PURPOSE: To review recent advances in the basic and clinical biology of Bartonella-related eye disease.

METHOD: A review of the pertinent medical literature was performed.

RESULTS: A number of novel Bartonella species have been identified over the past decade. Of these, Bartonella henselae, the etiologic agent in cat scratch disease, is most often associated with ocular complications, which may include Parinaud oculoglandular syndrome, neuroretinitis, and focal retinochoroiditis. Although cat and flea exposure appear to be the main risk factors for contracting cat scratch disease, the diagnosis of ocular bartonellosis relies primarily on the recognition of suggestive clinical signs in conjunction with positive serologic testing. B. henselae–associated ocular complications are usually self-limited but may be treated with doxycycline or erythromycin, with or without rifampin, when the infections are severe or sight-threatening.

CONCLUSIONS: B. henselae infection is common and should be considered in patients with Parinaud oculoglandular syndrome, neuroretinitis, or focal retinochoroiditis, particularly when there is a history of cat or flea exposure. (Am J Ophthalmol 2000;130:340–349. © 2000 by Elsevier Science Inc. All rights reserved.)

Bartonella species have only recently become recognized as important human pathogens. Until the mid-1990s, probably few ophthalmologists had heard of the genus Bartonella, and in fact, no organisms in this genus had yet been implicated as a cause of eye disease. Over the past decade, however, the application of molecular techniques to microbial discovery and diagnosis has led to the rapid identification of a number of novel Bartonella species, many of which cause human disease. One species in particular, B. henselae, has emerged as the etiologic agent in cat scratch disease and is now well-known to cause Parinaud oculoglandular syndrome, neuroretinitis, and focal retinochoroiditis. This focused review deals with recent advances in the basic and clinical biology of Bartonella species, with special attention to B. henselae and the ocular complications associated with infection by this organism. Comprehensive reviews of Bartonella species in general, and of the specific role of B. henselae in nonocular human disease, may be found elsewhere.

HISTORY AND TAXONOMY

The history of Bartonella infections of the eye begins with Henri Parinaud, who provided what was probably the first clinical description of ocular bartonellosis in 1889, when he reported three patients with chronic fever, regional lymphadenopathy, and a follicular conjunctivitis.10,11 Subsequent reports from the first half of the century noted a history of cat exposure in some patients with this syndrome, which later become known as Parinaud oculoglandular syndrome.12,13 Over the last 50 years numerous studies have confirmed an association between Parinaud oculoglandular syndrome and cat scratch disease,14,15 a systemic febrile illness associated with regional lymphadenopathy. It was initially described by Debre and associates in 1950.16 Sweeney and Drance17 first suggested an association between cat scratch disease and neuroretinitis in 1970, a finding subsequently confirmed by Gass18 and many others (reviewed in references 4 and 5). It was not until 1994, however, that Golnik and associates19 provided the first serologic evidence of systemic Bartonella infection in patients with neuroretinitis.

Identification of B. henselae as the etiologic agent for cat scratch disease required the cumulative efforts of a number of clinicians and scientists. In 1983 investigators at the Armed Forces Institute of Pathology identified a bacterial agent in lymph node specimens from patients with cat
These organisms appeared to be morphologically identical to those identified at about the same time by Stoler and associates in a human immunodeficiency virus (HIV)–infected patient with bacillary angiomatosis, a disorder observed in severely immunosuppressed patients that is characterized by the presence of cutaneous and subcutaneous vascular lesions, grossly similar to Kaposi sarcoma. In 1990 Relman and associates used a novel molecular approach based on conserved ribosomal gene sequences to identify a new organism as the cause of bacillary angiomatosis. This previously unknown organism was closely related to the etiologic agent of trench fever, at that time named \textit{Rochalimaea quintana}. Simultaneous and subsequent studies confirmed the presence of this new organism in immunocompromised patients with both bacillary angiomatosis and relapsing fever, and it was suggested that it be named \textit{Rochalimaea henselae}. Koehler and associates showed shortly thereafter that both \textit{R. henselae} and \textit{R. quintana} could be isolated from bacillary angiomatosis lesions in HIV-positive patients. Genotypic analysis performed by Brenner and associates revealed that the \textit{Rochalimaea} species (\textit{R. henselae}, \textit{R. quintana}, \textit{R. elizabethae}, and \textit{R. vinsonii}) were closely related to \textit{Bartonella bacilliformis}, an organism long implicated as the agent of Oroya fever and verruga peruana in Peru and Ecuador. This led to the reclassification of the \textit{Rochalimaea} species in the genus \textit{Bartonella} in 1993. Numerous studies have since provided irrefutable evidence that \textit{B. henselae} is the primary etiologic agent of cat scratch disease. Further taxonomic reclassification was undertaken in the late 1990s when the genus \textit{Grahamella} was renamed \textit{Bartonella}, giving rise to \textit{B. talpae} and \textit{B. peromysci}. Seven new \textit{Bartonella} species have since been added, including \textit{B. grahamii}, \textit{B. taylorii}, \textit{B. doshiae}, \textit{B. clarridgeiae}, \textit{B. tribocorum}, \textit{B. alsatica}, and \textit{B. koehlerae}, bringing the total number of \textit{Bartonella} species to 14.

Five of the currently recognized \textit{Bartonella} species have been implicated as causes of disease in humans, either by culture or polymerase chain reaction–based amplification of \textit{Bartonella} species-specific DNA (Table 1). In immunocompetent patients these diseases include cat scratch disease (\textit{B. henselae}), trench fever (\textit{B. quintana}), endocarditis (\textit{B. henselae}, \textit{B. quintana}, \textit{B. elizabethae}, \textit{B. vinsonii})

<table>
<thead>
<tr>
<th>\textit{Bartonella} Species</th>
<th>Presumed Primary Reservoir</th>
<th>Acute Bacteremic Syndromes</th>
<th>Chronic Vascular Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{B. bacilliformis}</td>
<td>Human</td>
<td>Oroya fever</td>
<td>Verruga peruana</td>
</tr>
<tr>
<td>\textit{B. henselae}</td>
<td>Domestic cat</td>
<td>Relapsing fever, POGS, endocarditis, focal retinocochoroiditis</td>
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<tr>
<td>\textit{B. quintana}</td>
<td>Human</td>
<td>Trench fever</td>
<td>Bacillary angiomatosis†</td>
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<tr>
<td>\textit{B. elizabethae}</td>
<td>Rodent</td>
<td>Endocarditis†</td>
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<tr>
<td>\textit{B. vinsonii}</td>
<td>Vole</td>
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<tr>
<td>\textit{B. vinsonii} subsp. berkhoffei</td>
<td>Dog</td>
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<tr>
<td>\textit{B. grahamii}</td>
<td>Rodent</td>
<td>Neuroretinitis‡</td>
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<td>\textit{B. doshiae}</td>
<td>Rodent</td>
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<td>\textit{B. taylorii}</td>
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<td>\textit{B. peromysci}</td>
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<td>Rodent</td>
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<td>\textit{B. claridgeiae}</td>
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<td>\textit{B. tribocorum}</td>
<td>Rodent</td>
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<tr>
<td>\textit{B. alsatica}</td>
<td>Rabbit</td>
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<tr>
<td>\textit{B. koehlerae}</td>
<td>Domestic cat</td>
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</tbody>
</table>

POGS = Parinaud oculoglandular syndrome.

*Documented by polymerase chain reaction, culture, or both.
†Immunocompromised.
‡Single case report.
subspecies arupensis), Oroya fever (B. bacilliformis), and verruga peruana (B. bacilliformis). Both B. henselae and B. quintana appear to be capable of producing unique forms of disease in immunocompromised patients, including prolonged or relapsing fever, occasionally related to endocarditis, bacillary angiomatosis, bacillary peliosis hepatis, and bacillary splenitis.

Cat scratch disease is the most frequently recognized form of systemic B. henselae infection. Most patients develop a mild to moderately severe flu-like illness associated with regional lymphadenopathy. Common systemic symptoms include headache, anorexia, nausea, vomiting, and sore throat. Transient skin reactions, including nonspecific maculopapular eruptions and erythema nodosum, may occur in some patients. Affected nodes are frequently tender and may even be suppurative. A papule or pustule at the site of primary cutaneous inoculation occurs in 25% to 60% of patients, usually 3 to 10 days after the injury and 1 to 2 weeks before the onset of constitutional symptoms. Ocular involvement occurs in 5% to 10% of patients with cat scratch disease.

Other less common manifestations of cat scratch disease include encephalitis (1% to 2%), osteomyelitis (less than 1%), and hepatosplenic disease (less than 1%).

MICROBIOLOGY AND MICROBIAL PATHOGENESIS

 Bartonella are small, fastidious, gram-negative rods (Figure 1). They are unable to oxidize glucose but can use glutamate and succinate as carbon sources. Incubation in enriched media allows for optimal growth (see below), which can take up to 4 weeks. Whereas B. henselae colonies tend to be rough and produce pitting of the agar, B. quintana colonies are usually smooth, with little or no pitting (Figure 2).

The pathogenesis of Bartonella infections depends both on the species involved and the immune status of the host. In immunocompetent patients, B. henselae infections tend to produce a necrotizing response, often associated with microabscess formation. Analysis of primary skin lesions shows a central area of necrosis surrounded by concentric layers of histiocytes, lymphocytes, and nucleated giant cells, forming a granuloma. Similar findings have been described in affected lymph nodes. In immunocompromised hosts, by contrast, the response tends to be vasoproliferative. The organisms are difficult to see with routine stains, but they can be demonstrated in and around blood vessel walls, in germinal centers, and associated with microabscesses of involved lymph nodes using special techniques such as the Warthin-Starry silver stain or electron microscopy.

 Bartonella organisms establish and maintain an intimate relationship with vascular endothelium, both within their hosts and in culture. In vitro, organisms tend to aggregate and colonize endothelial cells (Figure 3). This relationship has been suggested to be important for the production of a local vasoproliferative response, perhaps elicited by vascular endothelial growth or migration factors produced either by B. henselae itself or by colonized, host endothelial cells.

Flagellated Bartonella species, such as B. bacilliformis, demonstrate a strong propensity to parasitize red blood cells, a feature that explains the hemolysis and often life-threatening anemia that can accompany acute infec-
tion with this organism (Oroya fever). B. henselae has been observed to penetrate red blood cells in a fashion similar to that in cats but to a lesser extent. This phenomenon may explain the persistent bacteremia often observed in the setting of systemic B. henselae infection.

**EPIDEMIOLOGY**

The epidemiology of the different Bartonella species varies considerably. Only B. henselae infection will be considered here, because it is the most common ocular pathogen.

Systemic Bartonella henselae infection, or cat scratch disease, has been estimated to affect approximately 22,000 patients and to result in about 2,200 hospitalizations annually in the United States. The prevalence in other countries is unknown, although human infection by B. henselae is recognized to occur worldwide. Cats are the primary mammalian reservoir for B. henselae, and infection rates in cats appear to be higher in areas with more fleas. Moreover, B. henselae seropositivity in cats is higher in warmer regions or areas with higher amounts of annual rainfall, such as Hawaii, coastal California, and the Pacific Northwest. Importantly, regional rates of human seropositivity appear to mirror rates of infection observed in cats. Rates of cat infection also appear to be higher in kittens, in free-ranging cats, and in flea-infested cats. In fact, cat fleas have been demonstrated to transmit B. henselae from infected cats to specific-pathogen–free kittens in a controlled, arthropod–free environment and have even been suggested by Foley and associates to be the most important contributing factor in feline infection (Figure 4). The role of fleas in human infection is unknown, although flea feces remain infectious for extended periods of time and could conceivably transmit B. henselae by direct inoculation of open wounds or mucous membranes, such as the conjunctiva. Epidemiologic evidence supports this notion, in that patients with bacillary angiomatosis have a statistically higher association with previous cat contact, cat bites, cat scratches, and cat flea bites. Children and young adults are reported to be at increased risk for systemic B. henselae infection, which appears to have a
The predilection for fall and early winter months, at least in the United States. Multiple cases of cat scratch disease may occur in the same family, but recurrences in any given individual are uncommon, perhaps because of lasting immunity. Veterinarians appear to be at increased risk of infection.

**OCULAR COMPLICATIONS**

Although the eye is the most commonly affected nonlymphatic organ in patients with cat scratch disease, not all patients experience clinically appreciable symptoms, and a subset of patients with systemic *B. henselae* infection fail to provide a history of recent cat or flea exposure. In this sense, recognition of suggestive ocular findings often leads to specific serologic testing and the correct diagnosis.

Parinaud oculoglandular syndrome, as defined above appears to be the most common ocular complication of cat scratch disease, affecting approximately 5% of symptomatic patients. Patients with Parinaud oculoglandular syndrome typically complain of unilateral eye redness, foreign body sensation, and epiphora. Lid swelling, when present, is usually mild. Discharge is often noted and tends to be serous, although purulent discharge can occur in the setting of abscess formation and rupture. Conjunctival lesions may involve either the palpebral or bulbar surface, and necrosis with ulceration of the overlying epithelium is common (Figure 5). A regional lymphadenopathy involving the preauricular, submandibular, or cervical lymph nodes is the hallmark of the disease. Wear and associates provided the first demonstration of argyrophilic bacilli in specimens from patients with Parinaud oculoglandular syndrome. Polymerase chain reaction–based techniques and modified cultures have been used since that time to implicate *B. henselae* directly as a cause of Parinaud oculoglandular syndrome. The route of infection in patients with Parinaud oculoglandular syndrome resulting from *B. henselae* is unknown, although direct conjunctival inoculation, most likely with infected flea feces, seems to be most plausible. Bartonella-associated Parinaud oculoglandular syndrome has been reported in a single HIV-infected patient who responded well to prolonged systemic antibiotic therapy. Other considerations in patients with a unilateral granulomatous conjunctivitis include tularemia, tuberculosis, syphilis, sporotrichosis, and acute *Chlamydia trachomatis* infection (adult inclusion conjunctivitis).

Neuroretinitis is a unique form of optic neuropathy characterized by optic disk swelling in the presence of a partial or complete macular star (Figure 6). The true prevalence of neuroretinitis in patients with systemic *B. henselae* infection is unknown, although it appears to be uncommon, perhaps occurring in 1% to 2% of patients. Among patients who develop neuroretinitis, however, nearly two thirds show serologic evidence of past infection by *B. henselae*, suggesting that cat scratch disease is the most common cause of this syndrome. Simultaneous or consecutive retinitis or neuroretinitis in patients with Parinaud oculoglandular syndrome is uncommon but has been reported.

*B. henselae*–associated posterior segment complications have been well described. Neuroretinitis appears to be most common and is usually unilateral, although patients with bilateral optic disk swelling and macular star formation have been reported. Optic disk edema, often accompanied by a peripapillary subretinal fluid, usually predates the formation of a macular star by 2 to 4 weeks. Some patients, however, never form a macular star, whereas other patients develop massive disk swelling with widespread subretinal and intraretinal exudates. A multifocal retinitis and/or choroiditis accompanies the disk swelling in many patients, and when present retinochoroiditis provides strong support for the diagnosis of *B. henselae* infection.
Foci of retinochoroiditis can also be observed in the absence of disk edema or macular exudates.\(^5^5,5^7-6^0\) Complications observed in patients with cat scratch disease–associated focal retinochoroiditis include branch retinal artery\(^5^8,6^0,6^3\) and vein\(^5^5,6^3\) occlusions, and localized serous retinal detachment.\(^5^5,5^7\) Macular exudates may take months to resolve, and even then, patients may be left with mild to moderate optic disk pallor, subnormal contrast sensitivity, abnormal color vision, and abnormal evoked potentials.\(^5^7\) Other causes of optic disk edema associated with a macular star that should be considered in all patients include malignant hypertension, diabetes mellitus, pseudotumor cerebri, sarcoidosis, syphilis, tuberculosis, toxoplasmosis, toxocariasis, Lyme disease, and leptospirosis.\(^5^3\) Similar, as well as more severe, forms of cat scratch disease–associated neuroretinitis and retinochoroiditis have been described in HIV-infected patients.\(^5^2,6^3-6^5\)

The frequency with which infection by Bartonella species other than \textit{B. henselae} produce neuroretinitis and/or retinochoroiditis is unknown, but to date only \textit{B. henselae} has been linked microbiologically to ocular manifestations. However, O’Halloran and associates\(^6^6\) provided serologic evidence for systemic \textit{B. elizabethae} infection in a 31-year-old man with unilateral neuroretinitis associated with subretinal and intraretinal infiltrates. In addition, Kerkhoff and associates\(^6^7\) described a 55-year-old man with moderately severe, diffuse uveitis associated with posterior synechiae, neuroretinitis, and cystoid macular edema in each eye. Whereas serologic tests from this latter patient suggested previous infection by \textit{B. henselae}, polymerase chain reaction–based analysis of aqueous humor produced a DNA fragment consistent with \textit{B. grahamii} infection.

Most patients with \textit{Bartonella}-associated neuroretinitis or retinochoroiditis show some degree of vitreous or anterior segment inflammation.\(^5,5^8\) In addition, recent reports have suggested that \textit{Bartonella}-associated intermediate and diffuse forms of uveitis can occur in the absence of optic disk edema or focal retinochoroiditis.\(^6^9-7^1\) These latter cases have been based on a single, elevated anti–\textit{B. henselae} serum IgG antibody titer, however, so they remain presumptive. In fact, the prevalence of \textit{B. henselae} seropositivity in patients seen in uveitis clinics\(^7^0\) appears to be similar to the rate of seropositivity in the general population.\(^4^0\) Of note, Lappin and Black\(^7^2\) have suggested that uveitis may accompany systemic \textit{B. henselae} infection in cats.
DIAGNOSIS

THE CLASSIC CLINICAL DIAGNOSIS OF CAT SCRATCH DISEASE introduced many years ago requires that at least three of the following four criteria be met: (1) a history of traumatic cat exposure; (2) a positive skin test in response to cat scratch disease antigen; (3) characteristic lymph node lesions; and (4) negative laboratory investigations for unexplained lymphadenopathy. Although symptoms and signs of systemic cat scratch disease remain helpful, modern approaches rely much more on serologic testing, and to a lesser extent culture and polymerase chain reaction–based techniques, to establish the diagnosis.

An indirect immunofluorescence test for the detection of serum anti–B. henselae antibodies has been developed by the Centers for Disease Control and Prevention. The sensitivities and specificities of this assay appear to be 90% or better for immunocompetent patients, although they may drop below 70% in patients infected by HIV. Enzyme-linked immunosorbent assays have also been developed but have variable sensitivities and specificities. Such variation may in part account for the relatively frequent reporting of false-negative results on samples run by laboratories other than the Centers for Disease Control. All tests for B. henselae show cross-reactivity to B. quintana, and it is important to realize that the potential for cross-reactivity with other Bartonella species exists as well.

A polymerase chain reaction–based assay for the detection of B. henselae 16S ribosomal RNA gene was first developed by Relman and associates. Other polymerase chain reaction–based detection methods have since been developed by a number of investigators. These techniques are sensitive, and when combined with sequencing they can identify specific Bartonella species. The assays are not commercially available, however, so they have been used most often as research tools.

Isolation of Bartonella bacilli from biopsy specimens is extremely difficult but can be done using enriched agar incubated in 5% CO₂ at 35 C to 37 C. B. henselae tends to grow best on heart infusion agar with 5% defibrinated rabbit blood, whereas B. quintana prefers chocolate agar containing IsoviteX and hemoglobin. Optimal yield from blood cultures is obtained with the lysis-centrifugation system (Wampole, Cranbury, New Jersey), wherein freshly drawn blood is lysed and centrifuged. The resulting pellet is then plated directly onto enriched media. Growth of colonies from tissue or blood can take up to 4 weeks.

TREATMENT

BEFORE THE IDENTIFICATION OF B. HENSELAE, VIRTUALLY all immunocompetent patients with cat scratch disease or its ocular complications tended to do well without antimicrobial therapy. This observation alone suggests that B. henselae infection is usually self-limited and perhaps explains why no clear treatment recommendations have appeared, despite increased recognition of the infectious nature of this disorder. To compound matters, in vitro drug sensitivities performed on the various Bartonella species do not always correlate directly with observed clinical response. These observations notwithstanding, however, immunocompromised patients infected with either B. henselae or B. quintana do show a dramatic response to treatment with either erythromycin or doxycycline. Such favorable in vivo responses in HIV-positive patients have led to the recommendation that one of these antibiotics be used to treat severe ocular or systemic complications of B. henselae infection in immunocompetent patients as well, even though the effectiveness of antibiotic therapy has never been demonstrated in a controlled trial. Doxycycline (100 mg given orally twice daily) has better intraocular and central nervous system penetration than erythromycin and therefore is often preferred in patients older than 8 to 12 years of age where tooth discoloration is less of a concern. These medications may also be given intravenously or combined with rifampin (300 mg orally twice daily) for more severe infections. The duration of treatment is usually 2 to 4 weeks in immunocompetent patients and 4 months for immunocompromised patients. It should be noted that HIV-infected patients with disseminated disease may develop a Jarisch-Herxheimer reaction after the first several doses of antimicrobial agents and that recurrences have been observed in HIV-positive patients, even after prolonged treatment. Long-term use of doxycycline or a macrolide antibiotic such as erythromycin may be useful for preventing recurrences in HIV-positive patients. Children should be treated in consultation with a pediatric infectious disease specialist.

PREVENTION

PATIENTS WITH CAT SCRATCH DISEASE SHOULD BE COUNSELED about the risks of cat and flea exposure. Although infected, immunocompetent patients appear to retain lasting immunity and are therefore at relatively low risk for repeat infection by B. henselae, attempts should still be made to minimize free-ranging behavior and flea infestation of pet cats to protect both the cat and uninfected members of the household. Washing and disinfecting any wounds immediately after a cat scratch or bite is also recommended. Treating infected cats has been suggested, but it is controversial, both because treatment usually requires force-feeding of antibiotics and can be accomplished by an increased risk of more cat scratches and bites, and because recurrent bacteremia is common in cats, despite antibiotic therapy. Although B. henselae infections are uncommon in immunocompromised patients, and the benefits of owning a cat usually outweigh the risks, infections that do occur in this group of patients can be severe or even fatal. Immunocompromised patients should, there-
fore, be especially careful to avoid scratches and to control flea infestation. It is also important that these patients make their caregivers aware that they have a cat.

CONCLUSION

THE PAST DECADE HAS WITNESSED A TREMENDOUS INCREASE IN OUR UNDERSTANDING OF Bartonella species as human pathogens. Ocular complications of systemic B. henselae infection, particularly Parinaud ocular glandular syndrome, neuroretinitis, and focal retinochoroiditis, are relatively common. Serologic testing remains the best way to confirm the diagnosis of B. henselae infection in patients with suggestive eye findings, but it is laboratory dependent and, at present, is best performed by the Centers for Disease Control. The role of other Bartonella species in neuroretinitis and retinochoroiditis, and of Bartonella species in general in other forms of uveitis, remains largely unknown.

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