typical microorganism from two separate blood cultures in the absence of a primary focus (viridans streptococci, abiotrophia species, and granulicatella species; *Streptococcus bovis*, HACEK group, or community-acquired *Staphylococcus aureus* or enterococcus species); or
A persistently positive blood culture, defined as the recovery of a microorganism consistent with endocarditis from either blood samples obtained more than 12 hours apart or all three or a majority of four or more separate blood samples, with the first and last obtained at least 1 hour apart; or
A positive serologic test for Q fever, with an immunofluorescence assay showing phase 1 IgG antibodies at a titer >1:800
Echocardiographic evidence of endocardial involvement
An oscillating intracardiac mass on the valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation; or
An abscess; or
New partial dehiscence of prosthetic valve; or
New valvular regurgitation
Minor criteria
Predisposition: predisposing heart condition or intravenous drug use
Fever: temperature ≥38°C (100.4°F)
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
Microbiologic evidence: a positive blood culture but not meeting a major criterion as noted above, or serologic evidence of an active infection with an organism that can cause infective endocarditis†
Echocardiogram: Findings consistent with infective endocarditis but not meeting a major criterion as noted above

* The diagnosis of infective endocarditis is definite when a microorganism is demonstrated by culture of a specimen from a vegetation, an embolism, or an intracardiac abscess; when active endocarditis is confirmed by histologic examination of the vegetation or intracardiac abscess; or when two major clinical criteria, one major and three minor criteria, or five minor criteria are met. The modified Duke criteria are adapted from Li et al.[2] HACEK denotes haemophilus species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*.

† Excluded from this criterion is a single positive blood culture for coagulase-negative staphylococci or other organisms that do not cause endocarditis. Serologic tests for organisms that cause endocarditis include tests for brucella, *Coxiella burnetii,* chlamydia, legionella, and bartonella species.

This patient met one of the major Duke diagnostic criteria (echocardiographic abnormalities) and two of the minor criteria (a predisposing cardiac condition and a vascular factor — possible septic emboli of the spleen), suggesting a diagnosis of blood culture–negative infectious endocarditis (Table 2).[2]

CAUSES OF CULTURE-NEGATIVE ENDOCARDITIS

The causative agents of culture-negative endocarditis are fastidious bacteria, fungi, and the usual organisms (mainly streptococci) found in patients who have received antibiotic treatment before blood samples are obtained for culture (Table 3). Culture-negative endocarditis is most common in developing countries, where it may account for up to 50% of all cases of infectious endocarditis.[6] For years, the failure to identify an organism was considered a consequence of poor diagnostic tests; however, many cases are due to fastidious zoonotic agents such as *Bartonella quintana*, *Coxiella burnetii,* or brucella species.[6] A precise history taking, with detailed information about travel, environmental exposures to pathogens, and contact with animals, is essential to identify the causative agent of culture-negative endocarditis.

This patient has poor dental hygiene and sigmoid diverticulosis, both of which put him at risk for streptococcal endocarditis. The blood cultures obtained before antibiotic therapy was initiated were negative, and his lack of response to multiple courses of antibiotics suggests the presence of an uncommon organism.

INFECTION WITH C. BURNETII

Q fever, caused by infection with *C. burnetii*, is common in certain geographic areas and may cause

Table 3. Agents of Culture-Negative Endocarditis.*

Agent	Prevalence	Prosthetic Valve	Previous Valve Lesion	Clinical or Epidemiologic Features	Diagnostic Methods
Usual agent after antibiotic treatment					
Viridans streptococcus	Common			Poor dental status	PCR assay of valve
S. bovis	Common			Colic lesion	PCR assay of valve
Fastidious bacteria					
Coxiella burnetii	Common	Very common	Very common	Vegetation may be absent, contact with cats, neutropenia, fever may be absent, alcoholism rare	Specific serologic test, specific blood culture, PCR assay of blood or valve, test for antibodies to bartonella, test for antibodies to *C. burnetii*
Bartonella henselae	Common (1–3%)	Rare	Common	Vegetation, contact with cats, fever may be absent, alcoholism rare	Specific serologic test, specific blood culture, prolonged blood culture, PCR assay of valve, test for antibodies to bartonella, test for antibodies to *C. burnetii*
B. quintana	Common (0.5–12%)	Very rare	Rare	Vegetation, contact with cats rare, rural habitat, presence of body lice, fever may be absent, alcoholism common	Specific serologic test, PCR assay of valve or blood, specific blood culture, prolonged blood culture, test for antibodies to bartonella, test for antibodies to *C. burnetii*
Streptococci (granulicatella and abiotrophia species)	Common	Common	Very common	Vegetation, absence of fever rare, alcoholism rare	Use of cysteine-enriched medium for blood subculture, specific blood culture, PCR assay of valve, PCR assay of blood (if not tested)
Tropheryma whipplei	Very rare	Very rare	Very rare	Vegetation rare, alcoholism rare, chronic arthralgias preceding disease	Histologic examination of valve, PCR assay of valve or blood, specific blood culture
Mycoplasma and ureaplasma species	Very rare				PCR assay of valve, specific culture of valve
Legionella species	Very rare			Nosocomial infection of valvular prosthesis	Serologic test, specific culture, PCR assay of valve
Finegoldia species	Very rare				PCR assay of valve, strict anaerobic culture
Brucella species	Rare in developed countries, common in developing countries			Rural habitat	Serologic test, PCR assay of valve
Mycobacterium species	Very rare				PCR assay of valve
Fungi	Rare in general population	Very common	Very common	Vegetation, alcoholism (probable), absence of fever rare, intravenous drug use, valvular prosthesis	PCR assay of blood or of valve, specific blood culture, culture of emboli, specific serologic test

* Common denotes more than 100 cases reported in the literature, rare 50 to 100 cases, and very rare fewer than 50 cases. PCR denotes polymerase chain reaction. Data are from Brouqui and Raoult.[6]

3 to 10% of cases of infectious endocarditis.[7] In one study, *C. burnetii* was the leading cause of prosthetic-valve endocarditis in men less than 65 years old.[8] Outbreaks of cat-related Q fever have been reported in Maine, where this patient lives,[9] and there is a relatively high incidence of Q fever endocarditis in Maritime Canada.[10] The disease can be chronic and indolent, and patients may not have fever or valvular vegetations. Some patients have undergone several valve replacements before a diagnosis was made.[8] The major clinical presentation is unexplained illness in a patient with known valvular disease.[8] Because of the difficulty of obtaining positive cultures for this organism, the Duke criteria have been modified to make a positive serologic test for *C. burnetii* a major diagnostic criterion. Given the cross-reactivity of *C. burnetii* and bartonella antibodies, the presence of antibodies to bartonella in a patient in whom Q fever endocarditis is suspected paradoxically favors this diagnosis (Table 3). This patient's presentation, his residence in the northeastern United States, and his pet cats make *C. burnetii* infection a serious consideration.

Infection with Bartonella Species

Bartonella infection is a common cause of culture-negative endocarditis. The diagnosis is usually based on a postive serologic test or identification of bartonella nucleic acids on valvular material. *B. quintana* is the most common cause of bartonella endocarditis and is mainly diagnosed in patients with alcoholism or in homeless persons without previous valvular lesions.[11,12] The prevalence of this disease varies geographically[6]; the prevalence of *B. henselae* in cats in the United States is high,[13] and endocarditis caused by *B. henselae* is usually diagnosed in patients with previous valvular disease who own cats. This patient with previous valvular disease and three cats is at risk for infection with *B. henselae*.

Less Common Causes of Culture-Negative Endocarditis

Tropheryma whipplei is a very rare cause of culture-negative endocarditis and is usually not associated with gastrointestinal Whipple's disease. Fungal endocarditis, mainly observed in intravenous drug users and in patients who have undergone surgery, may be diagnosed on the basis of a polymerase-chain-reaction (PCR) assay of a blood sample or either a PCR assay or histologic examination of the valve. This patient has no particular risk factors or symptoms that would suggest the presence of either of these disorders.

DIAGNOSIS OF CULTURE-NEGATIVE ENDOCARDITIS

Serologic testing for fastidious organisms is central to making the diagnosis of culture-negative endocarditis.[4] Patients with Q fever may have cross-reacting antibodies to bartonella, which may make interpretation of the test results difficult.[14] Other organisms that may be tested serologically, depending on the epidemiologic situation, include brucella, *Legionella pneumophila*, and aspergillus.[4] Nucleic acid testing for organisms may be useful in detecting fungemia,[15] bartonella, Q fever, and *T. whipplei* endocarditis (Table 3).

Histologic examination of a removed valve may be useful in diagnosing culture-negative endocarditis. Standard staining allows confirmation or identification of infectious endocarditis and recognition of conditions that mimic endocarditis (myxoma, fibroelastoma, and rheumatoid nodules) and noninfectious endocarditis (marantic endocarditis, inflammation in degenerative valvular lesions, rheumatic endocarditis, and Libman–Sacks endocarditis). Immunohistochemistry may allow specific identification of causative agents, including bartonella, *C. burnetii*, and *T. whipplei*, and successful detection of organism-specific nucleic acids from valve material has been reported.[16] This technique makes it possible to test valves retrospectively. Despite the availability of sophisticated diagnostic tests, the causative agent may remain unknown in up to 7% of cases of infectious endocarditis.[8]

In this patient with culture-negative infectious endocarditis in the absence of fever, a fastidious agent is the most likely cause, and the two most likely agents are *C. burnetii* and bartonella species. This patient's exposure to cats puts him at risk for Q fever and *B. henselae* infection. However, the absence of valvular vegetations and the slow progression of the disease favor Q fever, which is the most likely diagnosis.

Additional testing to identify other Duke criteria should be performed. To complete the investigation in this patient, testing for rheumatoid factor and serologic testing for fastidious bacteria, including *B. henselae*, *B. quintana*, and *C. burnetii*, should be performed.[4]

Dr. Nancy Lee Harris (Pathology): Dr. Plank, can

you tell us your thinking and describe the diagnostic test?

Dr. Rebeca M. Plank (Infectious Diseases): When I evaluated this patient, very limited microbiologic data were available. The blood cultures that had been obtained before the initiation of antibiotic therapy were discarded after 5 days, leaving open the possibility of infection by slow-growing organisms. Therefore, the differential diagnosis was broad and included typical and atypical bacteria, fungi, and mycobacteria that are associated with prosthetic-valve endocarditis. When the infectious disease team saw this patient, we were particularly concerned about fastidious bacteria, including members of the HACEK group and less common organisms such as *Chlamydia pneumoniae*, mycoplasma, legionella, brucella, *T. whipplei*, bartonella, and coxiella.

Blood cultures obtained on the patient's admission to this hospital were held for 14 days and grew no organisms. Blood cultures for fastidious organisms, fungi, and mycobacteria were all negative. Urine tests for histoplasma and legionella antigens and serum tests for antibodies to cytomegalovirus, hepatitis B and C viruses, and syphilis were also negative. Serologic testing demonstrated prior infection with *Chl. pneumoniae* and was negative for mycoplasma, legionella, and brucella.

Because this patient owns cats, we suspected prosthetic-valve endocarditis caused by either *B. henselae* or *C. burnetii.*

The diagnostic procedure was aortic-valve replacement, which confirmed dehiscence of the valve and infection invading the aortic root and prosthetic valve.

CLINICAL DIAGNOSIS

Blood culture–negative infectious endocarditis due to *C. burnetii* or *B. henselae*.

DR. DIDIER RAOULT'S DIAGNOSIS

Blood culture–negative infectious endocarditis, most likely due to *C. burnetii* or possibly due to bartonella species.

PATHOLOGICAL DISCUSSION

Dr. Richard L. Kradin: Examination of the prosthetic valve revealed no vegetations. There was substantial chronic inflammation in the wall of the aortic-root tissue as well as small vegetations along the valvular surface (Fig. 3A). There was moderate fibrin deposition around the suture material. Microscopical examination of the valve disclosed collections of vacuolated histiocytes (Fig. 3B). Stains for routine bacteria, mycobacteria, and fungi were negative. A silver impregnation stain showed multiple small organisms within the histiocytes, which were consistent with coxiella (Fig. 3C).

Dr. Plank: A portion of the valve was sent for cultures; there was no growth of aerobic or anaerobic bacteria, nutritionally variant streptococci, HACEK organisms, fungi, or mycobacteria. Tissue specimens were tested for organism-specific nucleic acids and were negative for *Chl. pneumoniae*, *Chl. psittaci*, mycoplasma, legionella, brucella, and *T. whipplei.* Nucleic acid testing for *B. henselae* and *B. quintana* DNA was negative in two samples from the prosthetic valve. However, serologic tests showed the presence of antibodies against *B. henselae* (IgG at a titer of 1:256) and *B. quintana* (IgG at a titer of 1:1024) and very high titers of antibodies to *C. burnetii* (phase I IgG titer, 1:16,384; phase II IgG titer, 1:16,384). As Dr. Raoult mentioned, cross-reactivity between these tests is common, and, paradoxically, the presence of antibodies to bartonella supports the diagnosis of infection with *C. burnetii*.

Dr. Kradin: Coxiella infection causes two clinical syndromes. Acute Q fever has an incubation period of 9 to 28 days, followed by high fever, headache, myalgia, and atypical pneumonia. Hepatitis and rash are also common. Chronic hepatitis develops in one third of patients. The leading manifestation of chronic Q fever is a subacute endocarditis, as seen in this patient, which can occur from 1 to 20 years after exposure. The aortic valve is more commonly infected than the mitral valve, but both can be involved. Chronic Q fever endocarditis is characterized by inflammation with vacuolated histiocytes, as was the case in this patient. Definitive diagnosis is based on a history of exposure and positive serologic tests, with or without the identification of organisms by histochemical staining or nucleic acid testing.

Dr. Harris: Dr. Felsenstein, how did you treat the patient? How is he doing now?

Dr. Donna Felsenstein (Infectious Diseases): The patient was unable to tolerate doxycycline because of severe gastrointestinal side effects, even when he took the medication with food. Thus, he was

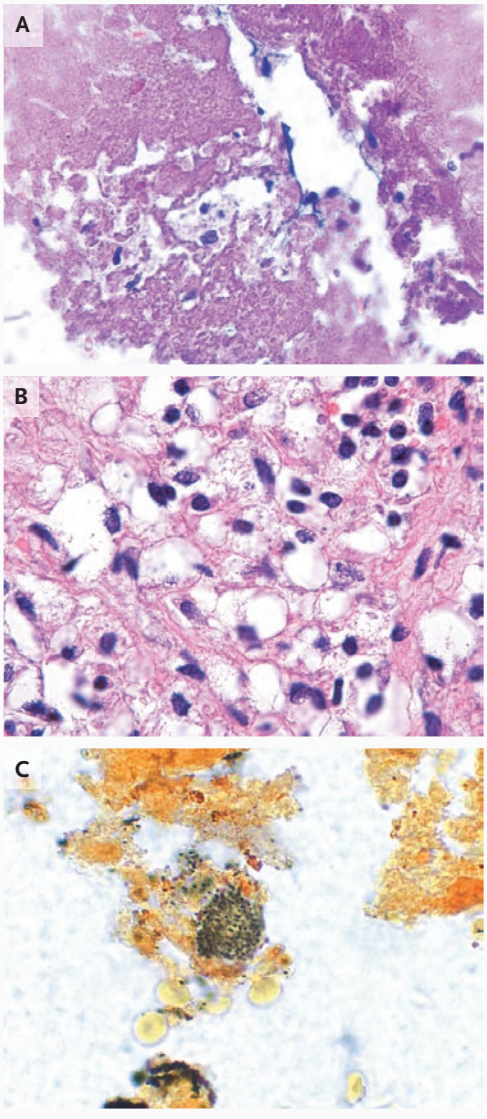


Figure 3. Resected Aortic Valve.

There is chronic inflammation and fibrosis of the aortic root (Panel A, hematoxylin and eosin). Collections of vacuolated histiocytes (Panel B, hematoxylin and eosin) are entrapped by the fibrin deposited around the suture material. Numerous coccobacillary forms within the cytoplasm of a histiocyte (Panel C, silver impregnation) are consistent with coxiella.

treated initially with moxifloxacin (400 mg daily). His weight and energy level gradually returned to normal. He was subsequently given minocycline and hydroxycholoroquine, which he continues to take; he remains well, 1 year and 9 months after the diagnosis. The titers of antibodies to coxiella have been falling in response to therapy. Dr. Raoult, what is your recommendation regarding antibiotic treatment and the duration of therapy for *C. burnetii* endocarditis?

Dr. Raoult: The recommended treatment is doxycycline plus chloroquine given for 18 months to 3 years. The main problem in treating coxiella is that the rate of failure of antibiotic therapy is high, especially when a single antibiotic is used. If patients are followed for a long enough period, there is always relapse. Even with the use of two antibiotics such as doxycycline and a fluoroquinolone, many patients still have a relapse of infection. If an agent other than doxycycline is chosen, treatment should be lifelong.

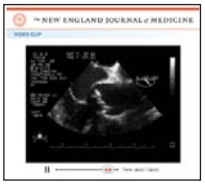
Dr. Harris: Do you think it is possible that this infection caused the first valve to fail?

Dr. Raoult: I am not sure, but it would be very interesting to obtain material from the valve and test specifically for *C. burnetii*.

ANATOMICAL DIAGNOSIS

C. burnetii (Q fever) endocarditis.

Dr. Raoult is cofounder and 5% owner of INODIAG. Dr. Abbara reports receiving consulting fees from or being a member of the paid advisory board of Siemens Medical and E-Z-Em and having equity ownership and stock options in Partners Imaging and Amirsys. No other potential conflict of interest relevant to this article was reported.



Videos showing echocardiographic images from this case are available with the full text of this article at www.nejm.org.

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